HORIZON THERAPEUTICS (A WHOLLY OWNED SUBSIDIARY OF AMGEN INC.)

A RANDOMIZED, DOUBLE-BLIND, MULTICENTER, PLACEBO-CONTROLLED PHASE 3 STUDY WITH OPEN-LABEL PERIOD TO EVALUATE THE EFFICACY AND SAFETY OF INEBILIZUMAB IN ADULTS WITH MYASTHENIA GRAVIS

Short Title: **M**yasthenia Gravis **IN**ebilizumab **T**rial (**MINT**)

Investigational Product	Inebilizumab
Protocol Number	VIB0551.P3.S1 (20230049)
Clinical Trial Registry Identifiers	EudraCT number: 2020-000949-14 EU CT number: 2023-510006-40-00 NCT number: 04524273
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Trade Name	Uplizna™
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STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practice (GCP) as outlined by International Council for Harmonisation E6(R2), and all applicable local and national regulatory requirements, including Regulation (European Union [EU]) No 536/2914. Enrollment at any clinical study site may not begin prior to that site receiving approval from the ethics committee of record for the protocol and all materials provided to potential subjects.

Any amendments to the protocol or changes to the consent document will be approved before implementation of that amendment. Reconsent of previously enrolled subjects may be necessary depending on the nature of the amendment.

The Principal Investigator will ensure that changes to the study plan as defined by this protocol will not be made without prior agreement from the Sponsor and documented approval from the ethics committee of record, unless such a change is necessary to eliminate an immediate hazard to the study subjects.

All personnel involved in the conduct of this study have completed Human Subjects Protection and GCP training as outlined by their governing institution.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AC	Adjudication Committee
AChR	acetylcholine receptor
AChR-Ab+	AChR antibody positive
ADA	anti-drug antibody(ies)
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Anti-HBc	hepatitis B core antibody
Anti-HBs	hepatitis B surface antibody
AQP4-IgG	autoantibodies against aquaporin-4
AR	adverse reaction
AST	aspartate aminotransferase
BP	blood pressure
CD	cluster of differentiation
CDM	Clinical Data Management
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
CRO	contract research organization
CSA	clinical study agreement
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug-Induced Liver Injury
DMC	Data Monitoring Committee
DMP	Data Management Plan
DSUR	Development Safety Update Report
ECG	electrocardiogram
eCRF	electronic case report form
EDV	Early Discontinuation Visit
ePRO	electronic patient-reported outcome
EU	European Union
FAS	Full Analysis Set
Fc	fragment crystallizable
Fcγ	fragment crystallizable gamma
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone

Abbreviation	Definition
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
huCD19 Tg	human CD19 transgenic
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
[redacted]	
IND	Investigational New Drug
IP	investigational product
IRB	Institutional Review Board
IRR	infusion-related reaction
IST	immunosuppressive therapy(ies)
ITT	intent-to-treat
IV	intravenous(ly)
IVIg	intravenous immunoglobulin
IXRS	interactive voice/web response system
mAb	monoclonal antibody
MAH	marketing authorization holder
MG	myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living
MGC	Myasthenia Gravis Composite
MGFA	Myasthenia Gravis Foundation of America
MGQOL-15r	Myasthenia Gravis Quality of Life-15, revised
MI	multiple imputation
MMRM	mixed-effects model for repeated measures
MRI	magnetic resonance imaging
MS	multiple sclerosis
MuSK	muscle-specific kinase
MuSK-Ab+	muscle-specific kinase antibody positive
[redacted]	
NMOSD	neuromyelitis optica spectrum disorder
NOAEL	no-observed-adverse-effect level
OLP	open-label period
PAS	Per-protocol Analysis Set
[redacted]	

Abbreviation	Definition
PGIC	Patient Global Impression of Change
[redacted]	
PK	pharmacokinetic(s)
PLEX	plasma exchange
PML	progressive multifocal leukoencephalopathy
PRO	patient-reported outcome
PT	preferred term
QMG	Quantitative Myasthenia Gravis
QOL	quality of life
RCP	randomized controlled period
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
SC	subcutaneous
SFUP	safety follow-up
SID	subject identification
Sle1	systemic lupus erythematosus susceptible 1
SOC	system organ class
SSc	systemic sclerosis
t½	terminal elimination half-life
TB	tuberculosis
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal

1 SYNOPSIS

Title	A Randomized, Double-blind, Multicenter, Placebo-controlled Phase 3 Study with Open-label Period to Evaluate the Efficacy and Safety of Inebilizumab in Adults with Myasthenia Gravis
Short Title	**M**yasthenia Gravis **IN**ebilizumab **T**rial (MINT)
Protocol Number	VIB0551.P3.S1 (20230049)
Phase	3
Study Design	Randomized, double-blind, placebo-controlled, parallel-group study with optional open-label extension
Rationale	Several case series report that B-cell depletion with an anti-cluster of differentiation (CD)20 monoclonal antibody (mAb) can reduce disease severity in the treatment of refractory generalized myasthenia gravis (MG) (Iorio et al, 2015). However, not all studies have found a benefit of anti-CD20 therapy in MG. Inebilizumab is a humanized mAb that depletes CD19+ B-cells. CD19 expression persists on late-stage, antibody-secreting B-cells (plasmablasts and some plasma cells) after CD20 expression has been lost, which may be important in diseases driven by pathogenic autoantibodies. This study seeks to determine whether depletion of CD19+ B-cells with inebilizumab reduces disability and improves outcomes in subjects with MG.
Target Population	Adult subjects aged ≥ 18 years with acetylcholine receptor antibody positive (AChR-Ab+) or muscle-specific kinase antibody positive (MuSK-Ab+) generalized MG.
Number of Subjects	A total study population of approximately 230 subjects, comprising 188 subjects (94 per treatment group) with AChR-Ab+ MG and 42 subjects (21 per treatment group) with MuSK-Ab+ MG, randomized 1:1 to receive inebilizumab or placebo.
Length of Participation	Screening Period: 28 days for both populations. Randomized controlled period (RCP): 52 weeks for the AChR-Ab+ population and 26 weeks for the MuSK-Ab+ population. Optional open-label period (OLP): 3 years (156 weeks) for both populations. Safety Follow-Up period (SFUP) after investigational product (IP) discontinuation: 104 weeks (730 days or 2 years).
Intervention	**Treatment group 1:** AChR-Ab+ population (active) – inebilizumab 300 mg administered intravenously (IV) on Days 1, 15, and 183 of the RCP [a]. **Treatment group 2:** AChR-Ab+ population (placebo) – IV placebo on Days 1, 15, and 183 of the RCP [b]. **Treatment group 3:** MuSK-Ab+ population (active) – inebilizumab 300 mg IV on Days 1 and 15 of the 26-week RCP [a]. **Treatment group 4:** MuSK-Ab+ population (placebo) – IV placebo on Days 1 and 15 of the 26-week RCP [b]. [a] Following the RCP, subjects from an active treatment group who elect to enter the OLP will receive inebilizumab 300 mg IV on OLP Day 1, IV placebo on OLP Day 15 (to avoid potential unblinding), and inebilizumab 300 mg IV on OLP Days 183, 365, 547, 729, and 911. [b] Following the RCP, subjects from a placebo treatment group who elect to enter the OLP will receive inebilizumab 300 mg IV on OLP Days 1, 15, 183, 365, 547, 729, and 911.

Primary Objective and Primary Endpoint	**Primary objective**: To assess whether inebilizumab can reduce MG-related disability. **Primary endpoint**: Change from baseline in Myasthenia Gravis Activities of Daily Living (MG-ADL) score at Week 26 in the overall study population (ie, the AChR-Ab+ and MuSK-Ab+ populations).
Secondary Objectives and Corresponding Endpoints	**Secondary objectives:** 1. To evaluate whether inebilizumab can reduce the frequency of MG exacerbations. 2. To evaluate whether inebilizumab can improve MG-related quality of life. 3. To evaluate the safety and tolerability of inebilizumab in MG. 4. To characterize the pharmacokinetic (PK) profile and immunogenicity of inebilizumab in subjects with MG. 5. To evaluate the effect of inebilizumab on corticosteroid usage. 6. To evaluate the ability of inebilizumab to elicit minimal symptom expression. **Key secondary endpoints:** 1. Change from baseline in Quantitative Myasthenia Gravis (QMG) score at Week 26 in the overall study population. 2. Change from baseline in MG-ADL score at Week 26 in the AChR-Ab+ population. 3. Change from baseline in QMG score at Week 26 in the AChR-Ab+ population. 4. Change from baseline in MG-ADL score at Week 26 in the MuSK-Ab+ population. 5. Change from baseline in QMG score at Week 26 in the MuSK-Ab+ population. **Additional secondary endpoints:** 1. The proportion of subjects with ≥ 3-point improvement in MG-ADL score at Week 26 and no use of rescue therapy [redacted] in the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and at Week 52 and no use of rescue therapy [redacted] in the AChR-Ab+ population. 2. Change from baseline in MG-ADL score at Week 52 in the AChR-Ab+ population. 3. Change from baseline in QMG score at Week 52 in the AChR-Ab+ population. 4. Change from baseline in Myasthenia Gravis Composite (MGC) score at Week 26 in the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and at Week 52 in the AChR-Ab+ population. 5. Change from baseline in Myasthenia Gravis Quality of Life-15 revised (MGQOL-15r) score at Week 26 in the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and at Week 52 in the AChR-Ab+ population. 6. Patient Global Impression of Change score at Week 26 in the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and at Week 52 in the AChR-Ab+ population. 7. Time to first MG exacerbation by Week 26 in the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and by Week 52 in the AChR-Ab+ population. 8. The safety and tolerability of inebilizumab as measured by the incidence of treatment-emergent adverse events, adverse events of special interest, and treatment-emergent serious adverse events. Laboratory measurements will also be evaluated as part of safety. 9. The proportion of subjects with steroid tapered to ≤ 5 mg/day at Week 26 for the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and at Week 52 for the AChR-Ab+ population +.

	10. The proportion of subjects in whom steroid dose was reduced by ≥ 50% by Week 26 for the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and by Week 52 for the AChR-Ab+ population. 11. The proportion of subjects achieving minimal symptom expression, defined as MG-ADL = 0 or 1, at Week 26. 12. Anti-drug antibody status and titer during the study in the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population.
Number of Sites	Approximately 120 sites

2 INTRODUCTION

2.1 Background

Myasthenia gravis (MG) is a rare autoimmune disorder caused by the binding of antibodies to the acetylcholine receptor (AChR) or functionally related molecules on the postsynaptic neuromuscular junction. The incidence ranges from 0.3 to 2.8 per 100,000 people, and it is estimated that more than 700,000 people worldwide are affected by MG (Sanders et al, 2016). There are reports of increasing incidences of MG, which may in part be attributed to improved diagnostics but may also be attributed to environmental factors (Gilhus et al, 2019; Yi et al, 2018).

Approximately 85% of subjects with MG are categorized as having generalized disease, with common symptoms including ptosis, diplopia, dyspnea, and generalized muscle weakness. Conversely, in approximately 15% of subjects with MG, symptoms are restricted to the ocular muscles (Gilhus et al, 2019). This protocol focuses on subjects with generalized MG who have moderate to severe disease.

Approximately 85% of subjects with MG have detectable antibodies against AChR, and approximately 7% have detectable antibodies against muscle-specific kinase (MuSK) (Hehir and Silvestri, 2018). Differentiation of MG subpopulations can be made based on subjects' antibody status or lack thereof, as well as various clinical features, such as early-onset, late-onset, thymoma and ocular forms of MG, scores of various patient-reported outcomes (PROs), and Myasthenia Gravis Foundation of America (MGFA) classification, all of which define the type and severity of an individual's MG condition.

Acetylcholine receptor antibody positive (AChR-Ab+) MG pathology is characterized by immunoglobulin (Ig)G_1 and IgG_3 antibodies produced by long-lived plasma cells largely residing in the tissue of the thymus (Fichtner et al, 2020a). AChR-specific antibodies mediate disease at the neuromuscular junction through 1) direct blockade of AChR signaling; 2) cross-linkage of AChRs, resulting in increased receptor endocytosis and degradation; and 3) complement-mediated cell death, resulting in tissue damage and synapse widening (Yi et al, 2018; Fichtner et al, 2020b). In contrast, MuSK antibody positive (MuSK-Ab+) MG is characterized by IgG_4 antibodies secreted by short-lived circulating plasmablasts, which mediate disease through direct disruption of the AChR cluster signaling pathway, which is required for efficient neuromuscular transmission (Yi et al, 2018; Fichtner et al, 2020b; Vergoossen et al, 2020). A unique property of IgG_4 antibodies is their ability to participate in fragment antigen-binding-arm exchange with other non-MuSK-specific IgG_4 antibodies, thereby increasing the total amount of circulating pathogenic MuSK-specific IgG_4 (Fichtner et al, 2020a; Vergoossen et al, 2020; Fichtner et al, 2020b).

The production of these pathogenic autoantibodies indicates a principal role for B-cells in MG pathogenesis. Therefore, B-cell-depleting agents could serve as effective therapies for MG as they would non-selectively inhibit the production of pathogenic autoantibodies, regardless of how they mediate disease. Rituximab, a cluster of differentiation (CD)20-specific chimeric monoclonal antibody (mAb) that depletes CD20+ B-cells, has previously demonstrated differential efficacy across MG subtypes, with > 95% of MuSK-Ab+ subjects reaching stable or pharmacological remission compared to approximately 56% of AChR-Ab+ subjects who

experience relapse within an average of 3 years posttreatment (Yi et al, 2018; Fichtner et al, 2020b). This difference in efficacy is likely due to phenotypic differences in the B-cell subsets responsible for producing the different disease-causing autoantibodies. As previously described, AChR-specific antibodies are produced by long-lived plasma cells residing in tissue, whereas MuSK-specific antibodies are produced by short-lived circulating plasmablasts. This is an important distinction given that CD20 expression is low to undetectable in long-lived plasma cells, whereas circulating plasmablasts express higher levels of CD20 (Fichtner et al, 2020a; Forsthuber et al, 2018).

When considering CD expression levels throughout B-cell development, CD20 is not expressed until B-cell activation and is lost after the plasmablast phase. In contrast, CD19 is expressed earlier in development, starting at the pro-B-cell phase and continuing through differentiation of plasmablasts into plasma cells (Fichtner et al, 2020b; Forsthuber et al, 2018). For this reason, a CD19+ B-cell-depleting drug would be expected to not only offer similar levels of efficacy in the MuSK-Ab+ population compared to CD20-specific therapies, but would also likely have the advantage of providing enhanced efficacy in the AChR-Ab+ population, given its ability to also target AChR-Ab-producing long-lived plasma cell populations (Fichtner et al, 2020b).

Anticholinesterases and immunosuppressive therapies (ISTs) are the standard of care for medical treatment and have notably reduced mortality and improved quality of life (QOL) for subjects with MG. Approximately 85-90% of subjects with MG respond to standard of care therapies (Urban et al, 2018), but not without limited durability of efficacy or side effects with long-term use that impact QOL. Additionally, 10-20% of subjects with MG do not respond to multiple combinations of therapies and are known as refractory subjects. Therefore, there is a need to develop new therapeutics for MG that have rapid onset of action, have good treatment durability, and can help refractory subjects. Oral corticosteroids are also commonly used for MG and are associated with considerable side effects; reduction in the need for oral corticosteroids is therefore another important goal of MG treatment.

As mentioned above, several small observational studies have shown that CD20-specific chimeric antibody rituximab eliminates CD20+ B-cells and can have good effects when used as a treatment for subjects with refractory MG, especially in MuSK-Ab+ subjects (Iorio et al, 2015). However, not all studies have found benefit of rituximab in MG. Furthermore, rituximab has not been approved by the Food and Drug Administration (FDA) for use in MG. Therefore, additional controlled studies are needed to determine if B-cell depletion can improve outcomes for subjects with MG.

The aim of the present study is to investigate whether the anti-CD19 mAb inebilizumab is safe and effective in the treatment of moderate to severe MG.

2.1.1 Description of Inebilizumab

Inebilizumab is a humanized, affinity-optimized, afucosylated $IgG_1\kappa$ mAb that targets and depletes CD19+ B-cells. The unique glycoengineering process of inebilizumab generates a homogenously afucosylated antibody with an approximate 10-fold increase in affinity for the fragment crystallizable gamma (Fcγ) receptor IIIA, resulting in significantly enhanced antibody-dependent cellular cytotoxicity (Agius et al, 2019). Inebilizumab is also able to induce antibody-dependent cellular phagocytosis; however, in contrast to rituximab, inebilizumab does not mediate complement-dependent cytotoxicity (Herbst et al, 2010).

2.1.2 Supportive Nonclinical Data for Inebilizumab

2.1.2.1 Pharmacology

Nonclinical evaluation demonstrates that inebilizumab specifically recognizes human CD19 and has poor or no cross-reactivity to CD19 in nonhuman primates, rabbits, or rodents. Therefore, the human CD19 transgenic (huCD19 Tg) mouse was selected as the relevant animal model for testing the pharmacodynamics (PD) and the safety of inebilizumab. In vivo, inebilizumab effectively depleted B-cells in blood and tissue. The duration of B-cell depletion was dose-dependent and was sustained for more than 10 weeks after treatment with a single 250 µg injection of inebilizumab in huCD19 Tg mice. An additional 4-6 weeks were required for the B-cells to recover to levels and maturities similar to those in the IgG control-treated animals. The effect of treatment with inebilizumab was limited to B-cells and did not have an impact on other immune cells in circulation, as assessed by [redacted] Thus, inebilizumab selectively targets and depletes B-cells.

In a nonclinical model of systemic sclerosis (SSc), inebilizumab reduced autoreactive B-cell numbers and pathogenic autoantibodies. Similarly, inebilizumab depleted blood and tissue B-cells, as well as spleen plasma cells in systemic lupus erythematosus susceptible 1 (Sle1)-huCD19 Tg mice, a model of autoimmune disease. Total serum Ig, autoantibodies, and inflammatory mediators in serum Sle1-huCD19 Tg mice were also reduced following inebilizumab administration. Using the classic experimental autoimmune encephalomyelitis model in huCD19 Tg mice, treatment with inebilizumab resulted in a reduction of autoantibodies and the inhibition of Ig and complement-mediated inflammation in the central nervous system; these findings demonstrate that inebilizumab is highly effective in targeting pathogenic B-cells in a neuro-inflammatory setting (Gallagher et al, 2016a; Gallagher et al, 2016b; Chen et al, 2016).

2.1.2.2 Nonclinical Toxicology

Nonclinical studies of inebilizumab in the huCD19 Tg mouse model demonstrated that there were no adverse effects after a single intravenous (IV) dose (up to [redacted] mg/kg), 5 weekly IV doses (up to [redacted] mg/kg), or up to 26 weekly IV doses (up to [redacted] mg/kg). Comparison of weekly subcutaneous (SC) to IV administration showed similar findings to the IV repeat-dose studies. The only findings from these toxicology studies were related to the pharmacologic action of B-cell depletion. In the SC/IV study, males who received inebilizumab by IV injection at [redacted] mg/kg/week had an increased incidence of bronchioloalveolar adenomas at the end of the recovery period. A similar increase was not seen in males who received [redacted] mg/kg/week inebilizumab by SC injection or in previous IV repeat-dose toxicology studies with inebilizumab. Additionally, results from a lifetime study with untreated huCD19 Tg mice demonstrated that bronchioloalveolar adenomas occurred as a background finding in males (Iverson et al, 2017). Therefore, the weight of evidence suggests that this was an incidental background finding, and it is not considered to represent a risk to subjects.

Results of a fertility and embryofetal development study showed a treatment-related reduction in fertility index and the number of mice that were pregnant/number of mice in cohabitation with no other adverse findings. Importantly, inebilizumab had no impact on embryofetal development. An IV study on the effects of inebilizumab on prenatal and postnatal development, including

maternal function in mice, showed no adverse effects on the F0 dams, F1 growth, survival, reproductive development and performance, and F2 fetuses at any dosage level. The no-observed-adverse-effect level (NOAEL) for F0 maternal, F1 systemic and reproductive, and F2 embryo/fetal developmental toxicity was considered to be [redacted] mg/kg, the highest dose level evaluated. F1 pups showed a diminished antibody response to keyhole limpet hemocyanin challenge at both inebilizumab dose levels after B-cells had repopulated. Accordingly, the NOAEL for F1 development and immunotoxicity could not be determined.

For additional details on nonclinical toxicity, refer to the inebilizumab Investigator's Brochure.

2.1.3 Supportive Clinical Data for Inebilizumab

Inebilizumab has been and continues to be investigated in both non-oncology and oncology clinical studies. In non-oncology studies, inebilizumab was investigated in subjects with SSc (Study MI-CP200) and multiple sclerosis (MS) (Study CD-IA-MEDI-551-1102). Inebilizumab is also being investigated in subjects with neuromyelitis optica spectrum disorder (NMOSD) (Study CD-IA-MEDI-551-1155). Inebilizumab has already been approved for NMOSD in the US and several other countries. In oncology studies, inebilizumab has been investigated in subjects with B-cell malignancies such as follicular lymphoma, diffuse large B-cell lymphoma, multiple myeloma, mantle cell lymphoma, and chronic lymphocytic leukemia (Studies MI-CP204, CD-ON-MEDI-551-1019, CD-ON-MEDI-551-1088, D2850C00001, D2852C00004, and J1340).

2.1.3.1 Phase 1 Dose-escalation Study in Systemic Sclerosis

The first clinical study of inebilizumab in an autoimmune disease was Study MI-CP200, a Phase 1, randomized, double-blind, placebo-controlled study evaluating the safety and tolerability of escalating single IV doses of inebilizumab [redacted] mg/kg) in 28 adult subjects with SSc who had at least moderate skin thickening in an area suitable for repeat biopsy. This study has been completed, with 4 subjects having received placebo and 24 subjects having received inebilizumab.

In Study MI-CP200, one subject in the [redacted] mg/kg inebilizumab dose group died during the study following renal crisis; the underlying cause of the terminal renal insufficiency was assessed as related to progression of SSc. The most frequent (incidence > 15% of subjects) treatment-emergent adverse events (TEAEs) in the inebilizumab group were nausea, arthralgia, pain in extremity, fatigue, and infusion-related reaction (IRR), with the majority of TEAEs being Grade 1 (mild) or Grade 2 (moderate) in severity. Treatment-emergent serious adverse events (TESAEs) occurred in 6 of 24 subjects (25.0%) in the inebilizumab group, with no events occurring in more than one subject. Two TESAEs (supraventricular tachycardia and subclavian vein thrombosis) were assessed by the Investigator as being possibly related to inebilizumab. Following a single IV administration, inebilizumab exhibited nonlinear pharmacokinetics (PK) in the dose range investigated [redacted] mg/kg). For inebilizumab doses of [redacted] mg/kg or higher, parallel terminal phases and similar terminal elimination half-life ($t_{½}$) (11.3-13.5 days) were observed. Inebilizumab caused rapid and sustained depletion of circulating B-cells in all subjects after a single IV infusion at doses of [redacted] mg/kg. Full B-cell recovery for subjects in the lower dose cohorts occurred sometime after Day 169, whereas full B-cell recovery for subjects enrolled in the highest dose group was observed even later, around Day 337 and beyond. [redacted]

[redacted] and [redacted] mg/kg). Mean reductions from baseline in the Modified Rodnan Total Skin Score were observed for all inebilizumab dose groups compared to placebo.

2.1.3.2 Phase 1 Dose-escalation Study in Multiple Sclerosis

Study CD-IA-MEDI-551-1102 was a Phase 1, multicenter, multinational, randomized, blinded, placebo-controlled, dose-escalation study evaluating the safety and tolerability of IV or SC doses of inebilizumab in 28 adult subjects with relapsing forms of MS. A total of 28 subjects were enrolled in the study to receive 2 IV administrations of inebilizumab ([redacted] or [redacted] mg) or placebo on Day 1 and Day 15, or a single SC dose of inebilizumab ([redacted] or 300 mg) or placebo over a 24-week period (Days 1 through 169) with long-term follow-up for all subjects for B-cell recovery starting after Day 169. This study has been completed, with 7 subjects having received placebo and 21 subjects having received inebilizumab. Dosing continued through the highest doses tested ([redacted] mg IV and 300 mg SC), and inebilizumab was reasonably tolerated at all doses tested. The most frequent TEAEs (incidence ≥ 14% of subjects) in the total inebilizumab group were IRR, nasopharyngitis, upper respiratory infection, blood pressure (BP) increased, pyrexia, urinary tract infection, and urinary tract inflammation, with the majority of TEAEs being Grade 1 or Grade 2 in severity. IRRs occurred in 2 of 5 subjects (40.0%) in the IV placebo group and 6 of 15 subjects (40.0%) in the total IV inebilizumab group, which were all Grade 1 or Grade 2 in severity and assessed as related to the investigational product (IP). IRRs occurred in none of the subjects in the SC placebo group and in one of 6 subjects (16.7%) in the total SC inebilizumab group. One of 7 subjects (14.3%) in the placebo group and 3 of 21 subjects (14.3%) in the inebilizumab groups had ≥ 1 TESAE. One subject in the 300 mg SC cohort had a TESAE of pyrexia that was related to the IP.

The mean number of cumulative new gadolinium-enhancing magnetic resonance imaging (MRI) lesions by Week 24 was lower in the inebilizumab group than in the placebo group, as was the mean number of new or newly enlarged T2 MRI lesions.

Following IV infusion of inebilizumab, the PK of inebilizumab was dose-proportional in the [redacted] mg range. The absorption from the SC dosing site was slow, and the apparent clearance (CL) after extravascular administration and $t_{½}$ values were similar between the 2 SC cohorts. Complete (> 99%) and sustained B-cell depletion was observed across all inebilizumab-treated groups. B-cells reached about 90% reduction from baseline prior to the second IV dose on Day 15 for all IV cohorts and the high-dose SC cohort (300 mg).

[redacted]

2.1.3.3 Phase 2/3 Efficacy and Safety Study in Neuromyelitis Optica Spectrum Disorder

Study CD-IA-MEDI-551-1155 (Study 1155; D2835C00001) was a randomized, double-blind, placebo-controlled study with an open-label extension of IV inebilizumab, evaluating the efficacy and safety of inebilizumab in adult subjects with NMOSD who were seropositive or seronegative for autoantibodies against aquaporin-4 (AQP4-IgG). In this study, inebilizumab (300 mg) or placebo was administered as a fixed IV dose on Days 1 and 15 (ie, 300 mg on Day 1

and 300 mg on Day 15) of a 28-week randomized controlled period (RCP). Thereafter, 300 mg IV inebilizumab was administered every 26 weeks in an open-label period (OLP) for ≥ 52 weeks. The primary endpoint of the study was the time (days) from Day 1 to onset of an Adjudication Committee (AC)-determined NMOSD attack on or before Day 197.

In total, 231 subjects were randomized in Study 1155, including 18 (7.8%) AQP4-IgG seronegative subjects and 213 (92.2%) AQP4-IgG seropositive subjects; 230 subjects overall were included in the intent-to-treat (ITT) population. A total of 223 subjects (97.0%) completed the RCP.

The primary endpoint of this study was met. In both the AQP4-IgG seropositive and total ITT populations, treatment with inebilizumab statistically significantly reduced the risk of an AC-determined NMOSD attack as compared to treatment with placebo. During the RCP, the hazard ratio of AC-determined attacks with inebilizumab treatment relative to placebo was 0.227 (95% confidence interval [CI]: 0.1214, 0.4232) for the AQP4-IgG seropositive population, and it was 0.272 (95% CI: 0.1496, 0.4691) for the total ITT population; $p < 0.0001$ for each comparison. Additionally, a statistically significant improvement with inebilizumab compared with placebo was demonstrated for 3 of 4 key secondary endpoints: worsening from baseline in Expanded Disability Status Scale, cumulative number of total active MRI lesions, and cumulative number of inpatient hospitalizations. One key secondary endpoint, low-contrast visual acuity, did not demonstrate a significant treatment effect with inebilizumab.

In Study 1155, repeated doses of inebilizumab in the RCP and OLP were well tolerated. The incidence of TEAEs was balanced across the treatment groups during randomized treatment (71.8% in the inebilizumab group and 73.2% in the placebo group). There were no deaths during the RCP. Similar proportions of subjects across the treatment groups experienced TESAEs, with no observed trends by preferred term (PT) or system organ class (SOC). Few subjects discontinued the IP due to a TEAE, and most TEAEs were mild to moderate in intensity (Grades 1 or 2). As of 18 December 2018 (primary analysis database lock) in the OLP, 15.5% of subjects had ≥ 1 TESAE and/or ≥ Grade 3 TEAE, 1 subject had a TEAE resulting in discontinuation, and 3 subjects had a TEAE resulting in dose interruption. Overall, the adverse event (AE) profile for inebilizumab remained generally consistent during the OLP. During the OLP, there were 2 fatal TEAEs (PTs of NMOSD and pneumonia). One subject in the placebo/inebilizumab group had an NMOSD attack of myelitis on study Day 31. The subject entered the OLP and died suddenly during sleep on Day 10 of the OLP; cause of death was reported as NMOSD. A second subject was randomized to inebilizumab and entered the OLP following an NMOSD attack of optic neuritis. On study Day 245, the subject had a fatal TESAE of pneumonia. The event was a complication of the development of new brain lesions for which a definitive diagnosis could not be established; the differential diagnosis was progressive multifocal leukoencephalopathy (PML), acute disseminated encephalomyelitis, or an atypical NMOSD attack.

No differences in PK were apparent in AQP4-IgG seropositive and AQP4-IgG seronegative subjects. The geometric mean CL of 202 mL/day and volume of distribution at steady state of 4210 mL are typical for therapeutic IgG mAbs. The $t_{½}$ of inebilizumab was approximately 18 days in adult subjects with NMOSD. Following treatment with inebilizumab, blood CD20+ B-cell counts were profoundly decreased during the 28-week RCP. Within the any

inebilizumab-treated population, 5.6% of subjects developed treatment-emergent anti-drug antibodies (ADA). The ADA had little or no apparent impact on PK, PD, or safety.

2.1.4 Risk Assessment for Inebilizumab

Identified risks for subjects treated with inebilizumab are IRRs, [redacted], neutropenia, lymphopenia, and arthralgia.

In the NMOSD study, IRRs occurred at similar rates in the inebilizumab and placebo groups (9.2% and 10.7%, respectively). All IRRs in the study were Grade 1 or 2 (mild or moderate) in severity. To reduce the risk and frequency of IRRs, all subjects in the present study will receive prophylaxis with IV methylprednisolone, oral diphenhydramine, and oral acetaminophen, or equivalent. In the NMOSD study, laboratory abnormalities were observed in some subjects.

[redacted]

After 2 years of inebilizumab treatment, severe hypogammaglobulinemia (IgG < 200 mg/dL) was observed in 1/81 subjects (1.2%); this case of severe hypogammaglobulinemia occurred after plasma exchange (PLEX) and was transient. Neutrophil counts between 1.0-1.5 × 10^9/L were observed in 6.9% of inebilizumab-treated subjects vs 1.8% of placebo-treated subjects. Neutrophil counts between 0.5-1.0 × 10^9/L were observed in 1.7% of inebilizumab-treated subjects vs 0% of placebo-treated subjects. Neutropenia was generally transient and not associated with serious infections. Subjects in the present study will be monitored for neutropenia, and the IP will be discontinued if there is persistent Grade 3 neutropenia. A reduction in lymphocyte counts can be observed with inebilizumab, consistent with its mechanism of action.

In the NMOSD study, the proportion of subjects with arthralgia was numerically higher in the inebilizumab group than in the placebo group (9.8% vs 3.6%) during the RCP (Cree et al, 2019). The rate of arthralgia was lower in the combined RCP and OLP inebilizumab population (5.36 per 100 person-years) than in the RCP inebilizumab population (20.6 per 100 person-years).

Based on its mechanism of action and nonclinical and clinical data, other important potential risks of inebilizumab are serious infection, cytopenia, hypersensitivity (including anaphylaxis and serious skin reactions), immune complex disease, and PML. One case of possible PML was reported in the NMOSD study, though evaluation could not confirm PML in that case. No cases of immune complex disease were reported in any inebilizumab studies.

The safety of inebilizumab during pregnancy is unknown. However, inebilizumab is an mAb, and Igs are known to cross the placental barrier. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other B-cell depleting antibodies during pregnancy (OCREVUS PI, 2017; RITUXAN PI, 2012). Three pregnancies occurred in Study CD-IA-MEDI-551-1155 in subjects exposed to inebilizumab. No unexpected complications occurred during the pregnancies, and no health problems were noted in the babies. There are no data on the presence of inebilizumab in human breast milk, but lactating women should be advised not to breastfeed during treatment.

Refer to the inebilizumab Investigator's Brochure for a complete summary of risks.

2.1.5 Anticipated Study Benefits and Risks

This study has been designed to minimize risks to subjects where possible. The risks of study participation include the risks of inebilizumab that are summarized in Section 2.1.4 and the Investigator's Brochure, risk of worsening of MG, and risk of loss of privacy. In prior clinical trials, inebilizumab was found to have an acceptable risk profile with a convenient dosing regimen and a low rate of IRRs. Subjects are allowed to use selected standard of care MG treatments during the study. Those treatments can be continued during the RCP with the exception of corticosteroids, which are tapered to prednisone 5 mg/day to reduce the potential risk and morbidity associated with long-term use of moderate- or high-dose corticosteroids. If symptoms worsen during the study, rescue therapy is allowed. The study inclusion and exclusion criteria reduce the risk to subjects by excluding those who may be at elevated risk of complications from the use of inebilizumab (eg, those with chronic infections or baseline cytopenia). The criteria for required discontinuation of the IP (Section 6.3.1) were designed to stop the IP in anyone for whom continued use may be an unjustified risk. An OLP is included in the study to ensure that all study subjects who complete the RCP have the opportunity to receive open-label inebilizumab.

The benefits of study participation include potential receipt of an IP that may reduce MG-related disability. This hypothesis is based on data from multiple case series showing that B-cell depletion with rituximab, a drug with a similar mechanism of action to inebilizumab, can improve outcomes in refractory MG subjects (Iorio et al, 2015). The subjects who will enter the study have moderate to severe MG symptoms despite use of standard of care treatments, including azathioprine, mycophenolate mofetil, mycophenolic acid, tacrolimus (Japan only), and/or corticosteroids. The potential benefits to subjects and society of testing the hypothesis that inebilizumab can reduce MG-related disability are believed to outweigh the potential risks.

2.2 Study Rationale

The production of autoantibodies indicates a principal role for B-cells in MG pathogenesis. Several case series have reported that rituximab, a chimeric mAb that depletes CD20+ B-cells, can reduce disease activity in the treatment of refractory MG, especially in MuSK-Ab+ subjects (Iorio et al, 2015). However, not all studies have found that rituximab is beneficial in MG, and rituximab is not approved for use in MG. Inebilizumab is a humanized mAb that targets and depletes CD19+ B-cells. CD19 expression is found to persist on late-stage, antibody-secreting B-cells (plasmablasts and some plasma cells) after CD20 expression has been lost, which may be important in diseases driven by pathogenic autoantibodies. A successful Phase 2/3 clinical study of inebilizumab in NMOSD, an antibody-mediated disease of the central nervous system, has completed the RCP (Cree et al, 2019). Inebilizumab has already been approved for NMOSD in several countries. Inebilizumab may benefit subjects with other antibody-mediated diseases such as MG. Therefore, this study seeks to determine whether depletion of CD19+ B-cells with inebilizumab reduces disability and improves other outcomes in subjects with MG.

2.3 Study Hypotheses

Primary Hypothesis: Depletion of CD19+ B-cells with inebilizumab will improve outcomes in subjects with MG.

Secondary Hypotheses: In subjects with MG, treatment with inebilizumab will:

- Reduce the frequency of exacerbations
- Improve QOL
- Offer an acceptable safety and tolerability profile

3 OBJECTIVES AND ENDPOINTS

3.1 Primary Objectives and Endpoints

3.1.1 Primary Objective

To assess whether inebilizumab can reduce MG-related disability.

3.1.2 Primary Endpoint

Change from baseline in Myasthenia Gravis Activities of Daily Living (MG-ADL) score at Week 26 in the overall study population (ie, the AChR-Ab+ and MuSK-Ab+ populations).

3.2 Secondary Objectives and Endpoints

3.2.1 Secondary Objectives

1. To evaluate whether inebilizumab can reduce the frequency of MG exacerbations.
2. To evaluate whether inebilizumab can improve MG-related QOL.
3. To evaluate the safety and tolerability of inebilizumab in MG.
4. To characterize the PK profile and immunogenicity of inebilizumab in subjects with MG.
5. To evaluate the effect of inebilizumab on corticosteroid usage.
6. To evaluate the ability of inebilizumab to elicit minimal symptom expression.

3.2.2 Secondary Endpoints

Key secondary endpoints:

1. Change from baseline in Quantitative Myasthenia Gravis (QMG) score at Week 26 in the overall study population.
2. Change from baseline in MG-ADL score at Week 26 in the AChR-Ab+ population.
3. Change from baseline in QMG score at Week 26 in the AChR-Ab+ population.
4. Change from baseline in MG-ADL score at Week 26 in the MuSK-Ab+ population.
5. Change from baseline in QMG score at Week 26 in the MuSK-Ab+ population.

Additional secondary endpoints:

1. The proportion of subjects with ≥ 3-point improvement in MG-ADL score at Week 26 and no use of rescue therapy [redacted] in the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and at Week 52 and no use of rescue therapy [redacted] in the AChR-Ab+ population.
2. Change from baseline in MG-ADL score at Week 52 in the AChR-Ab+ population.
3. Change from baseline in QMG score at Week 52 in the AChR-Ab+ population.
4. Change from baseline in Myasthenia Gravis Composite (MGC) score at Week 26 in the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and at Week 52 in the AChR-Ab+ population.
5. Change from baseline in Myasthenia Gravis Quality of Life-15 revised (MGQOL-15r) score at Week 26 in the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and at Week 52 in the AChR-Ab+ population.

6. Patient Global Impression of Change (PGIC) score at Week 26 in the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and at Week 52 in the AChR-Ab+ population.
7. Time to first MG exacerbation by Week 26 in the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and by Week 52 in the AChR-Ab+ population. (Note: see Section 9.4.3 for the definition of MG exacerbation.).
8. The safety and tolerability of inebilizumab as measured by the incidence of TEAEs, adverse events of special interest (AESIs), and TESAEs. Laboratory measurements will also be evaluated as part of safety.
9. The proportion of subjects with steroid tapered to ≤ 5 mg/day at Week 26 for the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and at Week 52 for the AChR-Ab+ population.
10. The proportion of subjects in whom steroid dose was reduced by ≥ 50% by Week 26 for the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and by Week 52 for the AChR-Ab+ population.
11. The proportion of subjects achieving minimal symptom expression, defined as MG-ADL = 0 or 1, at Week 26.
12. Anti-drug antibody status and titer during the study in the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population.

3.3 Exploratory Objectives and Endpoints

3.3.1 Exploratory Objectives

[redacted]

3.3.2 Exploratory Endpoints

[redacted]

4 STUDY PLAN

4.1 Study Design

This study is a Phase 3, randomized, double-blind, multicenter, placebo-controlled study to be conducted at approximately 120 study sites. Approximately 230 subjects (188 subjects with AChR-Ab+ MG and 42 subjects with MuSK-Ab+ MG) are planned to be enrolled. To account for the allowance of tacrolimus in Japan and potential introduction of heterogeneity in baseline therapy, the total number of subjects represents an upper estimated limit for recruitment and may be reduced, depending on the total number of Japanese subjects enrolled.

Subjects with MG who are positive for anti-AChR or anti-MuSK antibodies will be enrolled. Subjects with MGFA classification II, III, or IV disease at the time of screening and randomization; MG-ADL score at screening and randomization between 6 and 10 with > 50% of this score attributed to non-ocular items, or an MG-ADL score ≥ 11; QMG score ≥ 11 at the time of screening and randomization; and use of a corticosteroid and/or non-steroidal immunosuppressant will be included in the study. These criteria define a population of subjects with generalized MG and inadequate symptom control.

Within each population, subjects will be stratified by region first (non-Japan vs Japan). In the non-Japan population, subjects will be further stratified according to baseline disease severity ("Day 1 QMG score = 11-15" vs "Day 1 QMG score ≥ 16") and baseline corticosteroid use ("prednisone > 5 mg/day" vs "prednisone ≤ 5 mg/day"), and randomized 1:1 to receive either IV inebilizumab or placebo within each stratum (Figure 1). To quantify disease severity for stratification purposes, the QMG was chosen over the MG-ADL because the results are more likely to be consistent between individuals since the QMG is based on objective examination and the MG-ADL is based on subjective reporting.

In the Japan population, no further stratification will be applied due to the small sample size, and subjects will be randomized 1:1 to receive either IV inebilizumab or placebo. Subjects will be allowed to enter the study on a standard of care regimen, including acetylcholinesterase inhibitors, corticosteroids, and/or azathioprine, mycophenolate mofetil, and mycophenolic acid. In Japan, subjects will also be allowed to enter the study on tacrolimus.

The duration of the RCP is 52 weeks for the AChR-Ab+ population (Figure 2) and 26 weeks for the MuSK-Ab+ population (Figure 3).

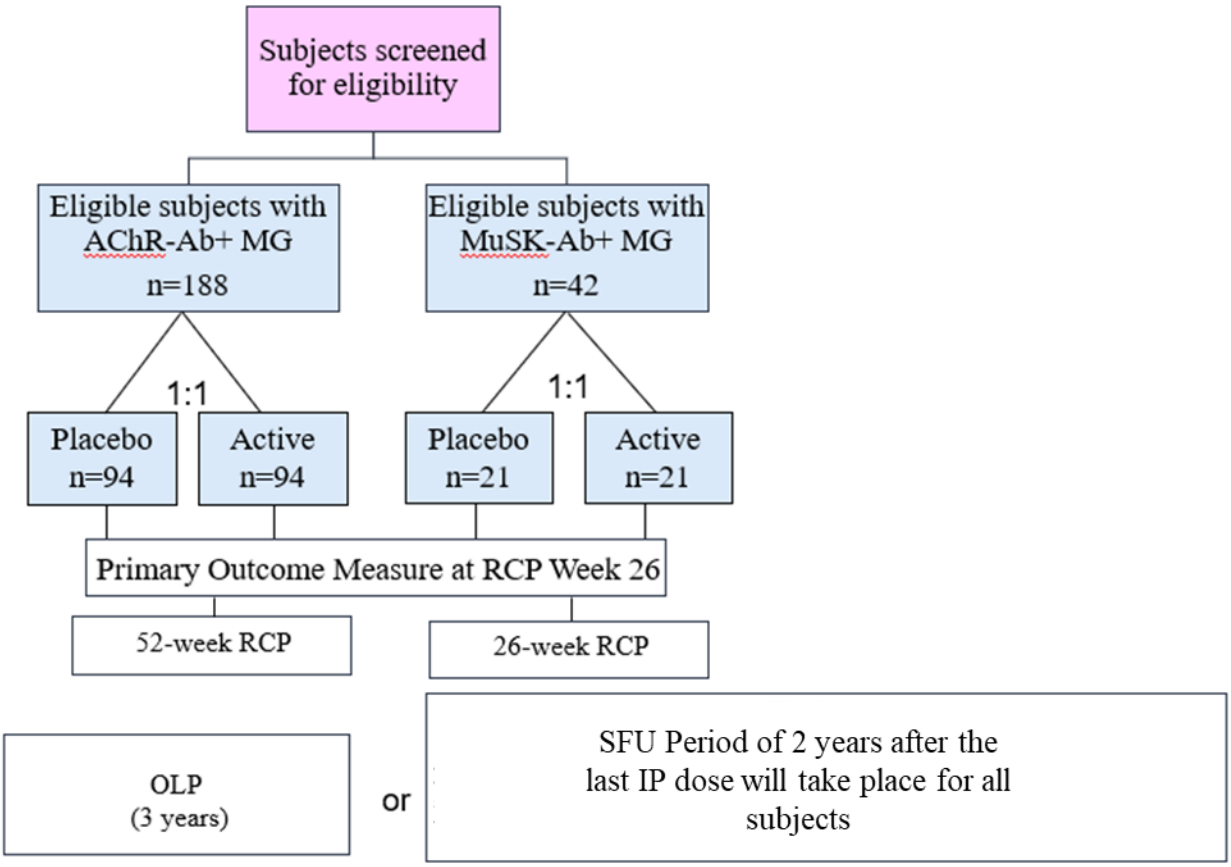
Subjects who enter the study on prednisone > 5 mg/day (or equivalent other corticosteroid) will have their corticosteroid dose tapered per protocol, starting at Week 4 of the RCP. Steroid tapering will continue until the subject is on a dose of prednisone 5 mg/day; the prednisone 5 mg/day dose will then be continued until the end of the RCP. Corticosteroids will not be initiated if the subject is not being treated with them at the time of randomization.

The dose of azathioprine, mycophenolate mofetil, mycophenolic acid, and acetylcholinesterase inhibitor will remain stable throughout the RCP. For subjects on tacrolimus (allowed in Japan only), the dose should not be increased during the RCP but may be reduced, based on the judgment of the Investigator, for safety reasons.

All subjects who complete the RCP will have the option to enroll in a 3-year (156 weeks) OLP. In the OLP, further tapering of azathioprine, mycophenolate mofetil, mycophenolic acid,

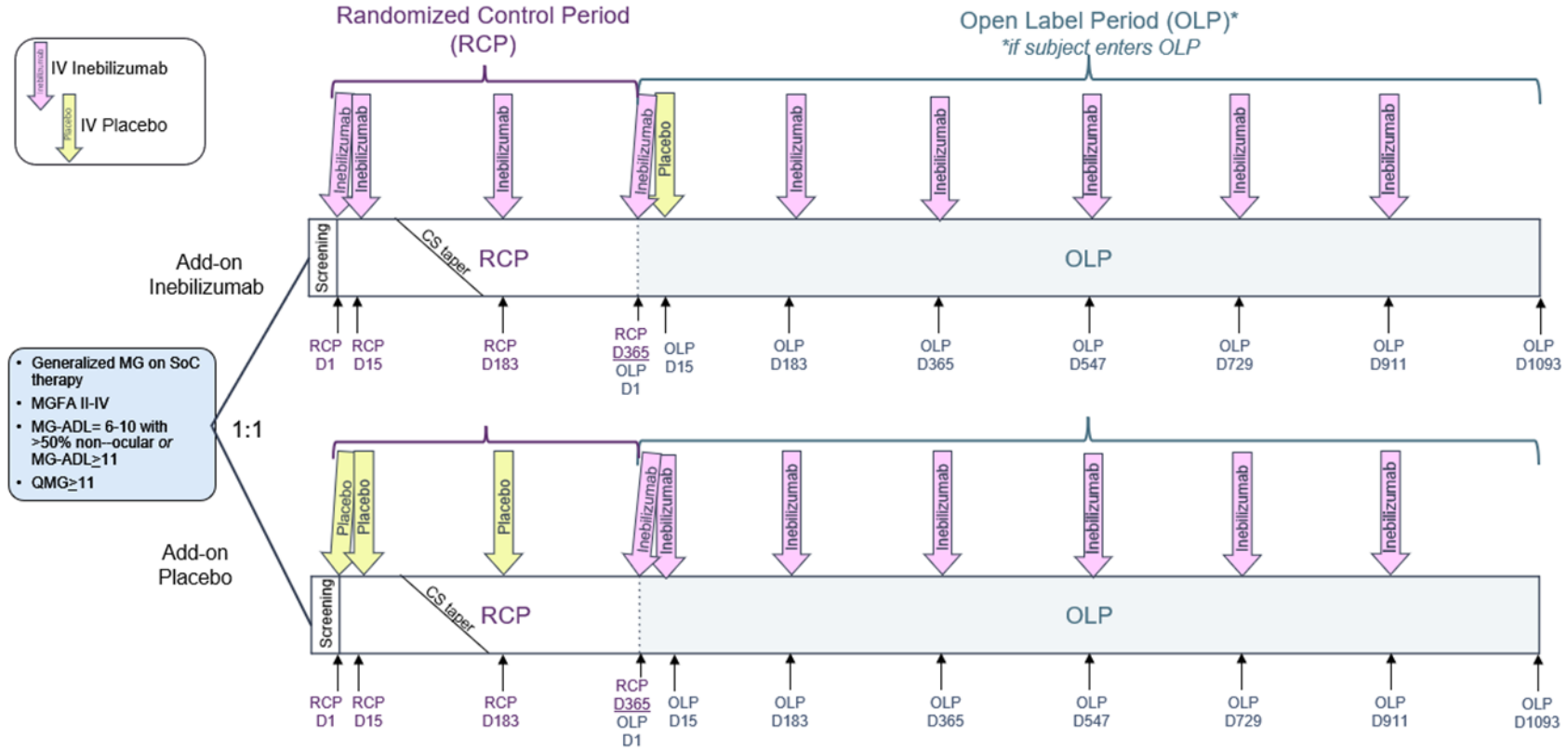
tacrolimus (if applicable), and corticosteroids is recommended. A safety follow-up (SFU) period of 2 years after the last IP dose will take place for all subjects.

Figure 1 Study Flow Diagram



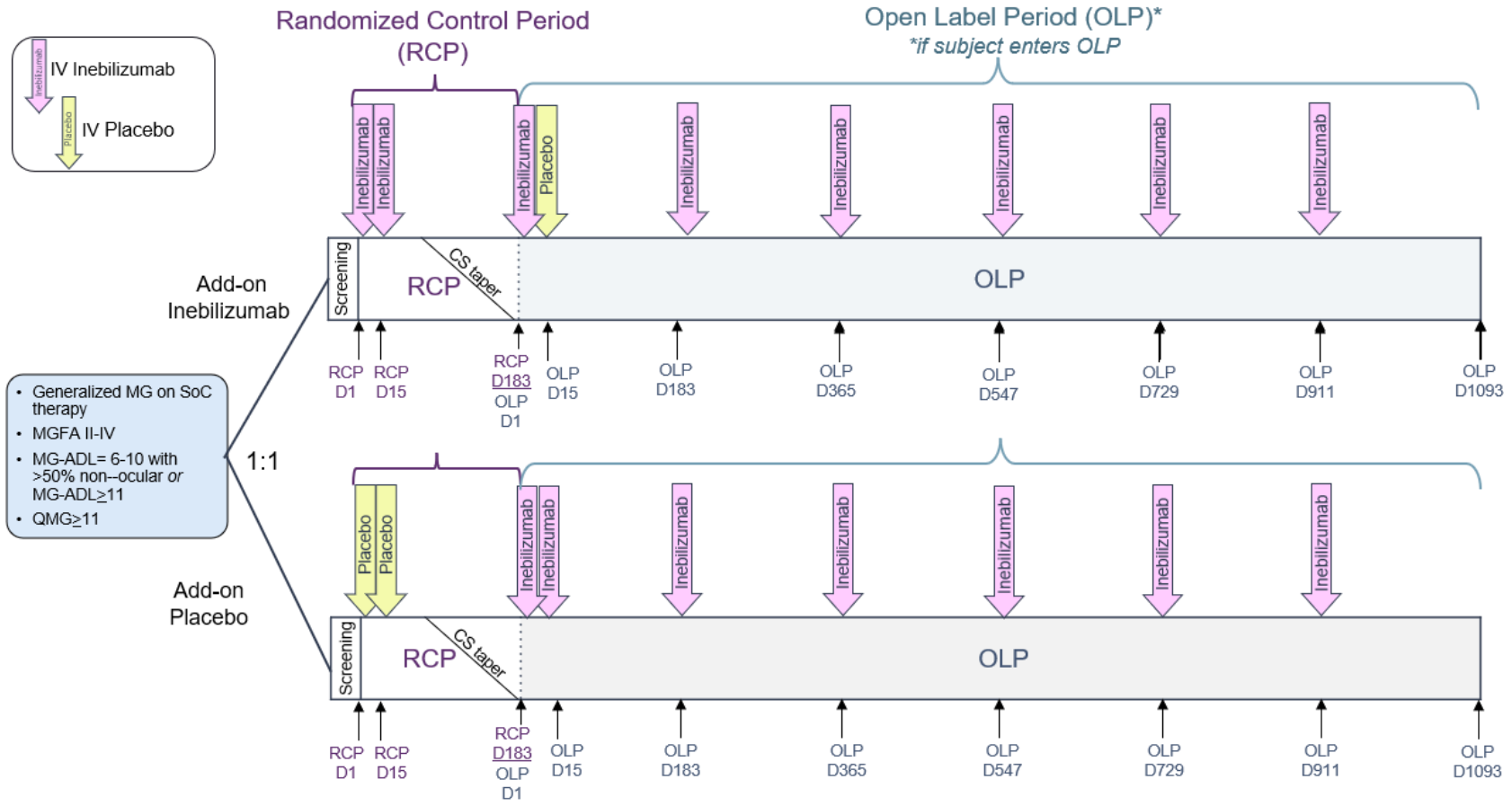
AChR-Ab+ = AChR antibody positive; **IP** = investigational product; **MuSK+ Ab** = positive for antibodies against muscle-specific kinase; **n** = number of subjects represent upper estimated limit and may be reduced based on enrollment of subjects in Japan; **OLP** = open-label period; **RCP** = randomized controlled period; **SFU** = safety follow-up.

Figure 2 Design Scheme for AChR-Ab+ Population



AChR-Ab+ = AChR antibody positive; **CS** = corticosteroid; **D** = Day; **IV** = intravenous(ly); **MG** = Myasthenia Gravis; **MG-ADL** = Myasthenia Gravis Activity of Daily Living score; **MGFA** = Myasthenia Gravis Foundation of America; **OLP** = Open-label Period; **QMG** = Quantitative Myasthenia Gravis; **RCP** = Randomized Controlled Period; **SoC** = Standard of Care.

Figure 3 Design Scheme for MuSK-Ab+ Population



CS = corticosteroid; D = Day; **IV** = intravenous(ly); **MG** = Myasthenia Gravis; **MG-ADL** = Myasthenia Gravis Activity of Daily Living score; **MGFA** = Myasthenia Gravis Foundation of America classification; **MuSK-Ab+** = the population of subjects who are antibody positive for muscle-specific kinase; **OLP** = Open-label Period; **QMG** = Quantitative Myasthenia Gravis; **RCP** = Randomized Controlled Period; **SoC** = standard of care.

4.2 Dose and Treatment Regimen Rationale

The dosing regimen of inebilizumab in this study for the AChR-Ab+ and MuSK-Ab+ populations is 300 mg IV on Day 1 and Day 15, followed by a single 300 mg infusion every 6 months thereafter. This regimen is the same as that administered to subjects with NMOSD in Study 1155. In Study 1155, the dosing regimen was well tolerated and achieved rapid and durable depletion of CD-19-specific B-cells in the vast majority of subjects. Since there is no expected difference in inebilizumab PK between subjects with NMOSD and MG, the proposed dose regimen is expected to be well tolerated and achieve a similar PD effect in subjects with MG.

The 300 mg dose resides at the efficacy plateau, minimizing the impact of PK variability. The second dose of inebilizumab (administered on Day 15) is timed to deplete newly circulating B-cells mobilized from lymphoid and other tissues. Subsequent doses administered at 6-month intervals are timed to maintain the PD effect based on observations in Study 1155, in which CD20+ B-cell counts were significantly reduced 8 days after the initial infusion and remained below the lower limit of normal in 100% of subjects at 4 weeks and 94% of subjects at 28 weeks.

4.3 Rationale for Study Population

The study will enroll male and female subjects ≥ 18 years old with AChR-Ab+ or MuSK-Ab+ generalized MG.

The inclusion criteria are designed to enroll subjects with moderate to severe disease activity to merit the use of a biologic disease-modifying drug, as well as to enable adequate quantification of any improvement of their condition. Only subjects who are MGFA class II (mild weakness affecting other than ocular muscles), III (moderate weakness affecting other than ocular muscles), or IV (severe weakness affecting other than ocular muscles) are eligible for the study. Subjects with MGFA classifications below II have ocular signs and symptoms only, and their disease is too mild for inclusion. Subjects with MGFA classifications above IV require mechanical ventilation (Jaretzki et al, 2000), and their disease is too severe for inclusion.

The study will enroll subjects with generalized MG who are receiving selected standard of care therapies. Subjects receiving corticosteroids at the time of randomization will stay at the same corticosteroid dose (prednisone or its derivatives), and dose tapering will begin at Week 4 of the RCP. The maximum allowed dose of prednisone at the time of randomization will be 40 mg/day or 80 mg every other day. The corticosteroid dose must not have been increased within the 4 weeks prior to randomization; reductions in dose during the screening period are allowed.

Subjects entering the study on an allowed non-steroidal IST must have been on the drug continuously for ≥ 6 months with no dose increase in the 4 months prior to randomization. Subjects will remain on the same dose of non-steroidal IST for the duration of the RCP unless dose reduction is deemed necessary for safety reasons. Azathioprine, mycophenolate mofetil, and mycophenolic acid are allowed non-steroidal ISTs. Tacrolimus is allowed in Japan only since it is the standard of care for treatment of MG in Japan.

Subjects on a stable dose of acetylcholinesterase inhibitors (pyridostigmine dose ≤ 480 mg/day) will be allowed to enroll. The acetylcholinesterase inhibitor dose must have been stable for ≥ 2 weeks prior to randomization. The acetylcholinesterase inhibitor dose must remain stable

throughout the RCP unless dose reduction is deemed necessary for safety reasons. No increase in acetylcholinesterase inhibitors will be allowed in the study. Acetylcholinesterase inhibitors must be held for ≥ 6 hours prior to every study visit so that objective testing can be performed without the confounding effect of the acetylcholinesterase inhibitor.

4.4 Rationale for Endpoint Selection

The primary endpoint for this study is the change from baseline in MG-ADL score at Week 26 in the overall study population (ie, the AChR-Ab+ and MuSK-Ab+ populations). MG-ADL was selected for the primary endpoint since it is a PRO that reflects impact of the disease on the subject's day-to-day function. The range of total MG-ADL score is 0-24, and the minimal clinically important difference is a 2-point improvement (Muppidi et al, 2011). Based on the previous study experience with inebilizumab in NMOSD, CD19-mediated B-cell depletion was efficacious within 26 weeks. Similar efficacy is anticipated in AChR-Ab+ and MuSK-Ab+ MG within 26 weeks, supported by clinical experience of using B-cell depleters in generalized MG.

The following 5 key secondary endpoints are identified:

1. Change from baseline in QMG score at Week 26 in the overall study population.
2. Change from baseline in MG-ADL score at Week 26 in the AChR-Ab+ population.
3. Change from baseline in QMG score at Week 26 in the AChR-Ab+ population.
4. Change from baseline in MG-ADL score at Week 26 in the MuSK-Ab+ population.
5. Change from baseline in QMG score at Week 26 in the MuSK-Ab+ population.

Additional secondary efficacy endpoints include:

1. The proportion of subjects with ≥ 3-point improvement in MG-ADL score at Week 26 and no use of rescue therapy [redacted] and no use of rescue therapy [redacted] in the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and at Week 52 and no use of rescue therapy [redacted] in the AChR-Ab+ population.
2. Change from baseline in MG-ADL score at Week 52 in the AChR-Ab+ population.
3. Change from baseline in QMG score at Week 52 in the AChR-Ab+ population.
4. Change from baseline in MGC score at Week 26 in the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and at Week 52 in the AChR-Ab+ population.
5. Change from baseline in MGQOL-15r score at Week 26 in the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and at Week 52 in the AChR-Ab+ population.
6. PGIC score at Week 26 in the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and at Week 52 in the AChR-Ab+ population.
7. Time to first MG exacerbation by Week 26 in the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and by Week 52 in the AChR-Ab+ population.
8. The safety and tolerability of inebilizumab as measured by the incidence of TEAEs, AESIs, and TESAEs. Laboratory measurements will also be evaluated as part of safety.

9. The proportion of subjects with steroid tapered to ≤ 5 mg/day at Week 26 for the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and at Week 52 for the AChR-Ab+ population.
10. The proportion of subjects in whom steroid dose was reduced by ≥ 50% by Week 26 for the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and by Week 52 for the AChR-Ab+ population.
11. The proportion of subjects achieving minimal symptom expression, defined as MG-ADL = 0 or 1, at Week 26.
12. Anti-drug antibody status and titer during the study in the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population.

Additional secondary efficacy endpoints utilize a number of PRO tools: time to first MG exacerbation (defined in Section 9.4.3), MGC score, MGQOL-15r score, and PGIC. The MGC score is a "mixed" outcome measure, as it incorporates both physician-evaluated and PRO items. Items are weighted, and the MGC may provide a more sensitive measure of treatment efficacy. The MGFA recommends inclusion of the MGC in all prospective MG studies. The MGQOL-15r is a disease-specific questionnaire that is included to evaluate whether treatment has an impact on subject-reported physical functioning, mental or psychological well-being, occupational status, and social interactions. The PGIC is a simple measure of the subject's opinion about the change in their disease since the start of the study.

4.5 Rationale for Steroid Taper

Corticosteroids are a first-line immunotherapy for MG due to their rapid effect. Once symptoms are stabilized on corticosteroids, it is generally advocated to taper the steroids in order to find the minimum dose needed to maintain good symptom control and reduce adverse effects (Gilhus et al, 2019). For subjects who enter the study on corticosteroids, a corticosteroid taper will occur regardless of clinical status. The rationale for tapering steroids is to be consistent with current clinical practice and to reduce morbidity associated with long-term steroid use. The rationale for making the taper independent of clinical status is that it reduces the risk of confounding the primary outcome if steroids were tapered differentially in the active and placebo arms.

5 POPULATION

5.1 Inclusion Criteria

To be included in this study, each individual must satisfy all the following criteria:

1. Male or female subjects ≥ 18 years old.
2. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the United States of America, European Union Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations. In countries where the legal adult age is > 18 years, subjects ≥ 18 years but under legal age for that country must also provide assent and have consent of a parent or other legally authorized representative.
3. Diagnosis of MG defined as:
    a. Positive serologic test for anti-AChR or anti-MuSK antibody titers as confirmed at screening (one retest allowed), and
    b. At least one of the following:
        - History of abnormal neuromuscular transmission test results demonstrated by single-fiber electromyography or repetitive nerve stimulation; or
        - History of positive anticholinesterase test (eg, edrophonium chloride test); or
        - Subject demonstrated improvement in MG signs on oral acetylcholinesterase inhibitors, as assessed by the treating physician; or
        - Clinical syndrome consistent with a diagnosis of MG and not otherwise explained by another condition.
4. MGFA Clinical Classification Class II, III, or IV at the time of screening and randomization.
5. MG-ADL score at the time of screening and randomization between 6 and 10 with > 50% of this score attributed to non-ocular items or an MG-ADL score ≥ 11.
6. QMG score of ≥ 11 or greater at the time of screening and randomization.
7. Subjects must be on:
    a. Corticosteroids only, with no dose increase within 4 weeks prior to randomization, or
    b. One allowed non-steroidal IST, with continuous use for ≥ 6 months prior to randomization and no dose increase within 4 months prior to randomization, or
    c. Combination of 1) corticosteroids with no dose increase within 4 weeks prior to randomization and 2) one allowed non-steroidal IST with continuous use for ≥ 6 months prior to randomization and no dose increase within 4 months prior to randomization.

    Allowed ISTs, alone or in combination with corticosteroids, are azathioprine, mycophenolate mofetil, and mycophenolic acid.

    Tacrolimus is allowed in Japan only, at a dose of ≤ 3 mg/day, with continued use for ≥ 6 months prior to randomization and no dose increase within 4 months prior to randomization.

8. Willing and able to comply with the protocol, complete study assessments, and return for follow-up visits.
9. Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least one highly effective contraception method (Table 1) from the time of screening and for 6 months after the final dose of IP. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

   Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or those who are not postmenopausal (defined as 12 months with no menses without an alternative medical cause and a follicle-stimulating hormone [FSH] level in the postmenopausal range [≥ 16.70 mIU/mL]). If the FSH level is not in the postmenopausal range in a subject with amenorrhea, she may still enroll in the study but must follow the same contraception requirements as women of childbearing potential.
10. Non-sterilized males who are sexually active with a female partner of childbearing potential must use a condom from Day 1 for the duration of the study and for 6 months after the last dose of IP. Because the male condom is not a highly effective contraception method, it is strongly recommended that female partners of a male study subject also use a highly effective method of contraception throughout this period (Table 1).
11. Vital signs, electrocardiogram (ECG), and laboratory parameters within the normal ranges at screening, or, if outside normal ranges, deemed not clinically significant by the Investigator.

Table 1 Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
• Intrauterine device • Intrauterine hormone-releasing system [a] • Bilateral tubal occlusion • Vasectomized partner [b] • Sexual abstinence [c]	• Combined oral (estrogen and progestogen containing hormonal contraception) • Injectable • Transdermal (patch) • Progestogen-only hormonal contraception associated with inhibition of ovulation [d] • Implantable • Intravaginal

a This is also considered a hormonal method.
b With appropriate post-vasectomy documentation of surgical success (absence of sperm in ejaculate).
c Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the subject.
d Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action (eg, minipill), is not accepted as a highly effective method.

5.2 Exclusion Criteria

If an individual meets any of the following criteria, he or she is ineligible for this study:

1. Any condition that, in the opinion of the Investigator, would place the subject at unacceptable risk of complications, interfere with evaluation of the IP, or confound the interpretation of subject safety or study results.
2. Lactating or pregnant females, or females who intend to become pregnant any time from signing the informed consent form (ICF) throughout the RCP plus 6 months following last dose of IP.
3. History of drug or alcohol abuse within < 1 year prior to screening, or any condition associated with poor compliance as judged by the Investigator.
4. Employees of the Sponsor, contract research organization (CRO), site staff, and their family members.
5. Currently committed to an institution by way of official or judicial order.
6. Subjects diagnosed with congenital myasthenic syndromes.
7. Known immunodeficiency disorder, including human immunodeficiency virus (HIV) infection.
8. Thymectomy within ≤ 12 months prior to baseline (Day 1) visit or planned thymectomy during the duration of the RCP.
9. Receipt of the following medications or treatments at any time prior to randomization:
    a. Alemtuzumab
    b. Total lymphoid irradiation
    c. Bone marrow transplant
    d. T-cell vaccination therapy
    e. Natalizumab
10. Receipt of rituximab, ocrelizumab, ofatumumab, obinutuzumab, inebilizumab, or any experimental B-cell depleting agent within the 6 months prior to Day 1, unless the subject has a CD19+ B-cell count ≥ 40 cells/µL according to the central laboratory at screening.
11. Receipt of Leflunomide within 1 year prior to Day 1.
12. Receipt of the following within the 3 months prior to Day 1:
    a. Tocilizumab
    b. Belimumab
    c. Eculizumab
    d. Cyclophosphamide
    e. Ravulizumab
    f. Neonatal fragment crystallizable (Fc) receptor blockers (efgartigimod alfa)
    g. Abatacept
    h. Etanercept
    i. Mitoxantrone
    j. Sirolimus

13. Receipt of the following within the 4 weeks prior to Day 1:
    a. Cyclosporine (except eye drops)
    b. Tacrolimus (except topical) (tacrolimus ≤ 3 mg/day is allowed in Japan only; see Inclusion Criterion #7c)
    c. Methotrexate
    d. Intravenous immunoglobulin (IVIg) or SC Ig
    e. PLEX treatment
    f. Thalidomide
    g. Tofacitinib
14. Current use of:
    a. Corticosteroids (prednisone > 40 mg/day or > 80 mg over a 2-day period, or equivalent dose of other corticosteroids)
    b. Acetylcholinesterase inhibitors (pyridostigmine > 480 mg/day) or unstable dose in the 2 weeks prior to Day 1
    c. Azathioprine > 3 mg/kg/day
    d. Mycophenolate mofetil > 3 g/day or mycophenolic acid > 1440 mg/day
    e. Any IST, alone or in combination with corticosteroids, except for azathioprine, mycophenolate mofetil, and mycophenolic acid
15. Concurrent/previous enrollment in another clinical study involving an investigational treatment within 4 weeks or 5 half-lives of the investigational treatment, whichever is longer, prior to Day 1.
16. Receipt of a live-attenuated vaccine within 4 weeks prior to randomization. Administration of inactivated (killed) vaccines is acceptable.
17. History of severe allergic or anaphylactic reactions to biologic agents or known allergy to any component of the IP formulation.
18. History of recurrent significant infections (eg, requiring hospitalization or IV antibiotics).
19. Within 2 weeks prior to the Screening Visit: clinically significant active infection requiring antimicrobial medication but allowing chronic nail infections.
20. Unresected thymoma (Note: subjects with a benign thymoma resected > 1 year prior to screening may enroll. Benign is defined as no known metastases and no extension into or beyond the capsule on pathological examination. Imaging to evaluate for thymoma must have been performed prior to randomization per standard of care).
21. History of cancer, except for the following:
    a. In situ carcinoma of the cervix treated with apparent success with curative therapy for > 12 months prior to screening
    b. Cutaneous basal cell or squamous cell carcinoma treated with apparent success with curative therapy for > 12 months prior to screening
    c. Prostate cancer treated with radical prostatectomy or radiation therapy with curative intent > 3 years prior to screening and without known recurrence or current treatment
    d. Malignant thymoma resected > 5 years prior to screening with no evidence of active disease and no therapy received over the previous 5 years

22. Spontaneous or induced abortion, still or live birth, or pregnancy ≤ 4 weeks prior to screening.
23. Any of the following laboratory abnormalities at screening (one repeat test may be conducted to confirm results prior to randomization within the same screening period):
    a. Elevated liver enzymes (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] > 2.5 × upper limit of normal [ULN])
    b. Total bilirubin > 1.5 × ULN (unless due to Gilbert's syndrome)
    c. Estimated glomerular filtration rate < 45 mL/min/1.73 m^2
    d. CD19+ B-cell count < 40 cells/µL
    e. Absolute neutrophil count < 1.2 × 10^3 cells/µl
    f. Platelet count < 75,000/µL (or < 75 × 10^9/L)
    g. Hemoglobin < 8.0 g/dL
    h. Total Ig < 600 mg/dL
24. Positive test for chronic hepatitis B infection at screening, defined as either 1) positive hepatitis B surface antigen (HBsAg) or 2) a positive hepatitis B core antibody (anti-HBc) PLUS negative hepatitis B surface antibody (anti-HBs).
    Note: Subjects with a positive anti-HBs only, or a positive anti-HBc plus positive anti-HBs and negative HBsAg, are eligible to enroll.
25. History of untreated hepatitis C infection, or positive antibody test for hepatitis C virus (HCV) unless the subject is considered to be cured following antiviral therapy and has an HCV viral load below the limit of detection ≥ 24 weeks after completion of treatment at site or central lab.
26. Positive HIV test.
27. Blood transfusion within 4 weeks prior to screening or during the screening period.
28. Inability to read.
29. History of active or latent tuberculosis (TB), or a positive QuantiFERON®-TB Gold test at screening, unless treatment for TB was completed per local guidelines. Subjects with latent TB or a positive QuantiFERON®-TB Gold test who are actively on anti-TB treatment can enroll if they have completed ≥ 1 month of anti-TB treatment and intend to complete the full course of anti-TB treatment. Subjects with an indeterminate QuantiFERON®-TB Gold test result can enroll if a repeat QuantiFERON®-TB Gold is negative or a tuberculin skin test is negative.
30. Hospitalization for any reason < 30 days prior to randomization.
31. Current or recent MG deterioration that has not returned to baseline/resolved within ≥ 30 days prior to randomization.

6 STUDY CONDUCT

6.1 Schedule of Study Assessments

6.1.1 Screening Period

All screening procedures will be performed within 28 days prior to randomization unless a screening extension is granted. The screening assessments for AChR-Ab+ and MuSK-Ab+ subjects are the same. The screening period may be extended by up to an additional 28 days to allow for repeat procedures (eg, laboratory tests), to await results of screening procedures or supplies, or to enable washout of prohibited medications. Re-screening is permitted if the original cause of screen failure has resolved. Re-screening a subject more than once requires the Sponsor's approval. Re-screened subjects will not be required to repeat serostatus testing for AChR-Ab+ or MuSK-Ab+ as long as their original central lab screening result was done within the prior 6 months and resulted in positive serostatus using the cut-off points associated with the validated tests. Table 2 shows all procedures to be conducted at the Screening Visit.

Table 2 Screening Procedures (Visit 1)

Study Period	**Screening**
Visit Number	**V1**
Procedure/Study Day	**Day -28 to Day -1**
Written informed consent	X
Review eligibility criteria	X
Medical and disease history	X
Demographics	X
Weight	X
ECG	X
Vital signs	X
Concomitant medications	X
MG-ADL score	X
QMG score [a]	X
Collect blood for [b]:	
Hematology and chemistry	X
Serum β-hCG (females of childbearing potential only)	X
FSH (postmenopausal female subjects only)	X
Hepatitis B, C; HIV	X
[redacted]	X
Serum for AChR or MuSK serostatus [c]	X
[redacted]	X

Table 2 Screening Procedures (Visit 1)

Study Period	**Screening**
Visit Number	**V1**
Procedure/Study Day	**Day -28 to Day -1**
Tuberculosis test (QuantiFERON®-TB Gold)	X
Physical examination	X
MGFA clinical classification	X
Assessment of AEs/SAEs	X

AChR = acetylcholine receptor; **AE** = adverse event; **β-hCG** = beta human chorionic gonadotropin; **ECG** = electrocardiogram; **FSH** = follicle-stimulating hormone; **HIV** = human immunodeficiency virus; [redacted]; **MG-ADL** = Myasthenia Gravis Activities of Daily Living; **MGFA** = Myasthenia Gravis Foundation of America; **MuSK** = muscle-specific kinase; **QMG** = Quantitative Myasthenia Gravis; **SAE** = serious adverse event; **TB** = tuberculosis; **V** = Visit.

a. Assessment should be performed at approximately the same time of day for all visits and, if possible, completed by the same assessor.
b. Blood draws do not need to be fasting.
c. Re-screened subjects will not be required to repeat serostatus testing for AChR or MuSK as long as their original central lab screening result was done within the prior 6 months and resulted in a positive serostatus using the cut-off points associated with the validated tests.

6.1.2 Randomized Controlled Period

The duration of the RCP will be 52 weeks for the AChR-Ab+ population and 26 weeks for the MuSK-Ab+ population. The primary efficacy endpoint will be measured at 26 weeks for both study populations.

Based on the previous study experience with inebilizumab in NMOSD, CD19-mediated B-cell depletion was efficacious within 26 weeks. Similar efficacy is anticipated in AChR-Ab+ and MuSK-Ab+ MG within 26 weeks, supported by clinical experience using B-cell-depleting agents in generalized MG.

All study assessments until Week 26 are common for both study populations.

The schedule of study assessments during the RCP is presented in Table 3 for the AChR-Ab+ population and in Table 4 for the MuSK-Ab+ population.

After 26 weeks of the RCP, MuSK-Ab+ subjects may progress to the OLP. AChR-Ab+ subjects will continue the RCP for a total of 52 weeks in a blinded fashion. To ensure the blinding of each subject's treatment assignment during the study, the study site personnel, the Sponsor personnel who are directly associated with the conduct of the study, and the subjects will remain blinded to the treatment assignment until completion of the RCP. Completion of the full 52 weeks of the RCP will provide additional safety data collected in an unbiased, double-blind manner.

The full RCP schedule of assessments is different for AChR-Ab+ and MuSK-Ab+ subjects.

All procedures must be completed prior to administration of the IP except for collection of AEs, specific postdose blood samples, and corticosteroid dispensing.

In Japan only, it is required for the site to call subjects every 2 weeks during the RCP beginning at Day 43 (Week 6). The purpose of the telephone call is to assess the clinical status of the subject. It is not necessary to call subjects during a week when a study visit will occur.

Table 3 Randomized Controlled Period Schedule of Study Assessments for the AChR-Ab+ Population

Study Period	**RCP**										
Study Week	**0**	**2**	**4**	**8**	**12**	**18**	**26**	**32**	**38**	**44**	**52**
Study Day (visit window)	**Day 1**	**Day 15 (±2d)**	**Day 29 (±3d)**	**Day 57 (±3d)**	**Day 85 (±3d)**	**Day 126 (±7d)**	**Day 183 (±7d)**	**Day 225 (±7d)**	**Day 267 (±7d)**	**Day 309 (±7d)**	**Day 365 [a] (±7d) or EDV [b]**
Verify eligibility criteria	X										
MGQOL-15r score; PGIC; [redacted]	X		X	X	X	X	X	X	X	X	X
C-SSRS (Baseline/Screening version)	X										
C-SSRS (Since Last Visit version)		X	X	X	X	X	X	X	X	X	X
Weight	X										X
Height	X										
ECG	X	X									X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
[redacted]											
MG-ADL score [c]	X	X	X	X	X	X	X	X	X	X	X
QMG score [c]	X		X	X	X	X	X	X	X	X	X
MGC score [c]	X		X	X	X	X	X	X	X	X	X
MGFA clinical classification	X						X				X
[redacted]											
Physical examination	X				X		X		X		X

Table 3 Randomized Controlled Period Schedule of Study Assessments for the AChR-Ab+ Population

Study Period	**RCP**										
Study Week	**0**	**2**	**4**	**8**	**12**	**18**	**26**	**32**	**38**	**44**	**52**
Study Day (visit window)	**Day 1**	**Day 15 (±2d)**	**Day 29 (±3d)**	**Day 57 (±3d)**	**Day 85 (±3d)**	**Day 126 (±7d)**	**Day 183 (±7d)**	**Day 225 (±7d)**	**Day 267 (±7d)**	**Day 309 (±7d)**	**Day 365 [a] (±7d) or EDV [b]**
Collect blood for [d]:											
Hematology and serum chemistry	X	X	X	X	X	X	X	X	X	X	X
Inebilizumab PK (serum) [e]	X	X	X	X	X		X	X	X		X
Inebilizumab ADA (serum)	X		X		X		X		X		X
[redacted]											
Urine pregnancy test [h]	X	X					X				
IP administration [i]	X	X					X				
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X
Corticosteroid dispense [j]	X		X	X	X		X		X		
Telephone follow-up (Japan only)	In Japan only, telephone calls should be made every 2 weeks starting from Day 43 (Week 6) and continuing for the duration of the RCP, except for study visit weeks										

[redacted]; **ADA** = anti-drug antibody(ies); **AE** = adverse event; **C-SSRS** = Columbia-Suicide Severity Rating Scale; **d** = Day; **ECG** = electrocardiogram; **EDV** = Early Discontinuation Visit; [redacted]; **IP** = investigational product; **MG-ADL** = Myasthenia Gravis Activities of Daily Living; **MGC** = Myasthenia Gravis Composite; **MGFA** = Myasthenia Gravis Foundation of America; **MGQOL-15r** = Myasthenia Gravis Quality of

Life-15, revised; [redacted]; **OLP** = Open-label Period; **PGIC** = Patient Global Impression of Change; [redacted] **PK** = pharmacokinetic(s); **QMG** = Quantitative Myasthenia Gravis; **RCP** = Randomized controlled period; [redacted]; **SAE** = serious adverse event; SFU = safety follow-up.

a. For subjects choosing to continue into the OLP, Day 365 visit procedures need to be completed prior to starting any procedures or doses of the first day of Open-label Extension. Subjects who decide not to participate in the OLP (but complete Day 365 visit), will be asked to enter the SFU Period (see Section 6.1.4).
b. An EDV should be performed for any AChR-Ab+ subject who withdraws prior to the RCP Week 52 visit (see Section 6.3.2); subjects that discontinue the IP will be asked to remain in the study and complete all RCP study visits and assessments with the exception of those related to directly to dosing (see Section 6.3.1).
c. Assessment should be performed at approximately the same time of day for all visits and, if possible, completed by the same assessor. Acetylcholinesterase inhibitors (if taken) must be held for 6 hours prior to the assessments; see Section 6.2.5.3 for additional information.
d. Fasting is not required.
e. On inebilizumab dosing days (Day 1, 15, and 183), inebilizumab PK serum samples are to be collected predose and approximately 15 minutes (± 5 minutes) after completion of the IP infusion. On non-dosing days, only one PK serum sample is required.
[redacted]
h. Females of childbearing potential only; must be found negative before the IP is administered.
i. On days of IP administration, all procedures and blood sampling, except for post dose PK, must be collected before IP administration.
j. For subjects on corticosteroids. Note: corticosteroid dispensation may occur outside of the scheduled visit timepoints if required/necessary to dispense the necessary quantity to subjects as needed. For corticosteroid tapering schedule, refer to Table 12.

Table 4 Randomized Controlled Period Schedule of Study Assessments for the MuSK-Ab+ Population

Study Period	**RCP**						
Study Week	**0**	**2**	**4**	**8**	**12**	**18**	**26**
Study Day (visit window)	**Day 1**	**Day 15 (±2d)**	**Day 29 (±3d)**	**Day 57 (±3d)**	**Day 85 (±3d)**	**Day 126 (±7d)**	**Day 183 [a] (±7d) or EDV [b]**
Verify eligibility criteria	X						
MGQOL-15r score; PGIC; [redacted]	X		X	X	X	X	X
C-SSRS (Baseline/Screening version)	X						
C-SSRS (Since Last Visit version)		X	X	X	X	X	X
Weight	X						X
Height	X						
ECG	X	X					X
Vital signs	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
[redacted]							
MG-ADL score [c]	X	X	X	X	X	X	X
QMG score [c]	X		X	X	X	X	X
MGC score [c]	X		X	X	X	X	X
MGFA clinical classification	X						X
[redacted]							
Physical examination	X				X		X
Collect blood for: [d]							
Hematology and serum chemistry	X	X	X	X	X	X	X
Inebilizumab PK (serum) [e]	X	X	X	X	X		X
Inebilizumab ADA (serum)	X		X		X		X

Table 4 Randomized Controlled Period Schedule of Study Assessments for the MuSK-Ab+ Population

Study Period	**RCP**						
Study Week	**0**	**2**	**4**	**8**	**12**	**18**	**26**
Study Day (visit window)	**Day 1**	**Day 15 (±2d)**	**Day 29 (±3d)**	**Day 57 (±3d)**	**Day 85 (±3d)**	**Day 126 (±7d)**	**Day 183 [a] (±7d) or EDV [b]**
[redacted]							
Urine pregnancy test [g]	X	X					
IP administration [h]	X	X					
Assessment of AEs/SAEs	X	X	X	X	X	X	X
Corticosteroid dispense [i]	X		X	X	X		
Telephone follow-up (Japan only)	In Japan only, telephone calls should be made every 2 weeks starting from Day 43 (Week 6) and continuing for the duration of the RCP, except for study visit weeks						

ADA = anti-drug antibody(ies); **AE** = adverse event; **C-SSRS** = Columbia-Suicide Severity Rating Scale; **d** = Day; **ECG** = electrocardiogram; **EDV** = Early Discontinuation Visit; [redacted]; **IP** = investigational product; **MG-ADL** = Myasthenia Gravis Activities of Daily Living; **MGC** = Myasthenia Gravis Composite; **MGFA** = Myasthenia Gravis Foundation of America; **MGQOL-15r** = Myasthenia Gravis Quality of Life-15, revised [redacted]; [redacted]; **OLP** = Open-label Period; **PGIC** = Patient global impression of change; [redacted]; **PK** = pharmacokinetic(s); **QMG** = Quantitative Myasthenia Gravis; **RCP** = Randomized Controlled Period; [redacted]; **SAE** = serious adverse event; **SFU** = safety follow-up.

a. For subjects choosing to continue into the OLP, Day 183 visit procedures need to be completed prior to starting any procedures or doses of the first day of Open-label Extension. Subjects who decide not to participate in the OLP (but complete Day 183 visit), will be asked to enter the SFU Period (see Section 6.1.4).
b. An EDV should be performed for any MuSK-Ab+ subject who withdraws prior to the RCP Week 26 visit (see Section 6.3.2); subjects that discontinue the IP will be asked to remain in the study and complete all RCP study visits and assessments with the exception of those related to directly to dosing (see Section 6.3.1).
c. Assessment should be performed at approximately the same time of day for all visits and, if possible, completed by the same assessor. Acetylcholinesterase inhibitors (if taken) must be held for 6 hours prior to the assessments; see Section 6.2.5.3 for additional information.
d. Fasting is not required.
e. On inebilizumab dosing days (Days 1 and 15), inebilizumab PK serum samples are to be collected predose and approximately 15 minutes (± 5 minutes) after completion of the IP infusion. On non-dosing days, only one PK serum sample is required.

[redacted]

h. Females of childbearing potential only; must be found negative before the IP is administered.
i. On days of IP administration, all procedures and blood sampling, except for post dose PK, must be collected before IP administration.
j. For subjects on corticosteroids. Note: corticosteroid dispensation may occur outside of the scheduled visit timepoints if required/necessary to dispense the necessary quantity to subjects as needed. For corticosteroid tapering schedule, refer to Table 12.

6.1.3 Open-label Period

Subjects who complete the RCP have the option to enroll in the OLP study. Subjects who discontinue the RCP early are not eligible to enter the OLP. Informed consent for OLP participation must be obtained at the time of OLP entry.

The study OLP duration is 3 years for both study populations, AChR+ and MuSK+. The OLP assessments are the same for both study populations.

Upon completing all the assessments at the last RCP visit, it is strongly recommended to perform the OLP Day 1 visit on the same day. The OLP Day 1 visit may occur for up to 14 days after the final RCP visit. Many assessments are common to both the final RCP visit and OLP Day 1 visit and do not need to be repeated if done within 14 days of the final RCP visit (see Table 5, footnote b). Subjects are not permitted to enter the OLP after 14 days after the final RCP visit without the Sponsor's written approval.

During the OLP, subjects' treatment assignment will remain blinded. The OLP will include IP infusions on OLP Days 1, 15, and 183, and every 6 months thereafter at Days 365, 547, 729, and 911. All subjects will receive inebilizumab on OLP Days 1, 183, 365, 547, 729, and 911. On OLP Day 15, subjects who received inebilizumab in the RCP will receive placebo and subjects who received placebo in the RCP will receive inebilizumab. This will allow subjects who are just beginning inebilizumab to receive the full 2-dose initial treatment course while maintaining blinding of the RCP treatment assignment.

For more details about OLP assessments, see Table 5.

Subjects will continue to be followed for an additional 26 weeks after the last dose of inebilizumab (at OLP Day 911) until OLP Day 1093.

It is recommended to taper non-steroidal ISTs (eg, azathioprine, mycophenolate mofetil, mycophenolic acid) per standard of care. For subjects on tacrolimus (allowed in Japan only), taper of tacrolimus is recommended. The rationale for tapering non-steroidal ISTs in the OLP is to reduce potential risks associated with long-term use of multiple ISTs.

Corticosteroids can either be continued at a dose of prednisone 5 mg daily or can be tapered at the discretion of the Investigator. If a subject receives a dose of prednisone that is > 10 mg daily for > 8 consecutive weeks in the OLP, then the IP must be discontinued (Section 6.3.1). The rationale for this requirement is to reduce the potential risk of adverse effects associated with long-term combination of moderate- or high-dose corticosteroids and inebilizumab.

Table 5 Open-label Period Procedures for AChR-Ab+ and MuSK-Ab+ Populations

Study Period	**OLP**										
OLP week	**0**	**2**	**13**	**26**	**39**	**52**	**65**	**78**	**104**	**130**	**156**
OLP Study Day (visit window)	**Day 1[a]**	**Day 15 (±2d)**	**Day 92 (±7d)**	**Day 183 (±7d)**	**Day 275 (±7d)**	**Day 365 (±7d)**	**Day 456 (±7d)**	**Day 547 (±7d)**	**Day 729 (±20d)**	**Day 911 (±20d)**	**Day 1093 (±20d) or EDV [k]**
Written ICF	X [b]										
Verify eligibility criteria	X										
MGQOL-15r score; PGIC; [redacted]	X [b]		X	X	X	X	X	X	X	X	X
C-SSRS (Since Last Visit version)	X [b]	X	X	X	X	X	X	X	X	X	X
Weight	X [b]					X					X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
[redacted]											
MG-ADL score [c]	X [b]	X	X	X	X	X	X	X	X	X	X
QMG score [c]	X [b]		X	X	X	X	X	X	X	X	X
MGC score [c]	X [b]		X	X	X	X	X	X	X	X	X
[redacted]											
MGFA clinical classification	X [b]			X		X		X	X	X	X
Physical examination	X [b]		X	X	X	X	X	X	X	X	X
Collect blood for: [d]											
Hematology and serum chemistry	X [b]	X	X	X	X	X	X	X	X	X	X
Inebilizumab ADA (serum)	X [b]		X	X	X	X		X	X	X	X

Table 5 Open-label Period Procedures for AChR-Ab+ and MuSK-Ab+ Populations

Study Period	**OLP**										
OLP week	**0**	**2**	**13**	**26**	**39**	**52**	**65**	**78**	**104**	**130**	**156**
OLP Study Day (visit window)	**Day 1[a]**	**Day 15 (±2d)**	**Day 92 (±7d)**	**Day 183 (±7d)**	**Day 275 (±7d)**	**Day 365 (±7d)**	**Day 456 (±7d)**	**Day 547 (±7d)**	**Day 729 (±20d)**	**Day 911 (±20d)**	**Day 1093 (±20d) or EDV [k]**
[redacted]											
Urine pregnancy test [h]	X	X		X		X		X	X	X	X
IP administration [i]	X	X		X		X		X	X	X	
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X
Corticosteroid dispense [j]	X		X	X	X	X	X	X	X	X	

[redacted]; **ADA** = anti-drug antibody(ies); **AE** = adverse event; **C-SSRS** = Columbia-Suicide Severity Rating Scale; **d** = Day; **ECG** = electrocardiogram; **EDV** = Early Discontinuation Visit; **ICF =** informed consent form; [redacted]; **IP** = investigational product; **MG-ADL** = Myasthenia Gravis Activities of Daily Living; **MGC** = Myasthenia Gravis Composite; **MGFA** = Myasthenia Gravis Foundation of America; **MGQOL-15r** = Myasthenia Gravis Quality of Life-15, revised [redacted]; **OLP** = Open-label Period; **PGIC** = Patient Global Impression of Change; [redacted]; **QMG** = Quantitative Myasthenia Gravis; [redacted]; **SAE** = serious adverse event; **SFU** = safety follow-up.

a. For subjects choosing to continue into the OLP, end of RCP visit procedures must be completed prior to starting any procedures or doses of the first day of OLP.
b. This procedure does not need to be repeated on OLP Day 1 if it was completed at the final RCP visit and the OLP Day 1 visit is done within 14 days of the final RCP visit.

c. Assessment should be performed at approximately the same time of day for all visits and, if possible, completed by the same assessor. Acetylcholinesterase inhibitors (if taken) must be held for 6 hours prior to the assessments; see Section 6.2.5.3 for additional information.
d. Fasting is not required.

[redacted]

h. Females of childbearing potential only; must be found negative before the IP is administered.
i. On days of IP administration, all procedures and blood sampling must be collected before IP administration.
j. For subject on corticosteroids; corticosteroid dispensation may occur outside of the scheduled visit timepoints if required/necessary to dispense the necessary quantity to subjects as needed.
k. Subjects who discontinue the IP during the OLP should complete an EDV and be asked to participate in the SFU Period (see Section 6.1.4).

6.1.4 Safety Follow-up

Following the last administration of IP (either the last scheduled dose of IP or the last administration prior to the IP discontinuation), all subjects will enter the SFUP. Safety Follow-Up Visits will occur for up to 2 years after the last administration of IP, or until recovery of peripheral CD20+ B cell counts and [redacted], whichever occurs first. During this time subjects will be seen every six months in-clinic for blood draws and other limited assessments.

Assessments and procedures during the SFU Period are detailed in Table 6.

Table 6 Safety Follow-up Period

Study Period	Safety Follow-up
Safety Follow-up Weeks	Every 26 weeks from time subject completes treatment/discontinues IP (up to 2 years)
Visit Window	± 4 weeks
Assessment of AEs and SAEs	X
Assessment of concomitant medications	X
Hematology and serum chemistry	X
Blood collection for: [redacted]	X

AE = adverse event; [redacted]; **IP** = investigational product; **SAE** = serious adverse event.

6.1.5 Special Visit Types (occurring during RCP and OLP)

6.1.5.1 Remote Visits and/or Procedures

In exceptional circumstances and with prior agreement of the medical monitor, particular study visits or procedures may be performed remotely (via teleconference, video conference, or similar) if the subject is not able to physically attend the clinic for that visit or procedure (eg, due to COVID-19 restrictions). Missed assessments during remote visits, regardless of medical monitor agreement, will incur protocol deviations. Refer to Table 7.

6.1.5.2 Clinical Deterioration Visit

A Clinical Deterioration Visit should be performed if a subject complains of worsening MG symptoms and use of rescue therapy is being considered. This should be performed before the rescue therapy is initiated. The procedures to be performed are listed in Table 7. Additional details on the use of rescue therapy can be found in Section 7.2.2.

6.1.5.3 Unscheduled Visit

An Unscheduled Visit is performed to address and complete scheduled trial-related activities that are not associated with Clinical Deterioration, such as to repeat hemolyzed blood samples or missing or incomplete assessments or as a follow-up for an AE, as needed. A potential list of the

assessments and procedures for unscheduled visits are listed in Table 7 and should be performed at the discretion of the Investigator.

Table 7 Procedures for Special Visit Types

Visit Type	Remote Visit	Clinical Deterioration Visit	Unscheduled Visit [h]
Prior approval from Medical Monitor	X		
MGQOL-15r score; PGIC; [redacted]	X	X	P
C-SSRS (Since Last Visit version)	X	X	P
ECG		P	P
Vital signs		X	P
Concomitant medications	X	X	P
[redacted]			
MG-ADL score [a]	X	X	P
QMG score [a]		X	P
MGC score [a]		X	P
MGFA clinical classification		X	P
[redacted]			
Physical examination		P	P
Collect blood for [b]:			
Hematology and serum chemistry		P	P
Inebilizumab PK (serum) [c]		X	P
Inebilizumab ADA (serum)		X	P
[redacted]			
IP administration			
Assessment of AEs/SAEs	X	X	X
Corticosteroid dispense [g]			P

ADA = anti-drug antibody(ies); **AE** = adverse event; [redacted]
C-SSRS = Columbia-Suicide Severity Rating Scale; **d** = Day; **ECG** = electrocardiogram; **EDV** = Early Discontinuation Visit; [redacted] **IP** = investigational product; **MG-ADL** = Myasthenia Gravis Activities of Daily Living; **MGC** = Myasthenia Gravis Composite; **MGFA** = Myasthenia Gravis Foundation of America; **MGQOL-15r** = Myasthenia Gravis Quality of Life-15, revised; [redacted] **P** = potential procedure/assessment to be performed at the discretion of the Investigator and with participant's agreement; **PGIC** = Patient Global Impression of Change; [redacted]; **PK** = pharmacokinetic(s); **QMG** = Quantitative Myasthenia Gravis; **RCP** = Randomized controlled period; [redacted] **SAE** = serious adverse event.

a. Assessment should be performed at approximately the same time of day for all visits and, if possible, completed by the same assessor. Acetylcholinesterase inhibitors (if taken) must be held for 6 hours prior to the assessments; see Section 6.2.5.3 for additional information.

b. Fasting is not required.
c. Inebilizumab PK (serum) is only collected during RCP; if special visit occurs during OLP, sample is not obtained.

[redacted]

f. Females of childbearing potential only; must be found negative before IP is administered.
g. For subject on corticosteroids; note: corticosteroid dispensation may occur outside of the scheduled visit timepoints if required/necessary to dispense the necessary quantity to subjects as needed.
h. If an Unscheduled Visit is performed, the Investigator should select the relevant subset of assessments to perform.

6.2 Description of Study Procedures

6.2.1 Informed Consent

All candidates for enrollment will sign an ICF prior to any protocol-related procedures, including screening activities. Informed consent must be obtained by the Investigator or a designee, such as an Investigator with Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved qualifications. See Section 10.3 for additional details.

Subjects who are ≥ 18 years of age but under the age of consent in their respective country must sign their assent, and their legally authorized representative must sign consent prior to any protocol-required procedures. If they reach the age of consent while on the study, they will be asked to sign an ICF in order to document their consent to be on the study.

In addition to the main study participation, subjects will be asked if they consent to 2 optional aspects (if applicable in that country): 1) use of leftover blood samples for future research, and 2) [redacted], efficacy, PK, and [redacted]. Additional details of the genetic analysis are found in Section 6.2.8.8.

After signing the ICF, each subject will be assigned a subject identification (SID) number that will be used on all subject documentation. Numbers will be assigned in ascending sequential order. This number will also correspond to the subject number entered on test materials. Re-screened subjects will receive a new SID number.

As noted in Section 6.1.3, in addition to the ICF signed for the RCP period, written informed consent for OLP participation must be obtained at the time of OLP entry.

6.2.2 Demographics, Medical, and Disease History

Demographic information to be collected includes year of birth, sex, race, and ethnicity. Medical history information to be collected includes all ongoing conditions and relevant/significant medical history (including all major hospitalizations and surgeries), as determined by the Investigator. Concomitant medications will be recorded. MG medication history will be recorded, including use of 1) chronic MG immunosuppressive medications and 2) use of rescue therapy in the prior 2 years.

6.2.3 Confirmation of Myasthenia Gravis Antibody Status

For subjects with a prior positive result for antibodies to AChR or MuSK, that specific antibody will be tested in the screening labs to confirm positivity. If antibody testing was not previously

done or the results of prior antibody testing are not known, the subject can still be screened and both AChR and MuSK antibodies should be tested during screening. If a subject is not confirmed to be positive for anti-AChR or anti-MuSK antibodies by the central laboratory, then the subject cannot be randomized and must fail the screen. If a site desires a retest due to an unexpected negative result, an Unscheduled Visit can be performed, and a new blood sample can be submitted for testing. If necessary, the screening period can be extended up to 28 days to accommodate the retest if approved by the medical monitor. If a subject is positive for both anti-AChR and anti-MuSK antibodies, the subject should be enrolled in the MuSK-Ab+ group.

6.2.4 Verification of Eligibility

At the start of screening, it is advisable to review eligibility criteria together with the subject to confirm that there are no immediate disqualifying factors (eg, age or use of a disqualifying medication). All eligibility criteria should be reviewed again once all screening results are available.

On RCP Day 1, MG-ADL and QMG assessments should be performed early in the visit to confirm that the subject qualifies before initiating randomization procedures. To qualify for randomization, the subject must have an MG-ADL score between 6 and 10, with > 50% of this score attributed to non-ocular items, or an MG-ADL score ≥ 11 and QMG ≥ 11 at both the Screening Visit and RCP Day 1 (randomization) visit.

It is recommended to alert subjects during screening that it will not be known for sure if they qualify for the study until some assessments are completed at the RCP Day 1 visit. The subject should be aware that if they come to the site for the RCP Day 1 visit, it is still possible that they will not qualify to be randomized and receive the IP.

6.2.5 Efficacy Assessments

6.2.5.1 Role of the Independent Rater

2 efficacy outcomes, the QMG and the MGC, will be assessed by an independent rater. The MG-ADL will be recorded by an independent rater by asking the subject questions.

The independent rater who performs the physical examination portion of the MGC should be a physician, physician assistant, nurse practitioner, physical therapist, or other healthcare provider who is experienced with neurological examination. The QMG can be performed by any independent rater who is experienced in performing the QMG and has completed the protocol training on QMG performance. To reduce the risk of bias, an independent rater should not otherwise be involved in the subject's care, either as the site Investigator/Sub-Investigator or primary study coordinator. Whenever possible, the same independent rater should be used for a subject throughout the study. A primary and back-up rater must be identified for each subject, although they need not be the same for all subjects at a site.

6.2.5.2 Collection of electronic Patient-reported Outcomes Assessments

All PRO assessments must be collected electronically, using either the TrialPACE app or the website (https://trialpace.medpace.com/) via any internet-connected device. Limited use of validated paper forms (not screenshots of electronic patient-reported outcome [ePRO] forms) for MG-ADL and QMG questionnaires will be allowed, but not during Screening or Day 1 visits.

The sites will receive specific instructions listing conditions under which these paper forms will be allowed. ePRO assessments outside of MG-ADL and QMG cannot be collected via paper. Any non-electronic collection of other ePRO data cannot be used and will be considered a protocol deviation.

6.2.5.3 Timing of Efficacy Assessments

Assessments should be done at approximately the same time of day for all visits to reduce the impact of diurnal variability of symptoms on the assessments. Acetylcholinesterase inhibitors (if taken) must be held (ie, should not be taken) for 6 hours prior to subject assessments. If acetylcholinesterase inhibitors were not held for 6 hours prior to evaluation, the evaluation should proceed, nonetheless. The time of assessment and time of the last acetylcholinesterase cholinesterase inhibitor use will be recorded in the ePRO system.

6.2.5.4 Myasthenia Gravis Activities of Daily Living

The MG-ADL will be recorded by an independent rater based on questions answered by the subject. The MG-ADL is a validated measure that requires no equipment and that can be administered in 10 minutes (Wolfe et al, 1999). The MG-ADL is an 8-item questionnaire that focuses on relevant symptoms and functional performance of activities of daily living in subjects with MG over the previous 7 days. The MG-ADL assesses disability secondary to ocular (2 items), bulbar (3 items), respiratory (1 item), and gross motor or limb (2 items) impairment related to effects from MG. In this functional status instrument, each response is graded 0 (normal) to 3 (most severe). The range of total MG-ADL scores is 0-24. The minimal important difference for this PRO questionnaire is a 2-point improvement (Barnett et al, 2018). The MG-ADL will be recorded in the ePRO system.

6.2.5.5 Myasthenia Gravis Quality of Life-15, revised

The MGQOL-15r is a PRO and does not require an independent rater. The MGQOL-15r is a validated, subject-scored instrument, which measures the impact of MG on health-related quality of life (HRQoL) (Burns et al, 2008). The 15 items in the questionnaire evaluate mobility (9 items), symptoms (3 items), general contentment (1 item), and emotional well-being (2 items) domains. Each item is rated on a 3-point scale ranging from 0 (“not at all”) to 2 (“very much”) based on their experience “over the past few weeks.” Item scores are summed to generate a total score ranging from 0 to 30, with higher scores indicating worse HRQoL. The MGQOL-15r will be recorded in the ePRO system.

6.2.5.6 Patient Global Impression of Change

The PGIC is a subject-reported, 7-point scale that evaluates whether there has been an improvement or decline in the subject’s disease-related status. The PGIC will be recorded in the ePRO system.

[redacted]

[redacted]

6.2.5.8 Quantitative Myasthenia Gravis Score

The QMG score is determined by an independent rater. The QMG is a validated outcome comprised of 13 items: ocular (2 items), facial (1 item), bulbar (2 items), gross motor (6 items), axial (1 item), and respiratory (1 item). Each item has a possible score of between 0 and 3 points. The total score range is 0-39 points, with a higher score indicating more severe disease. A 3-point improvement in the QMG score is considered clinically meaningful (Barohn et al, 1998; Zinman et al, 2008). The QMG score will be recorded in the ePRO system.

6.2.5.9 Myasthenia Gravis Composite Score

The MGC consists of test items from the MG-ADL and the QMG that measure symptoms and signs of MG, with weighted response options (Burns et al, 2010). Scores range from 0-50, with higher scores indicating worse disease manifestations. A 3-point improvement in score has been shown to correlate with improvement that is meaningful to the subject (Burns, 2012). The independent rater will determine the MGC score based on elements of the QMG, elements of the MG-manual muscle testing, and subject responses for the MG-ADL for that visit. The MGC score will be recorded in the ePRO system.

[redacted]

[redacted]

6.2.6 Safety Assessments

6.2.6.1 Electrocardiogram

A 12-lead ECG will be made with the subject in a supine position, having rested in this position for ≥ 5 minutes before the start of the ECG. A local ECG machine will be used. Date and time settings should be checked prior to the ECG. Skin preparation should be thorough and electrode positions should be according to standard 12-lead ECG placement.

Each ECG will include ventricular heart rate and intervals (PR, QRS, QT, QTc, RR). The Investigator or a qualified designee will review the ECG printout and document his or her review by signing with the date and time of review. On the eCRF, it should be indicated if the ECG was considered 1) normal, 2) abnormal, not clinically significant, or 3) abnormal, potentially clinically significant. The ventricular rate, PR interval, QRS interval, QTc interval, and description of any rhythm abnormalities will be recorded on the eCRF. Any clinically significant changes from the screening ECG will be recorded as an AE or serious adverse event (SAE). ECGs will not be read centrally.

6.2.6.2 Vital Signs

Vital signs, including systolic and diastolic BP (mmHg), pulse rate (beats/min), respiratory rate (breaths/min), and body temperature (ºC) will be measured. Subjects should be seated or supine when vital signs are obtained. When possible, vital signs should be measured before any blood is drawn. See Section 7.1.2 for additional details on measuring vital signs during the IP infusion.

6.2.6.3 Pregnancy Testing

A serum beta human chorionic gonadotropin pregnancy test will be completed during the screening period for all females of childbearing potential. At visits where an IP infusion will be administered, a negative urine pregnancy test result must be obtained prior to the administration of IV IP in female subjects capable of pregnancy. Urine pregnancy tests will be performed at the site using a licensed test (dipstick). Results will be entered in the eCRF.

6.2.6.4 Physical Examination

A general physical examination should be performed by the study Investigator or qualified designee per the schedule of assessments in Section 6.1 in order to monitor the general health of the study subject. At a minimum, the examination should evaluate the following: general appearance, head, neck, cardiovascular, respiratory, abdomen, skin, and nervous system. Any clinically significant change from the screening physical exam should be recorded as an AE or SAE. Height and weight should be recorded per the schedules of assessments.

6.2.6.5 Assessment of Adverse Events and Serious Adverse Events

See Section 8 for instructions on recording and reporting AEs/SAEs.

6.2.6.6 Columbia-Suicide Severity Rating Scale

To comply with regulatory requirements, suicidality will be assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS). The C-SSRS involves a series of probing questions that inquire about possible suicidal thinking and behavior and classifies these events of interest into 11 categories of interest as part of the assessment process. The Sponsor will provide materials for training of relevant site staff in C-SSRS administration. Documented evidence of training of the sites will be required prior to C-SSRS administration to subjects in the study. C-SSRS results will be recorded in the ePRO system.

The "Baseline/Screening" questionnaire will be administered at the Baseline Visit (RCP Day 1). This version of the scale combines the "Baseline" and "Screening" versions to assess suicidality in a subject's lifetime and over the 6 months prior to screening. This version can assess a subject's lifetime suicidality for data collection purposes. Although the C-SSRS is a detailed interview, the full questionnaire is needed only if the initial screening questions regarding suicidal ideation and behavior are positive.

After the Baseline Visit, the "Since Last Visit" version of the C-SSRS will be administered at all scheduled RCP and OLP visits. The "Since Last Visit" version assesses suicidality since the subject's last visit.

In the event that a subject is considered to be at risk based on the outcome of the C-SSRS, the Investigator should treat the subject according to their clinical judgment and report the AE according to AE/SAE definitions and reporting requirements outlined in this protocol (Section 8).

6.2.6.7 Safety Laboratory Tests

See Section 6.2.7 for description of laboratory tests.

6.2.7 Clinical Laboratory Assessments

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study.

Clinical laboratory safety tests will be performed in a licensed central clinical laboratory, unless preapproved by the Sponsor medical monitor. The results of all screening clinical laboratory assessments must be available and reviewed by the Investigator prior to randomization. It is not necessary for subjects to fast prior to blood collection.

The following clinical laboratory tests will be performed per the protocol schedule of assessments (see Section 6.1):

Hematology

- Complete blood count, with white blood cell count and differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), hemoglobin, hematocrit, and platelet count

Serum Chemistry

- Electrolytes (including sodium, potassium, chloride, calcium, bicarbonate)
- Creatinine
- Blood urea nitrogen
- Blood glucose
- Total protein
- Albumin
- Total bilirubin
- Indirect bilirubin
- AST
- ALT
- Alkaline phosphatase (ALP)
- Gamma-glutamyl transferase
- FSH (postmenopausal female subjects only)
- Serum [redacted]

Viral Serology

- HBsAg, anti-HBs, anti-HBc, hepatitis C antibody
- HIV antibodies

Tuberculosis Test (QuantiFERON®-TB Gold)

6.2.8 Pharmacokinetic, [redacted], Immunogenicity, and [redacted] Evaluations

Samples will be taken according to the schedule of assessments in Section 6.1.

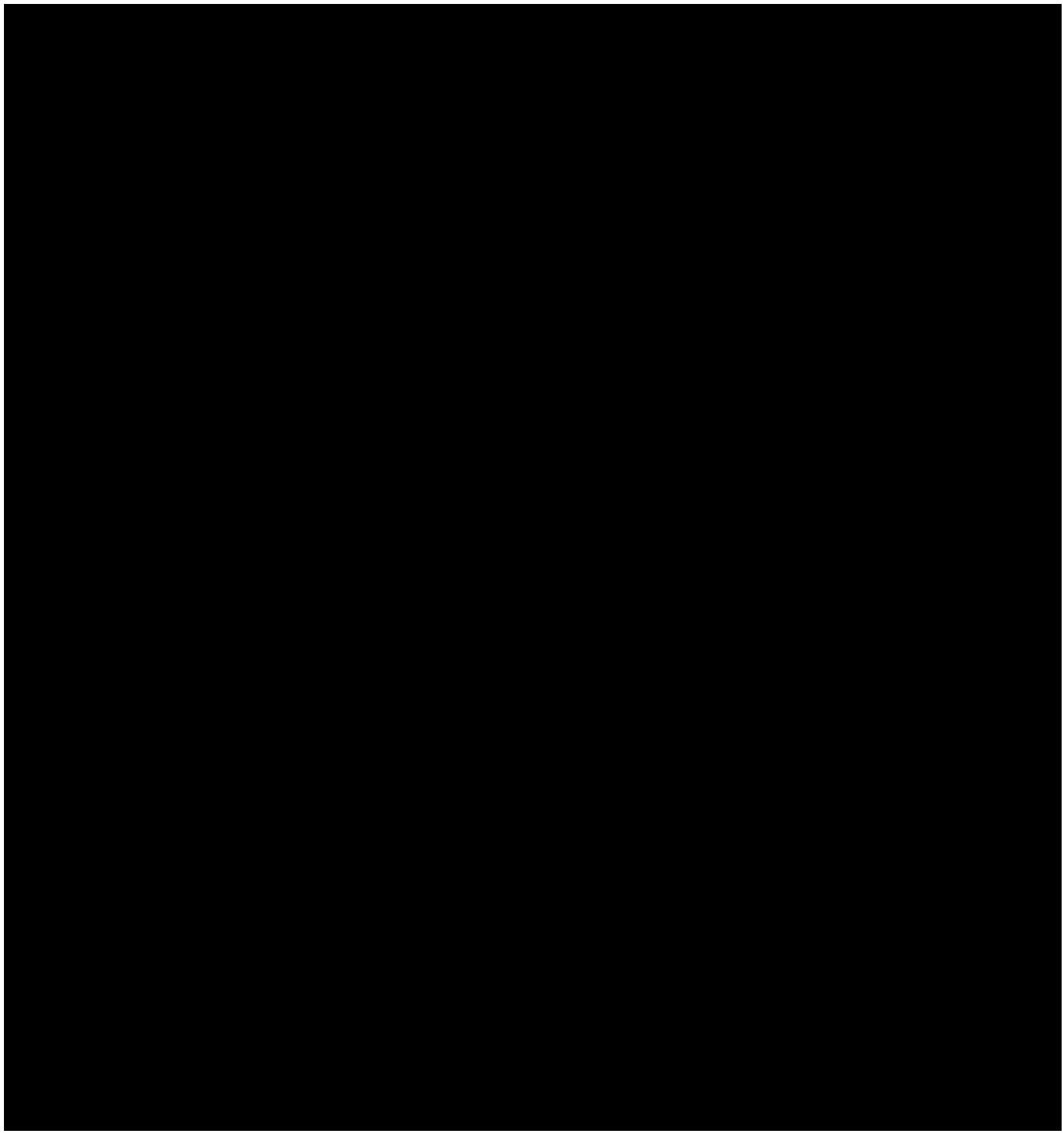
6.2.8.1 Pharmacokinetic Assessments

To determine the concentration of inebilizumab, serum samples will be taken according to the visits specified in the schedule of assessments in Section 6.1 and assessed using a validated immunoassay.

[redacted]

6.2.8.3 Immunogenicity Assessments

To assess immunogenicity (ADA to inebilizumab), serum samples will be taken according to the visits specified in the schedule of assessments in Section 6.1 and assessed using a validated immunoassay.



6.2.9 Corticosteroid Dispensing

Oral corticosteroids will be dispensed to study subjects who are required to use them per protocol. Please see Section 7.2.1 for additional information on corticosteroid dispensing.

6.3 Discontinuation or Withdrawal

6.3.1 Discontinuation of Treatment

The IP must be discontinued in the following circumstances:

1. If the Investigator determines that continuing treatment would result in a significant safety risk to the subject, and consult with the Sponsor medical director.
2. After randomization, if identified that a subject has not met the eligibility criteria and there is a potential safety risk, and consult with the Sponsor medical director.
3. Any life-threatening (Grade 4) clinical event related to the IP, and consult with the Sponsor medical monitor.
4. An AE that, in the opinion of the Investigator or the Sponsor, contraindicates further dosing.
5. Subject becomes pregnant.
6. Any of the following liver function abnormalities:
   a. ALT or AST $\geq 8 \times$ ULN
   b. ALT or AST $\geq 5 \times$ ULN for more than 2 weeks without alternative explanation
   c. ALT or AST $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN without alternative explanation
7. ALT or AST $\geq 3 \times$ ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($\geq 5\%$) without alternative explanation.
8. Neutrophil count $< 1.0 \times 10^3/\mu L$ (Grade 3 or 4 neutropenia) that does not improve to $\geq 1.0 \times 10^3/\mu L$ within 14 days as agreed upon consultation with the medical monitor.
9. Platelet count $< 50 \times 10^3/\mu L$ (Grade 3 or 4 thrombocytopenia) that does not improve to $\geq 50 \times 10^3/\mu L$ within 14 days as agreed upon consultation with the medical monitor.
10. Receipt of a prohibited medication that is considered to be an unacceptable risk following consultation with the medical monitor (see Section 7.5.2).
11. Use of corticosteroid (prednisone > 10 mg/day or equivalent) for more than 8 consecutive weeks in the OLP.
12. Unblinding of the treatment assignment while the subject is in the RCP.

Subjects participating in the RCP who are permanently discontinued from receiving the IP, whether due to meeting a discontinuation criterion or due to voluntary decision of the subject, should be asked to remain in the study and complete all RCP study visits and assessments with the exception of those assessments directly related to dosing. Upon completion of the RCP visit schedule, these subjects will be asked to follow the SFU visit schedule up to 2 years after the last IP dose unless consent is withdrawn, or the subject is lost to follow-up.

Subjects participating in the OLP who are permanently discontinued from receiving the IP, whether due to meeting a discontinuation criterion or due to voluntary decision of the subject, will enter the SFU Period (Section 6.1.4).

Subjects who choose to discontinue the IP will be asked for the reason for discontinuation, such as an AE, lack of efficacy, or other reason, and the reason will be recorded in the eCRF.

6.3.2 Withdrawal from Study

During both the RCP and OLP, subjects who are not willing to continue long-term study participation should be asked to participate, if willing, in an early discontinuation visit (EDV). If a subject withdraws during a scheduled study visit, that visit will change to an EDV and procedures should be conducted according to those presented for EDV. Subjects are free to withdraw from the study (IP and assessments) at any time without prejudice to further treatment.

Subjects who choose to withdraw from the study will be asked for the reason for discontinuation, such as an AE, lack of efficacy, or other reason, and the reason will be recorded in the eCRF.

6.3.3 Replacement of Subjects

Subjects will not be replaced.

6.3.4 Subjects Lost to Follow-up

For subjects who are lost to follow-up (ie, those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the Investigator should show “due diligence” by documenting in the source documents the steps taken to contact the subject, eg, dates of telephone calls, registered letters, etc.

Efforts to ensure complete subject follow-up include proactive site contact of subjects who have missed visits (≥ 3 documented attempts to reach by telephone and at least one documented attempt to reach by letter) or through emergency/other contact if subjects have provided such contacts.

6.4 Study Suspension or Termination

The Sponsor reserves the right to temporarily suspend or terminate this study at any time. The reasons for temporarily suspending or terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs indicates a potential health hazard to subjects.
- Subject enrollment is unsatisfactory.
- Noncompliance that might significantly jeopardize the validity or integrity of the study.
- Sponsor decision to terminate development.

If the Sponsor determines that temporary suspension or termination of the study is required, the Sponsor will communicate the reasons for taking such action to all participating Investigators (or head of the medical institution, where applicable). When feasible, the Sponsor will provide advance notice to all participating Investigators (or head of the medical institution, where applicable) of the impending action.

If the study is suspended or terminated for safety reasons, the Sponsor will promptly inform all Investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. The Sponsor or designee will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the Investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the Sponsor to resume the study, approval from the relevant regulatory authorities (and IRBs/IECs, when applicable) will be obtained prior to resuming the study.

6.5 End of Study

The study will be complete when the last active subject SFU Visits or withdraws from the study, discontinues the OLP, or (for subjects who have opted out of the OLP) completes the RCP.

The end of study date for the entire study is defined as the date when the last participant across all sites is assessed or receives an intervention for evaluation in the study (ie, last participant last visit), including any additional parts in the study (eg, long-term follow-up, antibody testing), as applicable.

6.6 Data Monitoring Committee

An unblinded, independent Data Monitoring Committee (DMC) will evaluate study data at regular intervals for the purpose of monitoring the safety of the study. The DMC will make recommendations to the Sponsor regarding further conduct of the study. Records of all meetings will be maintained by the DMC for the duration of the study. Records of all meetings will be transferred and stored in the trial master file at the conclusion of the study. Additional details of the function of the DMC are in a separate DMC charter.

7 STUDY INTERVENTIONS

7.1 Description of Investigational Products

Both study populations will receive IV inebilizumab or placebo (Table 8).

Table 8 Description of Investigational Products and Dosing Regimens

Investigational Product	Concentration and Formulation as Supplied	Route Dose	RCP Dosing Regimen	OLP Dosing Regimen	Manufacturer
Inebilizumab ([redacted] mg per vial, nominal)	Inebilizumab for IV administration is supplied as a sterile liquid [redacted]. Each vial contains inebilizumab [redacted]	IV 300 mg	AChR-Ab+: RCP Days 1, 15, and 183 MuSK-Ab+: RCP Days 1 and 15	Those randomized to placebo in the RCP: OLP Days 1, 15, 183, 365, 547, 729, and 911; those randomized to inebilizumab in the RCP: OLP Days 1, 183, 365, 547, 729, and 911	[redacted]
Placebo (IV infusion)	IV infusion placebo is supplied [redacted]	IV	AChR-Ab+: RCP Days 1, 15, and 183 MuSK-Ab+: RCP Days 1 and 15	Those randomized to placebo in the RCP: none; those randomized to inebilizumab in the RCP: OLP Day 15	[redacted]

AChR-Ab+ = AChR antibody positive; **IV** = intravenous; **MuSK-Ab+** = muscle-specific kinase antibody positive; [redacted] **OLP** = Open-label Period; **RCP** = Randomized Controlled period; **w/v** = weight/volume.

7.1.1 Investigational Products Inspection, Storage, Dose Preparation, and Handling

7.1.1.1 Investigational Product Inspection

Each vial selected for dose preparation should be inspected. Both inebilizumab and placebo are supplied as a clear to slightly opalescent, colorless to slightly yellow solution, free from or practically free from visible particles. Inebilizumab is a sterile liquid drug product ([redacted] mg inebilizumab per vial, nominal) intended for IV infusion following dilution in normal saline. Placebo is a sterile liquid product intended for IV infusion following dilution in normal saline.

If there are any defects noted with IP, the Investigator, site monitor, and Sponsor should be notified immediately as per Section 7.1.3.

7.1.1.2 Investigational Product Storage

The IP to be diluted for IV use will be appropriately labeled in accordance with national laws and regulations. The IP is provided as 3 vials per blinded kit.

The IP should not be shaken and requires no special biohazard handling. It must be stored at 2ºC to 8ºC (36ºF to 46ºF) in a refrigerator with adequate temperature monitoring. The IP must not be frozen. It should be stored in the original outer package in a location with limited access.

7.1.1.3 Dose Preparation

Inebilizumab for IV administration and placebo for IV administration are supplied as a sterile liquid in a 10R glass vial at a nominal fill volume of [redacted] mL with 20 mm stopper and flip-off cap over seal.

No incompatibility has been observed between inebilizumab or placebo and IV infusion bags made of polyolefin or polyvinyl chloride. Inebilizumab and placebo do not contain preservatives and any unused portions must be discarded. Preparation of the IP and IV bags is to be performed aseptically.

To prepare each inebilizumab or placebo dose, 3 vials of IP, one [redacted] mL IV bag containing 0.9% weight/volume saline, and one IV infusion pump are required. Each vial should be used only one time to prepare a single dose. If [redacted] mL IV 0.9% saline bags are not available, the Sponsor should be contacted for instructions and permission to use [redacted] or [redacted] mL IV 0.9% saline bags.

The dose preparation steps are as follows:

- The tab portion of the vial cap should be removed, and the rubber stopper cleaned with 70% ethyl alcohol or equivalent.
- For each dose, [redacted] mL of blinded IP will be obtained from 3 vials by withdrawing [redacted] mL from each vial. Use a new needle for each withdrawal.
- Add [redacted] mL of blinded IP to the saline bag using aseptic technique.
- Gently mix the contents of the IV bag by inversion. Do not shake the solution. The saline bag should then be inspected to ensure the solution is clear.

Total in-use storage time from needle puncture of the IP vials to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). Although the IP is stable at these storage temperatures for up to 24 hours, the dose of IP should be mixed on the day of administration. If storage time exceeds these limits, a new dose must be prepared from new vials.

The prepared infusion solution should be at room temperature prior to the start of the IV infusion. Please note, the time required to prepare the IP and equilibration of infusion solution will need to be subtracted from the total time allowed for room temperature storage.

7.1.1.4 Dosing and Administration

Prior to the IP infusion, Investigators must determine whether there is a clinically significant infection. In case of infection, the IP infusion will be delayed until the infection resolves.

Premedication with a corticosteroid (eg, methylprednisolone 100 mg IV or equivalent; equivalent methylprednisolone dose should be calculated using Table 9 below) will be administered

approximately 30-60 minutes prior to each inebilizumab infusion, and an antihistamine (eg, diphenhydramine 25-50 mg orally or equivalent) and an anti-pyretic (eg, acetaminophen 500-650 mg orally or equivalent) will be administered approximately 30-60 minutes prior to each IP infusion. Sites should use local supplies of these premedications.

Table 9 Predose IV Corticosteroid Dose Conversion

Corticosteroid (IV)	Equivalent glucocorticoid dose (mg)
Methylprednisolone	100
Triamcinolone	100
Prednisolone	125
Hydrocortisone	500
Dexamethasone	18.8*
Betamethasone	18.8*

IV = intravenous.
The table shows equivalence to a dose of IV methylprednisolone. For example, 125 mg of IV prednisolone is equivalent to 100 mg of IV methylprednisolone.
*Dose can be rounded to the nearest vial for ease of use (ie, 20 mg).

Vital signs will be obtained prior to the start of each IP infusion. An experienced and qualified staff member will place the IV access.

Prior to the start of the infusion, please be sure that the bag content is at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures. The prepared solution will be IV administered via an infusion pump at an increasing rate over approximately 90 minutes through an IV line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter according to the schedule in Table 10.

Table 10 Infusion Rate for Investigational Product After Dilution in a [redacted] mL Intravenous Bag

Elapsed Time (minutes)	Recommended Infusion Rate (mL/hour)
0 to 30	42
31 to 60	125
61 to end of infusion	333

If an infusion reaction occurs, the site should slow or, if this does not help, stop the infusion. Resumption of the infusion is at the discretion of the site qualified personnel. Unless an infusion reaction occurs resulting in discontinuation of the infusion, the entire infusion bag contents must be administered, and the tubing must be flushed with a volume of saline at least as large as that of the tubing to ensure complete delivery of the IP. When flushing the tubing, the infusion rate should not exceed 333 mL/hour.

After the completion of the infusion, subjects will be observed for at least one hour.

Medically qualified personnel must be immediately available to respond to emergencies during administration of the IP. Appropriate drugs and medical equipment to treat acute hypotensive, bronchoconstrictive, or anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat these reactions. Additionally, appropriate drugs

and medical equipment to treat IRRs must be immediately available, and study personnel must be trained to recognize and treat IRRs.

Duration of Administration is defined as the amount of time elapsed from the infusion pump start time to the infusion pump stop time plus the time required to clear the infusion line of residual IP. The duration of administration will be recorded in the eCRF.

7.1.1.5 Investigational Product Accountability

Study site staff will maintain a record of the IP doses received, dispensed, administered, and destroyed. All records will be maintained with controlled access. The Investigator will administer the IP only to subjects included in this study and according to the procedures established in this study protocol. Each administration of the IP will be documented and transferred to the eCRF.

7.1.1.6 Investigational Product Handling and Disposal

The Investigator or designee must return any unused IP to the Sponsor or designee regardless of whether the study was completed or terminated prematurely. At the time of return, the Investigator must verify that unused or partially used IPs have been returned and that no IPs remain at the site. As an alternative to returning unused IPs at the end of the study, the Investigator may destroy unused IPs on site with agreement from the Sponsor.

7.1.2 Monitoring of Dose Administration

Vital signs (body temperature, BP, pulse rate, and respiratory rate) must be taken with the subject in a seated position as follows:

- Within 60 minutes prior to administration of the IP
- 15 (± 5) minutes after the start of the infusion and then every 30 (± 10) minutes until completion of infusion
- At the completion of infusion (± 10 minutes)
- 60 (± 10) minutes after dosing (repeated as needed until stable)

If a hypersensitivity reaction occurs during the infusion, vital signs will be taken more frequently, as warranted by the severity of the reaction.

7.1.3 Reporting Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution to market or clinic by either the Sponsor, distributors, or partners for whom the Sponsor manufactures the material. This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts.

Report product complaints to the Sponsor within one business day of discovery by completing the applicable product complaint form found in the Pharmacy Manual and submitting a copy as instructed via the Pharmacy Manual. Retain product unit(s) associated with the complaint in quarantine under labeled storage conditions until the Sponsor advises whether product should be

destroyed or returned be evaluated, or for a maximum of 45 calendar days after reporting the product complaint to Sponsor.

7.2 Additional Study Medications

7.2.1 Oral Corticosteroid Taper

Subjects who enter the study receiving oral corticosteroids will continue to receive oral corticosteroids at the time of randomization (Section 4.1).

Corticosteroids may only be used in the following circumstances:

1. The subject was on corticosteroids at the time of randomization and is using corticosteroids per protocol, or
2. For short-term use of non-MG medical conditions (eg, asthma exacerbation) when approved by the medical monitor.

Initial Corticosteroid Dose at Randomization: Subjects entering the study may or may not already be receiving a corticosteroid. Subjects who are already receiving a corticosteroid at the time of randomization will continue to receive a corticosteroid. Subjects who are not already receiving a corticosteroid at time of randomization will not start corticosteroid treatment.

Prednisone will be used as the preferred oral corticosteroid, to be provided to the subject as part of study procedures. Prednisolone is an allowed alternative to prednisone and should be used at the same dose as prednisone. If prednisone or prednisolone are not available locally, an alternative oral corticosteroid can be used following discussion with the medical monitor and agreement on the correct prednisone equivalent dose.

Subjects may be receiving up to 40 mg prednisone daily or 80 mg every other day or an equivalent dose of an alternate corticosteroid. If a subject is on an alternate corticosteroid, the equivalent prednisone dose should be calculated using Table 11. If a subject enters on a dose of prednisone (or equivalent) not shown in the table (eg, 35 mg prednisone daily), then the next lowest dose shown in the table should be used as the starting dose for that subject (30 mg prednisone daily in this example). Any subject on an every other day steroid regimen will be changed to an equivalent daily steroid regimen (eg, 40 mg every other day = 20 mg daily).

Table 11 Corticosteroid Dose Conversion

Corticosteroid	Equivalent glucocorticoid dose (mg)
Prednisone	5
Prednisolone	5
Triamcinolone	4
Methylprednisolone	4
Dexamethasone	0.75
Betamethasone	0.6
Hydrocortisone	20

The table shows equivalence to a dose of prednisone. For example, 5 mg of prednisolone is equivalent to 5 mg of prednisone; 4 mg of methylprednisolone is equivalent to 5 mg of prednisone.

RCP Corticosteroid Tapering Procedure: Starting at the RCP Week 4 visit, all subjects who are on corticosteroids will undergo the protocol-specified corticosteroid taper shown in Table 12. Tapering will occur until a subject is on prednisone 5 mg daily, at which time the subject will remain on that dose during the remainder of the RCP. A site may elect to use prednisone 10 mg every other day as an alternative to prednisone 5 mg daily. If a subject begins the study on a prednisone dose that is ≤ 5 mg daily but > 0 mg, then the subject should continue on that dose without tapering during the RCP. To maximize compliance with the corticosteroid taper, sites are encouraged to remind subjects (eg, by a phone or an email reminder) of tapering timepoints that do not align with a study visit (eg, RCP Week 16, RCP Week 20, and RCP Week 24). Any deviation from the corticosteroid tapering schedule should be reviewed with a study medical monitor.

Table 12 Randomized Controlled Period Prednisone Tapering Schedule

RCP Baseline dose (Day 1) (mg/day)	RCP Week 4 dose (Day 29) (mg/day)	RCP Week 8 dose (Day 57) (mg/day)	RCP Week 12 dose (Day 85) (mg/day)	RCP Week 16 dose (Day 113) (mg/day)	RCP Week 20 dose (Day 141) (mg/day)	RCP Week 24 dose through end of RCP (Day 169) (mg/day)
40	30	20	15	10	7.5	5
30	20	15	10	7.5	5	5
20	15	10	7.5	5	5	5
15	10	7.5	5	5	5	5
10	7.5	5	5	5	5	5
7.5	5	5	5	5	5	5
≤5	No taper					

RCP = randomized controlled period.

OLP Corticosteroid Tapering: Subjects who are receiving corticosteroids at the time of OLP entry can remain on prednisone 5 mg daily or the dose can be tapered further at the discretion of the Investigator. If a dose of prednisone >10 mg daily is used for more than 8 consecutive weeks in the OLP, the IP must be discontinued. The rationale for this requirement is to reduce the potential risk of adverse effects associated with long-term use of moderate- or high-dose corticosteroids.

7.2.2 Rescue Medications

Worsening of symptoms in MG can occur due to precipitating factors that include disease progression, infection, tapering of therapies, or certain medications (Wendell and Levine, 2011). This worsening can range from mild to severe. Rescue therapy can be used in any of the following circumstances:

1. QMG score is ≥ 4 points higher than the baseline score, or
2. QMG score increases ≥ 4 points between study visits, or
3. The Investigator is concerned that the subject's health is in jeopardy (eg, significant worsening of bulbar function).

The protocol-allowed rescue therapy options include IVIg or PLEX. Intravenous Ig is recommended over PLEX for subjects in this study since PLEX may remove the IP from circulation, thus potentially decreasing its therapeutic effect (Khatri et al, 2009). Subjects who are treated with a protocol-allowed rescue therapy can continue in the study. High-dose corticosteroids are not a protocol-allowed form of rescue therapy (eg, IV methylprednisolone).

Rescue therapies should be recorded on the study's rescue therapy dedicated eCRF pages.

Rescue therapy is considered standard of care treatment; information about Sponsor coverage of out-of-pocket costs incurred by subjects treated with rescue therapy will be included in the site contract.

7.3 Treatment Assignment and Bias Minimization

7.3.1 Treatment Allocation

Acetylcholine receptor antibody positive (AChR-Ab+) and MuSK-Ab+ subjects will be randomized in a 1:1 ratio to receive inebilizumab or placebo.

The IP will be administered on Day 1 after randomization. If there is a delay in the administration of the IP such that it will not be administered within the specified timeframe, the site monitor must be notified immediately.

7.3.2 Randomization Strategy and Procedure

An interactive voice/web response system (IXRS) will be used for randomization to a treatment group and assignment of IP kit numbers. Subjects will be enrolled into either the AChR-Ab+ or MuSK-Ab+ population. Within each population, subjects will be stratified by region first (non-Japan vs Japan). In the non-Japan population, subjects will be further stratified according to baseline disease severity ("Day 1 QMG score = 11-15" vs "Day 1 QMG score ≥ 16") and baseline corticosteroid use ("prednisone > 5 mg/day" vs "prednisone ≤ 5 mg/day") and randomized 1:1 to receive either inebilizumab or placebo within each stratum. In the Japan population, no further stratification will be applied due to the small sample size, and subjects will be randomized 1:1 to receive either IV inebilizumab or placebo.

A subject is considered randomized into the study when the Investigator notifies the IXRS that the subject meets eligibility criteria and the IXRS provides the assignment of treatment group and allocates treatment, including IP kit number.

Additional details are provided in the IXRS Manual.

7.3.3 Extent and Maintenance of Blinding

This is a double-blind study in which the IV inebilizumab and IV placebo are matching in appearance.

The Sponsor will remain blinded until after the database lock for primary efficacy analysis, which will occur after all subjects have completed Week 26 or discontinued early from the study. After Week 26, the AChR-Ab+ subjects who haven't completed the RCP will complete the remaining visits during the RCP per protocol. The Sponsor personnel who are directly associated with the conduct of the study will remain blinded to the treatment assignment until all subjects have completed the RCP or discontinued early from RCP. Subjects, site staff, and contract research organization (CRO) personnel will not be unblinded to individual subject treatment assignment until the completion of the study, except as specified herein. Prior to the completion of the study, individual treatment assignment may be revealed to the site and/or subject as required by the sponsor for execution of business activities; such unblinding is anticipated to be infrequent and will in no circumstance occur prior to the subject having completed at least 1 year in the OLP or exited the study.

Potentially unblinding laboratory data will not be available to the sites until after treatment assignments are unblinded to sites. The potentially unblinding laboratory results include B-cell counts and [redacted] after randomization up to and including the OLP Day 15 visit. Investigators and treating physicians must not request potentially unblinding laboratory results at a local laboratory.

If treatment allocation for a subject becomes known to the Investigator or other study staff involved in the management of study subjects, the Sponsor must be notified immediately.

7.3.4 Unblinding Procedures

In the event of a medical emergency, the Investigator may unblind an individual subject's IP allocation. Instructions for unblinding an individual subject's IP allocation are contained in the IXRS Manual. In general, unblinding should only occur if management of the medical emergency would be different based on the subject having received IP. In the majority of cases, the management of a medical emergency would be the same whether or not IP was received by the subject. If this was the case, the IP allocation should not be unblinded. In non-emergency situations where unblinding is being considered, the site should discuss the situation with a study medical monitor.

If a site unblinds the treatment assignment for a subject while in the RCP, the IP must be discontinued for that subject. The subject should remain in the study and complete all study assessments except those directly related to dosing.

7.4 Assessment and Verification of Compliance

Site staff will administer all IPs IV at the study center. The dose and date of administration of the IP must be recorded in the subject's eCRF. Treatment compliance will be assessed based on this information.

7.5 Concomitant Medications and Treatments

Subjects should receive all medications that are considered by their physician to be necessary for their health and well-being except for the medications that are specifically prohibited in Section 7.5.2.

All concomitant medications given to the subject during the study will be recorded on the source document, including the start and stop dates, route of administration, and reason for administration.

The Sponsor recommends that Investigators ensure that all subjects are up to date with required vaccinations prior to entry into the study.

7.5.1 Immunosuppressive Medications During the Screening Period

Azathioprine, mycophenolate mofetil, or mycophenolic acid can be used during the screening period; the dose can be lowered but cannot be increased during the 4 weeks prior to randomization. The same applies for tacrolimus (allowed in Japan only).

Corticosteroids can be used during the screening period; the dose can be lowered but it cannot be increased within 4 weeks prior to randomization.

Acetylcholinesterase inhibitors (pyridostigmine dose ≤ 480 mg/day) can be used during screening, but the dose must be stable for 2 weeks prior to randomization.

7.5.2 Prohibited Medications and Treatments

Subjects receiving corticosteroids at the time of randomization will stay at the same corticosteroid dose (prednisone or its derivatives), and dose tapering will begin at Week 4 of the RCP. The maximum allowed dose of prednisone at the time of randomization will be 40 mg/day or 80 mg every other day. The corticosteroid dose must not have been increased within the 4 weeks prior to randomization; reductions in dose during the screening period are allowed. Subjects who are not already receiving a corticosteroid at time of randomization will not start corticosteroid treatment.

Subjects entering the study on an allowed non-steroidal IST must have been on the drug continuously for ≥ 6 months with no dose increase in the 4 months prior to randomization. Subjects will remain on the same dose of non-steroidal IST for the duration of the RCP unless dose reduction is deemed necessary for safety reasons. Azathioprine, mycophenolate mofetil, and mycophenolic acid are allowed non-steroidal ISTs. Tacrolimus is allowed in Japan only since it is the standard of care for treatment of MG in Japan.

Subjects on a stable dose of acetylcholinesterase inhibitors (pyridostigmine dose ≤ 480 mg/day) will be allowed to enroll. The acetylcholinesterase inhibitor dose must have been stable for at least 2 weeks prior to randomization. The acetylcholinesterase inhibitor dose must remain stable throughout the RCP unless dose reduction is deemed necessary for safety reasons. No increase in acetylcholinesterase inhibitors will be allowed in the study. Acetylcholinesterase inhibitors must be held for at least 6 hours prior to every study visit so that objective testing can be performed without the confounding effect of the acetylcholinesterase inhibitor.

Please refer to the exclusion criteria in Section 5.2 for a list of medications that are not allowed during study. In addition, immunosuppressive medications other than those outlined in Section 5.1, Inclusion Criterion #7, are prohibited unless agreed upon following consultation with the Sponsor medical monitor. Please keep in mind that several medications allowed as continuous, if they were started prior to study entry and were kept at stable dosing for a certain period of time, may not be allowed as newly prescribed drugs during study.

During the SFUP:

- Receipt of medications that target B cells or immunoglobulins during the SFUP requires immediate withdrawal from the SFUP. This includes any immunomodulatory or immunosuppressive drugs which have a pharmacodynamic effect on B cells and/or immunoglobulins (eg, rituximab, ocrelizumab, ofatumumab, obinutuzumab, or any experimental B cell depleting or modulating agent).
- Receipt of other protocol-defined prohibited medications (Section 7.5.1), such as azathioprine or mycophenolate mofetil during the SFUP must be discussed with the Sponsor to determine whether the subject may continue participation in the SFUP.

8 SAFETY ASSESSMENT

8.1 Definitions

- **Adverse event** – An AE is any untoward medical occurrence associated with the use of an intervention in humans, whether or not it is considered intervention-related. MG exacerbations are an endpoint in this study and, therefore, will not be recorded as AEs or SAEs (with the exception of exacerbations that involve myasthenic crisis or death).
- **Serious adverse event** – An SAE is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:
  - Death.
  - A life-threatening AE. An event is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction (SAR) that, had it occurred in a more severe form, might have caused death.
  - Inpatient hospitalization or prolongation of existing hospitalization. Any hospitalization requiring admission will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a preexisting condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
  - A congenital anomaly/birth defect.
  - Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 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.
- **Causality or relatedness** – The Investigator is required to provide an assessment of the relationship of AEs and SAEs to the IP. An event will be considered "not related" to use of IP if any of the following tests are met:
  - An unreasonable temporal relationship between administration of the IP and the onset of the event (eg, the event occurred either before or too long after administration of the IP for it to be considered IP-related).
  - A causal relationship between the IP and the event is biologically implausible (eg, death as a passenger in an automobile accident).

- A clearly more likely alternative explanation for the event is present (eg, typical adverse reaction [AR] to a concomitant drug and/or typical disease-related event).

  Individual AE/SAE reports will be considered "related" to use of the IP if the "not related" criteria are not met.

  "Related" implies that the event is considered to be "associated with the use of the drug" meaning that there is "a reasonable possibility" that the event may have been caused by the product under investigation (ie, there are facts, evidence, or arguments to suggest possible causation).

- **Adverse reaction** – An AR is any AE caused by a drug.

- **Suspected adverse reaction** – An SAR is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. SAR implies a lesser degree of certainty about causality than AR.
- **Unexpected** – An event is considered unexpected if it is not listed in the Investigator's Brochure, is not listed at the specificity or severity that has been observed, or, if an Investigator's Brochure is not required or available, is not consistent with the risk information described in the General Investigational Plan or elsewhere in the IND. Unexpected also refers to events that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular IP.

- **Severity or intensity** – Severity will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0). The determination of severity for events not listed in the CTCAE should be made by the Investigator based upon medical judgment and the severity categories of Grade 1 to Grade 5 as defined below:

  - Grade 1 (mild): An event of mild intensity that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
  - Grade 2 (moderate): An event of moderate intensity that is usually alleviated with additional, specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the subject.
  - Grade 3 (severe): A severe event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
  - Grade 4 (life-threatening): An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc.).
  - Grade 5 (fatal): Death (loss of life) as a result of an event.

8.2 Documenting Adverse Events

AEs spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), severity, causality, action taken, serious outcome (if applicable), and whether or not it caused the subject to discontinue the study. The AE term should be reported in standard medical terminology when possible.

8.3 Reporting Adverse Events

All AEs (related and unrelated) will be recorded from the time of the written ICF signature up to the end of the study, whether or not they are related to the IP. Any SAEs considered related to the IP and discovered by the Investigator at any time after the study should be reported.

All SAEs must be reported immediately and no later than 24 hours of awareness by submitting an SAE Report Form as indicated below.

To:	**Email:** svc-ags-in-us@amgen.com **US-only** Fax number: +1-888-814-8653 (*fax should only be utilized as back-up to email) **Ex-US Fax number:** +44 (0)207-136-1046 (*fax should only be utilized as back-up to email)

Additional follow-up information, if required or available, should all be reported within 1 business day of receipt, should be completed on a follow-up SAE form, placed with the original SAE information, and kept with the appropriate section of the eCRF and/or study file.

The Sponsor or designee will work with the Investigator to ensure that all the necessary information is provided within 1 calendar day of initial receipt for fatal and life-threatening events and within 5 calendar days of initial receipt for all other SAEs.

The Sponsor or designee is responsible for notifying the relevant regulatory authorities of certain events globally. It is the Principal Investigator's responsibility to notify the IRB/IEC of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical study. Each site is responsible for notifying its IRB/IEC of these additional SAEs. Marketing authorization holder (MAH) or designee is responsible for notifying the relevant regulatory authorities of certain events in Japan.

8.4 Other Events Requiring Immediate Reporting

8.4.1 Pregnancy and Lactation

Pregnancy in a female study subject who has received IP is required to be reported to the Sponsor or designee immediately and no later than 24 hours of awareness, by email or fax, using the Clinical Trial Drug Exposure During Conception/Pregnancy Report Form (see Section 8.3 for contact information).

Subjects who become pregnant during the study period must not receive additional doses of IP but will not be withdrawn from the study. If the subject requests to know which treatment she

received, this information will be provided to her. The pregnancy will be followed for outcome of the mother and child (including any premature terminations) and the outcome information should be reported to the Sponsor or designee immediately and no later than 24 hours of awareness (see Section 8.3 for contact information).

Should the Investigator become aware of a pregnancy in the partner of a male study subject who has received IP, this should be reported to the Sponsor or designee immediately and no later than 24 hours of awareness, by fax or email, using the Clinical Trial Drug Exposure During Conception/Pregnancy Report Form (see Section 8.3 for contact information). The Sponsor will endeavor to collect follow-up information on such pregnancies provided the partner of the study subject provides consent.

Participants With Partners Who Become Pregnant (or Were Pregnant at the Time of Enrollment)

- In the event a participant's partner becomes pregnant during treatment (or is pregnant at the time of enrollment), and for an additional 6 months after the last dose of IP, the information will be recorded on the Pregnancy Notification Form (Figure 4). The form must be submitted to the Sponsor's Global Patient Safety immediately and no later than 24 hours of the Investigator's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or region's local privacy laws).
- Participants with pregnant partners or whose partners become pregnant during treatment and for an additional 6 months after the last dose of IP must practice sexual abstinence or use a barrier method of contraception (as described above) through 6 months after the last dose of IP.
- The Investigator will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant partner to obtain additional pregnancy information.
- After obtaining the pregnant partner's signed consent for release of pregnancy and infant health information, the Investigator will collect pregnancy outcome and infant health information on the pregnant partner and their baby and complete the pregnancy questionnaires. This information will be forwarded to the Sponsor's Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to the Sponsor's Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any participant who breastfeeds while taking IP through 6 months after the last dose of IP.
- Information will be recorded on the Lactation Notification Form (see below) and submitted to the Sponsor's Global Patient Safety immediately and no later than 24 hours of the Investigator's awareness of the event.

- Study treatment will be discontinued if a participant breastfeeds during the study as described in the exclusion criteria (see Section 5.2).
- With the participant's signed consent for release of parent and infant health information, the Investigator will collect mother and infant health information and complete the lactation questionnaire on any participant who breastfeeds while taking IP through 6 months after the last dose of IP.

Figure 4 Pregnancy and Lactation Notification Forms (Paper-based Form)

AMGEN Form

TITLE	DOCUMENT NO	VERSION
Clinical Trial Drug Exposure During Conception/Pregnancy	FORM-510390	1.0
	EFFECTIVE DATE 25 Apr 2024	PAGE Page 1 of 4

For healthcare professional use only

Subject ID/Number:	Protocol Number:	Country:

Data Concerning Mother and Father / Family History

Parents	Trial Participant/Patient	Age (years)
Mother	☐ Yes, subject number: ☐ No	
Father	☐ Yes, subject number: ☐ No	

Hereditary diseases, malformations, chronic disease of expectant parents and in their families: ☐ Yes (if yes, please specify): ☐ No ☐ Unknown

Previous Pregnancies

Number of previous pregnancies:

Number of healthy children (no birth defects):

Number of children with birth defect: If any with birth defect please list (use 1 line per child):

Sex (m/f)	Birth Defects

Number of induced abortions:

Number of spontaneous abortions:

Number of stillbirths:

Current Pregnancy

Pregnancy is already terminated: ☐ Yes ☐ No* ☐ Unknown

*Week of gestation at the time of reporting:

First day of last menstruation:

Expected due date:

Period regular: ☐ Yes ☐ No ☐ Unknown

Drugs Used by the Trial Participant or Patient (Mother or Father)

Drug/IMP	Daily Dose (unit)	Indication	Therapy Date (from-to) dd-mmm-yyyy	

Drugs Used by the Mother During Pregnancy

Page 1 of 4
Legacy # FOR-PHV-0002

AMGEN Form		
TITLE Clinical Trial Drug Exposure During Conception/Pregnancy	DOCUMENT NO FORM-510390	VERSION 1.0
	EFFECTIVE DATE 25 Apr 2024	PAGE Page 2 of 4

Subject ID/Number: Protocol Number: Country:

Trade Name/INN	Daily Dose (unit)	Mode of Application	Indication	Therapy Date (from-to) dd-mmm-yyyy	

☐ Please tick if additional page is attached

Course of Pregnancy

Prenatal Examinations	Date	Normal	Abnormal	If abnormal, please specify
Amniocentesis		☐	☐	
Testing of alpha-foetoproteins		☐	☐	
Chorionic villus sampling (CVS)		☐	☐	
Genetic Screening		☐	☐	
Ultrasound (US):		☐	☐	
1st US (9th to 12th week of gest.)		☐	☐	
2nd US (19th to 23rd week of gest.)		☐	☐	
3rd US (28th to 32nd week of gest.)		☐	☐	

Regular preventive medical checkups:	☐ Yes ☐ No ☐ Unknown
Potential Risks (drug, smoking, alcohol, x-ray examinations, etc.) and complications (e.g., hospitalization, infections during pregnancy, etc.)	☐ Yes (if yes, please specify): ☐ No ☐ Unknown

Data Concerning Childbirth and Child

Outcome of Pregnancy:
Date of Birth / Abortion / Stillbirth: or ☐ Unknown

Gestation Week	Vaginal Birth	Caesarian	Ventouse/Vacuum Extractor	pH of cord blood

AMGEN Form		
TITLE Clinical Trial Drug Exposure During Conception/Pregnancy	DOCUMENT NO FORM-510390	VERSION 1.0
	EFFECTIVE DATE 25 Apr 2024	PAGE Page 3 of 4

Subject ID/Number:		Protocol Number:		Country:
	☐	☐	☐	

Child	Sex	APGAR Score			Circumference of the Head	Birth Weight and Height		Fetal Lie	Outcome*	Abnormality	
	m/f	1	5	10	cm	Kg	Cm			Yes	No
1										☐	☐
2										☐	☐
3										☐	☐

*Outcome:
1. Live-birth
2. Spontaneous abortion (up to 20th week)
3. Stillbirth (20th – 27th week)
4. Stillbirth (from 28th week)
5. Induced abortion
6. Death of mother and child
7. Ectopic pregnancy, e.g. tubal pregnancy

Were there any complications during childbirth?	☐ Yes, please specify: ☐ No ☐ Unknown, please specify:
Does the child have any birth defect? *(Please also specify in cases of induced or spontaneous abortion, stillbirth, or death of neonate)*	☐ Yes, please specify: ☐ No ☐ Unknown, please specify:

Treating Gynecologist / Obstetrician*

*Please only complete if known and if consent is provided to contact the Gynecologist/Obstetrician

Identical with reporting physician: ☐ Yes ☐ No ☐ Unknown

Name: Street:

Postal Code/City: Telephone:

Pediatrician*

*Please only complete if known and if consent is provided to contact the Pediatrician

Pediatrician unknown: ☐ Yes ☐ No

Name: Street:

Postal Code/City: Telephone:

Comment / Assessment

If pregnancy was terminated early, or if any complications occurred during childbirth or with the neonate

AMGEN Form		
TITLE Clinical Trial Drug Exposure During Conception/Pregnancy	DOCUMENT NO FORM-510390	VERSION 1.0
	EFFECTIVE DATE 25 Apr 2024	PAGE Page 4 of 4

Subject ID/Number:	Protocol Number:	Country:

In your view, is there reasonable evidence that these events are to be attributed to the drug exposure during pregnancy?

☐ Yes
☐ No
☐ Not Assessable, please explain (please add diagnostic findings if applicable):

Further comments:

☐ Please tick if additional page is attached

Investigator or Reporter

Printed Name:

Title:

Country:

Email:

Phone:

Fax:

Specialization:

Investigator or Reporter Signature: _____ **Date:**

Please return the completed form immediately and no later than 24 hours of awareness and submit via
Email (worldwide) to: svc-ags-in-us@amgen.com
or
Fax to: +1-888-814-8653 (toll-free, within USA) or to: +44 (0)207-136-1046 (for non-USA)

Amgen Proprietary - Confidential

AMGEN Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20230049

Study Design: ☒ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):**____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

Internal Use Only General and Administrative

8.4.2 Overdose or Misuse

Any instance of overdose of IP (suspected or confirmed) must be reported within 24 hours by submitting an SAE Report Form as indicated in Section 8.3. Any associated AEs and SAEs must also be reported, and their management should be recorded.

8.5 Adverse Events of Special Interest

An AESI is an event of scientific and medical interest specific to the understanding of the IP and which may require close monitoring and collection of additional information by the Investigator. An AESI may be serious or non-serious.

The following events are considered AESIs for this study:

- Anaphylaxis and serious hypersensitivity reactions
- IRRs
- Immune complex disease
- Cytopenia
- Serious and/or opportunistic infections, including PML. See Appendix 4 for a list of opportunistic infections.

Once an AE is identified as an AESI, it should be reported within 24 hours by submitting an SAE Report Form as indicated in Section 8.3.

For anaphylaxis, serious hypersensitivity reactions, and IRRs, additional details will be captured in the eCRF.

8.6 Medical Monitor Coverage

Each subject will be provided with contact information for the Investigator. In addition, each subject will receive a phone number intended to provide the subject's physician access to a medical monitor 24 hours a day, 7 days a week, in the event of an emergent situation where the subject's health is deemed to be at risk. In this situation, when a subject presents themselves to a medical facility where the treating physician or healthcare provider requires access to a physician who has knowledge of the IP and the clinical study protocol and the Investigator is not available, the treating physician or healthcare provider can contact a medical monitor through this system.

8.7 Regulatory Reporting Requirements for Safety Information

If participant is permanently withdrawn from IP because of a serious adverse event, this information must be submitted to the Sponsor or designee.

Prompt notification by the Investigator to the Sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the external review body and Investigators.

Individual safety reports for suspected unexpected serious adverse reactions will be reported by the Sponsor according to local regulatory requirements (eg, electronic submission to the Eudravigilance database in the EU as per EU Clinical Trial Regulation 536/2014) as well as the Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the Sponsor will file it along with the Investigator's Brochure and will notify the external review body, if appropriate according to local requirements.

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of participants who develop serious, unexpected, and related AEs may be unblinded by the Sponsor before submission to regulatory authorities. Aggregate analyses may also be unblinded by the Safety Assessment Team, as appropriate. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

The Sponsor will prepare a single Development Safety Update Report (DSUR) (also referred to as Annual Safety Report in the EU) for the IP. To ensure that consolidated safety information for the study is provided, this single DSUR will also include appropriate information on any other IP used in the clinical study, if applicable.

9 STATISTICAL CONSIDERATIONS

9.1 General Considerations

Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics.

This section summarizes the planned statistical analyses. Further details will be provided in a comprehensive statistical analysis plan (SAP), which will be prepared prior to randomization of the first subject, with final amendments completed prior to database lock. Any deviations from this plan will be reported in the Clinical Study Report.

9.2 Determination of Sample Size

The primary endpoint is the change from baseline in MG-ADL score at Week 26 in the overall study population (ie, the AChR-Ab+ and MuSK-Ab+ populations). Sample sizes were estimated using a 2-sided t-test. Approximately 230 subjects (188 subjects with AChR-Ab+ MG and 42 subjects with MuSK-Ab+ MG) will be randomized in a 1:1 ratio to either inebilizumab or placebo. This sample size will provide more than 95% power to detect a true mean (population) treatment difference of 2 in the overall study population with a 2-sided 0.05 alpha level, assuming a common standard deviation of 4 using a 2-sided t-test.

The sample size of AChR-Ab+ subjects was also estimated using a 2-sided t-test, which will provide at least 90% power to detect a true mean (population) treatment difference of 2 in change from baseline of MG-ADL with a 2-sided 0.05 alpha level. The sample size of MuSK-Ab+ subjects was estimated based on the feasibility of the enrollment. Assuming a common standard deviation of 4 and a 2-sided 0.05 alpha level, the minimum detectable difference in the MuSK-Ab+ population is 2.5.

9.3 Analysis Sets

Full Analysis Set: The "Full Analysis Set" (FAS) will include all subjects randomized who received at least 1 dose of IP in the study and have baseline and at least 1 postbaseline observation. Subjects will be analyzed according to the treatment randomized. The efficacy analysis will be based on the FAS.

Safety Analysis Set: The "Safety Analysis Set" will include all subjects who received any dose of IP during the RCP. Subjects will be analyzed according to the treatment that they actually received. The safety and ADA analysis in the RCP will be based on the Safety Analysis Set.

Open-label Analysis Set: The "Open-label Analysis Set" will include all subjects who received any dose of inebilizumab during the OLP.

Any Inebilizumab Analysis Set: The "Any Inebilizumab Analysis Set" will include all subjects who received any dose of inebilizumab.

Pharmacokinetic Analysis Set: The "PK Analysis Set" will include all subjects who received IP and have at least 1 quantifiable serum PK observation post first dose. Subjects will be analyzed according to the treatment that they actually received. The PK analysis will be based on the PK Analysis Set.

Per-protocol Analysis Set: The "Per-protocol Analysis Set" (PAS) will include all subjects in the FAS who are sufficiently compliant with the protocol. Major reasons to exclude subjects from the PAS analysis set are listed below:

[redacted]

The protocol deviations will be reviewed and documented prior to the database lock. The efficacy analysis based on the PAS will be conducted for primary and key secondary endpoints as a sensitivity analysis.

9.4 Methods for Statistical Analyses

[redacted]

Treatment-policy strategy: The analyses will include all data captured during the RCP, defined as the period after randomization to the conclusion of the last scheduled RCP visit regardless of the rescue therapy use.

While on-treatment strategy: The analyses will include all data captured during the RCP, defined as the period after randomization to [redacted] after the last treatment visit regardless of the rescue therapy use.

All efficacy analyses described below apply to the RCP unless stated otherwise. For subjects in the OLP and/or in the SFU Period, the efficacy may also be summarized over the combined study periods (ie, combined RCP and OLP, etc.) to characterize the durability of the treatment effect, if applicable.

The safety endpoints will be summarized for the RCP, OLP, combined RCP and OLP, and SFU if applicable, respectively.

9.4.1 Analysis of the Primary Efficacy Endpoint

The primary endpoint is the change from baseline in MG-ADL score at Week 26 in the overall study population (ie, the AChR-Ab+ and MuSK-Ab+ populations).

For the primary analysis, the primary estimand is defined as follows:

- Population: Subjects in the FAS.
- Variable (endpoint): change from baseline in MG-ADL score at Week 26.
- Intercurrent events:
  - Rescue therapy initiated on or after Day 28 during the RCP will be analyzed using a composite strategy. The data collected on or after the initiation of the rescue therapy will be imputed using the subject's worst observation collected before initiation of the rescue therapy.
  - Rescue therapy initiated before Day 28 during the RCP and treatment discontinuation will be analyzed using a treatment policy strategy. Subjects who discontinue treatment early will be asked to attend scheduled evaluations until the end of the RCP. The data collected after treatment discontinuation for reasons other than death or rescue therapy will be included in the analysis.
- Population-level summary: Mean difference between inebilizumab and placebo.

Rationale for estimand: The occurrence of the intercurrent event of rescue therapy is informative about the effect of treatment. If a subject is administered rescue therapy after Day 28, it may be considered that the allocated treatment was not effective, and the subject was not successfully treated. Taking rescue therapy will confound treatment effect. The intercurrent event of treatment discontinuation is considered to be part of the treatments being compared, reflecting the Intention-to-treat principle.

Supplementary analysis will be performed for the primary efficacy endpoint using a treatment policy strategy to address both intercurrent events of rescue therapy and treatment discontinuation (ie, including data collected after rescue or therapy and treatment discontinuation in the analysis). Details will be specified in the SAP.

The primary endpoint will be analyzed using a mixed-effects model for repeated measures (MMRM) analysis with covariates of treatment group, baseline antibody status (AChR-Ab+ or MuSK-Ab+), visit, the interaction of visit and treatment group, baseline steroid use, baseline QMG score, and baseline MG-ADL score. The estimate of the treatment effect estimator will be based on a contrast from this MMRM model. The variance-covariance matrix will be assumed to be unstructured. If the procedure doesn't converge, then a compound symmetric variance-covariance matrix will be applied.

To assess the robustness of the treatment effect, for each estimand, additional sensitivity analyses utilizing multiple imputation (MI) approaches will also be conducted with the missing data imputed for the subjects who discontinue the study early based on the different missing data mechanism assumptions, including those expected to be more conservative such as missing not at random. For example, the missing data would be imputed [redacted]. Full details of the analyses will be prespecified in the SAP.

9.4.2 Analysis of Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints include:

1. Change from baseline in QMG score at Week 26 in the overall study population.
2. Change from baseline in MG-ADL score at Week 26 in the AChR-Ab+ population.
3. Change from baseline in QMG score at Week 26 in the AChR-Ab+ population.
4. Change from baseline in MG-ADL score at Week 26 in the MuSK-Ab+ population.
5. Change from baseline in QMG score at Week 26 in the MuSK-Ab+ population.

The primary estimand of the changes from baseline is defined as follows:

- Population: Subjects in the FAS.
- Variable (endpoint): Change from baseline at Week 26.
- Intercurrent events:
  - Rescue therapy initiated after Day 28 during the RCP will be analyzed using a composite strategy. The data collected on or after the initiation of the rescue therapy will be imputed using the subject's worst observation collected before initiation of the rescue therapy.
  - Rescue therapy initiated on or before Day 28 during the RCP and treatment discontinuation will be analyzed using a treatment policy strategy. Subjects who discontinue treatment early will be asked to attend scheduled evaluations until the end of the RCP. The data collected after treatment discontinuation for reasons other than rescue therapy will be included in the analysis.
- Population-level summary: Mean difference between inebilizumab and placebo.

Supplementary analysis will be performed using a treatment policy strategy to address both intercurrent events of rescue therapy and treatment discontinuation (ie, including data collected after rescue or therapy and treatment discontinuation in the analysis).

The estimate of the treatment effect estimator for the overall study population will be based on a contrast from an MMRM model with covariates of treatment group, baseline antibody status (AChR-Ab+ or MuSK-Ab+), visit, the interaction of visit and treatment group, baseline steroid use, baseline QMG score, and baseline MG-ADL score.

The estimate of the treatment effect estimator for the AChR-Ab+ population or for the MuSK-Ab+ population will also be based on a contrast from an MMRM model but with covariates of treatment group, visit, the interaction of visit and treatment group, baseline steroid use, baseline QMG score, and baseline MG-ADL score.

Additional sensitivity analyses using MI approaches will also be conducted based on different missing data mechanism assumptions as suitable.

Details of the key secondary efficacy analyses will be included in the SAP.

9.4.3 Analysis of Additional Secondary Efficacy Endpoints

The additional secondary efficacy endpoints include:

1. The proportion of subjects with ≥ 3-point improvement in MG-ADL score at Week 26 and no use of rescue therapy between Day 28 and Week 26 in the overall study

population, the AChR-Ab+ population, and the MuSK-Ab+ population, and at Week 52 and no use of rescue therapy between Day 28 and Week 52 in the AChR-Ab+ population.
2. Change from baseline in MG-ADL score at Week 52 in the AChR-Ab+ population.
3. Change from baseline in QMG score at Week 52 in the AChR-Ab+ population.
4. Change from baseline in MGC score at Week 26 and no use of rescue therapy between Day 28 and Week 26 in the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population, and at Week 52 and no use of rescue therapy between Day 28 and Week 52 in the AChR-Ab+ population.
5. Change from baseline in MGQOL-15r score at Week 26 in the overall study population, AChR-Ab+, and MuSK-Ab+ and at Week 52 in AChR-Ab+ Week 26 in the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and at Week 52 in the AChR-Ab+ population.
6. PGIC score at Week 26 in the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and at Week 52 in the AChR-Ab+ population.
7. Time to first MG exacerbation by Week 26 in the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and by Week 52 in the AChR-Ab+ population. Where an exacerbation is defined as one of the following:

- Use of protocol-defined rescue therapy, or
- Myasthenic crisis, defined as worsening of myasthenic weakness requiring intubation or noninvasive ventilation to avoid intubation, except when these measures are employed during routine postoperative management, or
- Significant symptomatic worsening to a score of 3 or a 2-point increase from baseline on any one of the individual MG-ADL items other than double vision or eyelid droop.

8. The safety and tolerability of inebilizumab as measured by the incidence of TEAEs, AESIs, and TESAEs. Laboratory measurements will also be evaluated as part of safety
9. The proportion of subjects with steroid tapered to ≤ 5 mg/day at Week 26 for the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and at Week 52 for the AChR-Ab+ population.
10. The proportion of subjects in whom steroid dose was reduced by ≥ 50% by Week 26 for the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population and by Week 52 for AChR-Ab+ population.
11. The proportion of subjects achieving minimal symptom expression, defined as MG-ADL = 0 or 1, at Week 26.
12. Anti-drug antibody status and titer during the study in the overall study population, the AChR-Ab+ population, and the MuSK-Ab+ population.

9.4.3.1 Analyses of the proportion

The primary estimand of the proportion of subjects is defined as follows:

- Population: Subjects in the FAS.
- Variable (endpoint): responder at the timepoint of interest (ie, a subject who achieved ≥ 3-point improvement from baseline in MG-ADL score at Week 26 [or Week 52] and received no rescue therapy between Day 28 and Week 26 [or Week 52] will be considered as an MG-ADL responder).
- Intercurrent events:

  - Rescue therapy: no rescue therapy after Day 28 during the RCP was part of the definition of the key secondary binary endpoints. A subject will be considered as a non-responder if rescue therapy was used between Day 28 and the timepoint of interest (Week 26 or Week 52).
  - Rescue therapy initiated on or before Day 28 during the RCP and treatment discontinuation will be analyzed using a treatment policy strategy. Subjects who discontinue treatment early will be asked to attend scheduled evaluations until the end of the RCP. The data collected after treatment discontinuation for reasons other than rescue therapy will be included in the analysis.

- Population-level summary: difference of the inebilizumab vs placebo groups in the proportion of the responders regardless of treatment discontinuation.

Subjects will be considered as non-responders if they discontinue from the study before the timepoint of interest (Week 26 or Week 52).

The estimate of the treatment effect estimator will be evaluated using logistic regression with covariates of treatment group, baseline antibody status (AChR-Ab+ or MuSK-Ab+), baseline steroid use, baseline MG-ADL, baseline QMG score, and the corresponding baseline score. Sensitivity analyses may also be conducted for the proportions using a Cochran-Mantel-Haenszel test controlling for baseline antibody status (AChR-Ab+ or MuSK-Ab+), baseline steroid use, and baseline disease severity.

9.4.3.2 Analyses of the changes from baseline

The primary estimand of the changes from baseline is the same as the one defined for the key secondary endpoints as mentioned in Section 9.4.2. The estimate of the treatment effect estimator will also be based on a contrast from an MMRM approach with covariates of treatment group, baseline antibody status (AChR-Ab+ or MuSK-Ab+; this covariate is only needed for overall study population), visit, the interaction of visit and treatment group, baseline steroid use, baseline MG-ADL, baseline QMG score, and the corresponding baseline score (if the endpoint is not MG-ADL or QMG). For example, the estimate of the treatment effect estimator for change from baseline in MGC at Week 26 in the overall study population will be based on a contrast from an MMRM approach with covariates of treatment group, baseline antibody status, visit, the interaction of visit and treatment group, baseline steroid use, baseline MG-ADL, baseline QMG score, and baseline score MGC.

9.4.3.3 Analyses for the time to first exacerbation

The primary estimand with a treatment policy strategy is defined by the following:

- Target population: Subjects in the FAS.
- Variable: Time in days from Day 1 (dosing) to the date of the first exacerbation by the timepoint of interest (Week 26 or Week 52).
- Intercurrent event: All data captured from Day 1 to the timepoint of interest will be used for analysis. Subjects who do not complete the timepoint of interest and who have not had an exacerbation between Day 1 and the timepoint of interest will be censored at the time of discontinuation or at the timepoint of interest, whichever is earlier.
- Population-level summary: Hazard ratio between inebilizumab versus placebo.

The hazard rate in the inebilizumab group will be compared to that in the placebo group using a Cox proportional hazard model with covariates of treatment group, baseline antibody status (AChR-Ab+ or MuSK-Ab+), baseline steroid use status, baseline QMG score, and baseline MG-ADL score.

Details of the analyses will be prespecified in the SAP.

9.4.4 Analysis of Exploratory Efficacy Endpoints

[redacted]

9.4.5 Multiplicity Control

The type I error will be controlled at 0.05 (2-sided) across the primary and the key secondary endpoints. A hierarchical approach will be applied for multiplicity control, and the testing strategy is proposed as follows:

- Step 1: Test the primary endpoint at a significance level of 0.05; if the p-value is < 0.05, then proceed to Step 2. Otherwise, no null hypothesis is rejected.
- Step 2: Test the key secondary endpoints at a significant level of 0.05 sequentially at alpha level 0.05 in the following order:
  - Change from baseline in QMG score at Week 26 in the overall study population.
  - Change from baseline in MG-ADL at Week 26 in the AChR-Ab+ population.
  - Change from baseline in QMG score at Week 26 in the AChR-Ab+ population.
  - Change from baseline in MG-ADL at Week 26 in the MuSK-Ab+ population.
  - Change from baseline in QMG score at Week 26 in the MuSK-Ab+ population.

9.4.6 Subgroup Analyses

To explore the consistency of treatment effect, subgroup analyses will be performed for the primary and the key secondary endpoints in the following subgroups:

- Baseline antibody type (AChR-Ab+ vs MuSK-Ab+).
- Gender (Male vs Female).
- Age (≥ 18 < 65 years vs ≥ 65 years).
- Baseline MG disease duration (< 5 years vs ≥ 5 years).
- Baseline steroid use (prednisone ≤ 20 mg/day vs prednisone > 20 mg/day).
- Baseline IST use (steroid only vs steroid plus 1 other IST).
- Baseline QMG score (≤ 15 vs ≥ 16).
- Baseline MGFA class (Class II vs III vs IV).
- Region (US vs non-US; Japan vs non-Japan; China vs non-China; Asia vs non-Asia; EU vs non-EU).
- Racial/ethnic subgroups as needed for national/regional regulatory filings.

All the analyses will be performed on the FAS. Additional subgroup analyses by the length of inebilizumab exposure may be performed on the Any Inebilizumab Analysis Set. Details would be included in the SAP.

9.4.7 Safety Analysis

The safety analysis will be based on the Safety Analysis Set using treatment-policy strategy and while on-treatment strategy. Safety endpoints will be summarized for the RCP, OLP, combined RCP and OLP, and SFU if applicable, respectively. The number and percentage of subjects reporting TEAEs will be summarized by SOC and PT, severity, and relationship to the IP. The number and percentage of subjects reporting SAEs and AESIs will also be summarized. The rate of AEs per 100 person-years at risk, calculated as (total number of AEs)/(total person-years) × 100, will also be reported. The risk difference and corresponding 95% CI will be presented for the analysis based on the RCP, if applicable. Laboratory, vital signs, and ECG measurements, including changes from baseline and shift from baseline if applicable, will be summarized descriptively.

9.4.8 Pharmacokinetics Analysis

PK analyses will be based on the PK Analysis Set. Descriptive statistics of inebilizumab concentration data will be summarized.

9.4.9 Immunogenicity Analysis

The ADA status and titer will be summarized using descriptive statistics. The impact of ADA on PK, PD, safety, and efficacy will be evaluated if data allow.

9.5 Planned Analyses

Primary analyses: The primary analysis will be conducted when all subjects have completed Week 26 or, if a subject discontinues early from the study before Week 26. All efficacy and safety data collected during the RCP and prior to the data cut-off for the primary analysis will be analyzed. In addition, the safety data collected during the OLP and prior to the data cut-off will also be analyzed. The AChR-Ab+ subjects who haven't completed the RCP will complete the remaining visits during the RCP per protocol.

Final analysis: The final analysis will be conducted when all subjects have completed (or discontinued early from) the study.

10 ETHICAL CONSIDERATIONS

10.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure, Investigational Directions for Use, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study subjects.
- The Investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations

10.2 Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB/IEC, as appropriate. The Investigator must submit written approval to the Sponsor or representative before he or she can enroll any subject into the study.

The Principal Investigator is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB/IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB/IEC upon receipt of amendments and annually, as local regulations require. The Principal Investigator is also responsible to adhere to requirements stipulated by the respective IRB/IEC and for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from

any other study conducted with the IP. The Sponsor will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/IEC according to local regulations and guidelines. Copies of all correspondence between the Investigator and the IRB/IEC are provided to the Sponsor's representative.

10.3 Informed Consent

The Investigator or other members of the study site's treatment team will ensure that the subject or legally authorized representative is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Subjects or legally authorized representatives must also be notified that they are free to discontinue from the study at any time. The subjects or legally authorized representatives will be informed that their study record and medical records/documents that pertain directly to the study will be reviewed and possibly copied by the Sponsor or its designee, or a governmental agency (such as FDA), and that every effort will be made to maintain subject confidentiality. The subject or legally authorized representative should be given the opportunity to ask questions and allowed time to consider the information provided.

The ICF must be witnessed and dated by the Investigator or his/her designee, and the original retained by the Investigator/study site as part of that subject's record. The site should document the consent process.

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject or legally authorized representative.

The ICF must be fully approved by an IRB/IEC prior to its use with study subjects.

10.4 Data Privacy

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is obtained from the Sponsor. However, authorized regulatory officials, IRB/IEC personnel, and the Sponsor and its authorized representatives, are allowed full access to the records.

Identification of subjects and eCRFs shall be by screening and treatment numbers only.

10.5 Disclosure

Sponsor is responsible for preparing and providing the appropriate regulatory authorities with Clinical Study Reports, according to the applicable regulatory requirements. Mitsubishi Tanabe Pharma Corporation, is responsible for providing the Clinical Study Reports to the applicable regulatory authorities in regions where they are the MAH.

10.6 Biological Specimens and Data

Biological Samples Obtained for the Main Study

Study data are protected by the use of an SID number, which is specific to each subject. The Investigator is in control of the information needed to associate a study sample with a subject. A subject's consent to the use of data does not have a specific expiration date, but the subject

may withdraw consent at any time by notifying the Investigator. If consent is withdrawn, any samples collected prior to that time may still be given to and used by the Sponsor, but no new samples will be collected unless specifically required to monitor safety of the subject.

In applicable countries, if the subject consents to have their samples used for future research, this additional research may not start immediately and may start at any time during the storage period. The subject's sample(s) will be stored by the Sponsor with similar samples from other subjects at a secure laboratory. The subject's samples will not be kept for more than 25 years after the end of the study in which they were collected. If the subject does not consent to allow their study samples to be used for future research, the samples will be destroyed by the Sponsor once they are no longer required for the study. However, if the subject's samples have already been used for research, the Sponsor is not required to destroy results of this research. In this case, only the remaining sample(s) will be destroyed.

11 OVERSIGHT

11.1 Quality Control and Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Refer to Section 11.3 for details regarding the audit process.

11.2 Monitoring

Before an investigational site can enter a subject into the study, a representative of the Sponsor or the CRO will visit the investigational study site to:

- Determine the adequacy of the facilities.
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement (CSA) between the Sponsor and the Investigator.

During the study, a representative from the Sponsor will have regular contact with the investigational site for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm compliance with the principles of GCP and regulatory requirements.
- Review of written ICFs for subjects screened/enrolled.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that IP accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject medical records at the hospital or practice, and other records relevant to the study for accuracy and completeness. This will require direct access to all original medical and other study-related records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously reported to the Sponsor.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm that any SAEs have been forwarded to the Sponsor or representative, and those SAEs that met criteria for reporting have been forwarded to the IRB.
- During scheduled monitoring visits, the Investigator and the investigational site staff must be available to meet with the site monitor in order to discuss the progress of the study, make necessary corrections to case report form entries, respond to data clarification requests, and respond to any other study-related inquiries from the monitor.

11.3 Serious Breach

Suspected Serious Breaches must be reported to the study team or the Clinical Out-of-Hours Support Program: https://wwwext.amgen.com/science/clinical-trials/clinical-out-of-hours-support-program immediately and no later than 1 calendar day from the time of awareness.

A Serious Breach is a breach of any of the following:

- GCP
- The clinical trial protocol
- An applicable regulation

That is likely to impact to a significant degree either of the following:

- The safety, physical, or mental integrity and the rights of the subject
- The reliability and robustness of the data and the scientific value of the trial

11.4 Audits

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or its authorized representatives may conduct a quality assurance audit.

Authorized representatives of the Sponsor, a regulatory authority, an IRB/IEC may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements.

Initial IRB approval and all materials approved by the IRB for this study, including the ICF and recruitment materials, must be maintained by the Investigator and made available for inspection.

In addition to the above, representatives of the Sponsor's auditing staff or government inspectors may review the conduct/results of the study at the investigational site. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection. The Investigator cooperates with the auditor(s) and/or inspectors, makes available to them all requested documentation, and ensures that issues detected during the course of these audits or inspections are satisfactorily resolved. The Investigator supplies the Sponsor with copies of all documentation and correspondence related to regulatory agency audits as outlined in the CSA. If the results of the audit result in a Form FDA-483 (or similar document from another regulatory agency), the Investigator promptly provides a copy to a Sponsor representative and a draft response to the Sponsor prior to submission to the regulatory agency.

11.5 Records

11.5.1 Data Capture and Management

Clinical Data Management (CDM) will be performed according to the Data Management Plan (DMP). The DMP will document procedures, roles, and responsibilities related to CDM activities, including data validation, data transfer and reconciliation, CDM communications, medical coding and dictionaries, CDM reports, and data formats.

A 21 CFR Part 11-compliant electronic data capture system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the eCRF Completion Guidelines provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the CSA. The Investigator will sign the completed eCRFs electronically. Upon completion of the study, a copy of the completed eCRFs will be provided to the study site for archival purposes.

11.5.2 Source Documentation

The Sponsor and its representatives will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, IP stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

11.5.3 Records Retention

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval and until there are no pending or contemplated marketing applications in an ICH region, or, if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or the regulatory authority to review any documentation relating to the study, the Investigator must permit access to such records.

For EU countries, study documentation will be retained for a minimum of 25 years and will be governed by the Clinical Trial Agreement.

11.6 Results Reporting

Results will be reported to clinical study registries in accordance with applicable regulatory requirements. The final summary results will be reported after the global end of study (as defined in Section 6.5) to ensure data from all sites globally are included in the reported results.

12 PUBLICATION POLICY

The Sponsor's publication policy is discussed in the Investigator's Clinical Research Agreement. All site Investigators who randomized a study subject will be offered the opportunity to be included as a member of the study group for authorship on the primary results manuscript.

13 PROTOCOL CHANGES

All changes described below have been incorporated into the current version of the protocol.

13.1 Version 9.0

Reason for Amendment	Primary: Change in strategy	Other: New safety information available Administration, typographical, and formatting changes were made throughout the protocol
Amendment Summary	IB update Safety follow-up is being made mandatory for all subjects Update to unblinding plan Sponsor address change Updates to requirements for Japan safety reporting after UPLIZNA is approved in Japan Initials are no longer a valid form of patient identification	
Is this amendment likely to have a substantial impact on:		
- safety or rights of the participants		Yes, due to safety follow-up made mandatory for all subjects
- the reliability and robustness of the data generated in the clinical trial		Yes, due to change to blinding plan

- Section Title Page: Updated amendment number, version number, and Sponsor address.
- Section 1 (Synopsis): Revised the text for length of participation, to provide a succinct description of the safety follow-up visit and its duration. The revised text also aligns with MITIGATE study (Study 20230068).
- Section 6.1.4 (Safety Follow-up): Revised the language in this section to clarify that the safety follow-up is mandatory for all study subjects, regardless of the subjects not entering the open-label phase or if they discontinue the investigational product at any point in the study. Associated changes were made throughout the protocol to reflect updates to safety follow-up.
- Section 7.1.3 (Reporting Product Complaints): Clarification was added to the definition of product complaints and updates were made to the reporting process.

- Section 7.3.3 (Extent and Maintenance of Blinding) and Section 9.5 (Planned Analyses): Updated the language in these sections to clarify the conditions and duration of blinding for study and sponsor personnel and the subjects.
- Section 7.5.2 (Prohibited Medications and Treatments): Added language to outline the prohibited medications and treatments during SFUP.
- Section 8.3 (Reporting Adverse Events): Added language to clarify adverse event reporting requirements of certain events in Japan and globally.
- Section 10.4 (Data Privacy): Removed initials as a form of identification for subjects and eCRFs as it is no longer a valid form of subject identification.
- Section 10.5 (Disclosure): Added new section to outline the responsible personnel for dissemination of clinical study reports.

13.2 Version 8.0

- Section Title Page: Added EU Number and Trade Name. Updated Sponsor name and address, and Medical Officer name and contact information.
- Section 1 (Synopsis): Deleted exploratory objectives and endpoints as this section will be publicly distributed.
- Section 3.3.2 (Exploratory Endpoints): [redacted]
- Section 4.1 (Study Design): Updated Figure 1 (Study Flow Diagram) to include the SFU Period.
- Section 5.1 (Inclusion Criteria): Corrected to update that non-sterilized males who are sexually active with a female partner of childbearing potential must use a condom for 6 months after the last dose of IP (criterion number 10).
- Section 6.1.5.1 (Remote Visits and/or Procedures): Added text regarding missed assessments during remote visits.
- Section 6.5 (End of Study): Added the definition of end of study date.
- Section 6.6 (Data Monitoring Committee): Added text regarding meetings archived in the trial master file.
- Section 7.1.1.1 (Investigational Product Inspection): Added a reference to the Sponsor's contact information (Section 7.1.3).
- Section 8.3 (Reporting Adverse Events): Added language to align with Amgen safety standards. Updated contact details (email address and fax numbers).
- Section 8.4.1 (Pregnancy and Lactation): Added pregnancy and lactation language to align with Amgen safety standards.

- Section 8.7 (Regulatory Reporting Requirements for Safety Information): Added text regarding regulatory reporting requirements for safety information to align with current regulatory requirements.
- Section 9.3 (Analysis Sets): Revised text regarding the Per-protocol Analysis Set to simplify the definition.
- Section 9.4.1 (Analysis of the Primary Efficacy Endpoint) and 9.4.2 (Analysis of Key Secondary Efficacy Endpoints): Removed '(as a continuous variable)' from the baseline QMG score.
- Section 9.4.6 (Subgroup Analyses): Added 'China' to the Region subgroup. Removed '3 or more ISTs' from the Baseline IST use subgroup.
- Section 9.5 (Planned Analyses): Clarified text regarding the collection of efficacy and safety data.
- Section 11.3 (Serious Breach) and Section 11.6 (Results Reporting): Added new sections to align with regulatory requirements.
- Section 11.5.3 (Records Retention): Added text regarding study documentation retention according to Clinical Trial Agreement.
- In various sections, replaced "patient(s)" with "subject(s)" when describing participants in the study to be consistent with Version 7.0 and Version 6.0 changes.
- Additional minor editorial revisions to text were made throughout the document for clarity.

13.3 Version 7.0

- Section 2.1 (Background): Revised text to describe how MG subpopulations are differentiated and how MuSK antibody positive MG is characterized. Added text on the role of B-cells in MG pathogenesis, the differential efficacy observed with the depletion of CD20+ B-cells in studies, and the potential of a CD19+ B-cell-depleting therapy to offer enhanced efficacy across MG subpopulations.
- Section 2.1.1 (Description of Inebilizumab): Revised text to note inebilizumab's increased affinity for the Fcγ receptor IIIA and its ability to induce antibody-dependent cellular phagocytosis.
- Section 2.1.2.1 (Pharmacology): Added text on nonclinical findings that demonstrated the effectiveness of inebilizumab in targeting pathogenic B-cells in a neuro-inflammatory setting.
- Section 2.1.3 (Supportive Clinical Data for Inebilizumab): Added the US as a country in which inebilizumab has already been approved.
- Section 2.1.4 (Risk Assessment for Inebilizumab): Added lymphopenia to the list of identified risks. Added the respective severity (mild or moderate) for Grade 1 or 2 IRRs. Added the study (Study CD-IA-MEDI-551-1155) in which 3 pregnancies occurred in exposed subjects and a summary of the effects observed.

- Section 2.1.5 (Anticipated Study Benefits and Risks): Revised the rationale for the tapering of prednisone to emphasize the risk of morbidity associated with long-term use of moderate- or high-dose corticosteroids.
- Section 3.1.2 (Primary Endpoint): Revised the primary endpoint to state that MG-ADL score will be measured for the overall population at Week 26, instead of separately for the 2 populations at different timepoints (ie, Week 52 for AChR-Ab+ subjects). The shortened duration is based on previous study experience with inebilizumab in NMOSD, in which CD19-mediated B-cell depletion was efficacious within 26 weeks. The pooling of the 2 populations is supported by the expectation that a CD19 B-cell-depleting drug will offer similar levels of efficacy in both populations, as CD19 B-cells are expressed earlier in development than CD20 B-cells.
- Section 3.2.1 (Secondary Objectives): Relocated the following objectives from Exploratory to Secondary:
    - To evaluate the effect of inebilizumab on corticosteroid usage.
    - To evaluate the ability of inebilizumab to elicit minimal symptom expression.
- Section 3.2.2 (Secondary Endpoints):
    - Key secondary endpoints: Revised endpoints to note that all changes will be measured from baseline at Week 26. Added endpoints for MG-ADL scores and QMG scores for the MuSK-Ab+ population. Relocated an endpoint (for the proportion of subjects who demonstrated improvement in scores and did not initiate rescue therapy) to additional secondary endpoints, and revised the endpoint to state that it is measured in the overall study population and the MuSK-Ab+ population at Week 26, and the period of no rescue therapy is [redacted], and measured in the AChR-Ab+ population at Week 52, and the period of no rescue therapy is [redacted]
    - Additional secondary endpoints: Revised endpoints to note that all changes will be measured from baseline. Revised endpoints for MGC score, MGQOL-15r score, and PGIC score so they will be measured at Week 26 in the overall population, AChR-Ab+, and MuSK-Ab+, and at Week 52 for the AChR-Ab+ population. Revised an endpoint on ADA status and titer so they will be measured during the study in the overall study population, AChR-Ab+, and MuSK-Ab+. Relocated the following endpoint from Exploratory to Additional secondary: The proportion of subjects achieving minimal symptom expression, defined as MG-ADL = 0 or 1, at Week 26. Removed an endpoint for PK profile of inebilizumab. Added the following endpoints:
        - Change from baseline in MG-ADL score at Week 52 in the AChR-Ab+ population.
        - Change from baseline in QMG score at Week 52 in the AChR-Ab+ population.
        - Time to first MG exacerbation by Week 26 in the overall study population, AChR-Ab+, and MuSK-Ab+ and by Week 52 in AChR-Ab+.

        - The proportion of subjects with steroid tapered to ≤ 5 mg/day at Week 26 for the overall study population, AChR-Ab+, and MuSK-Ab+ and at Week 52 for AChR-Ab+.
        - The proportion of subjects in whom steroid dose was reduced by ≥ 50% by Week 26 for the overall study population, AChR-Ab+, and MuSK-Ab+ and by Week 52 for AChR-Ab+.
    - Exploratory endpoints: [redacted]

- Section 4.1 (Study Design): Revised the number of subjects enrolled to 230 total, with 188 subjects with AChR-Ab+ MG and 42 subjects with MuSK-Ab+ MG. Removed text on the separate analysis of the 2 populations.
- Figure 1 (Study Flow Diagram): Updated the total number of subjects who are MuSK+ to 42, moved the primary outcome to reflect the same timepoint (Week 26) for both populations, and revised the open-label period so that it applies to both populations. Added duration of SFU Period and criteria for subjects who will be encouraged to complete SFU to the footnotes.
- Section 4.2 (Dose and Treatment Regimen Rationale): Revised text so the dosing regimen will be the same for each population and matches that used in Study 1155. Revised rationale for the dosing regimen.
- Section 4.3 (Rationale for Study Population): Removed text on the separate analysis of the 2 populations. Revised the description of inclusion criteria.
- Section 4.4 (Rationale for Endpoint Selection): Updated the primary endpoint. Added text on efficacy observed within 26 weeks in previous study experience with inebilizumab, and similar expectations in this study. Updated secondary endpoints.
- Section 5.2 (Exclusion Criteria): Added SC Ig to the list of substances prohibited within 4 weeks prior to Day 1 (criterion number 13).
- Section 6.1.2 (Randomized Controlled Period): Updated the duration of the RCP for each population and the timepoint for the primary efficacy endpoint. Added text on efficacy observed in previous studies with inebilizumab. Added description of study conduct after Week 26 for each population. Added description of blinding procedures and data handling.
- Section 6.1.3 (Open-label Period): Added the study OLP duration (3 years) for both populations.
- Section 6.1.4 (Safety Follow-up): Added text on study conduct for subjects who discontinue IP.
- Section 6.2.5.2 (Collection of ePRO Assessments): Added text on the use of paper forms.

- Section 6.2.5.9 (Myasthenia Gravis Composite Score): Removed the statement that the MGC score is determined by an independent rater.
- Section 6.3.1 (Discontinuation of Treatment): Added that consult with the Sponsor medical director is needed in circumstances 1 and 3. Added text on study conduct for subjects who discontinue IP.
- Section 7.1.1.4 (Dosing and Administration): Language revised on response to infusion reactions for clarification.
- Section 7.2.1 (Oral Corticosteroid Taper): Revised the rationale for the tapering of prednisone to emphasize the risk of morbidity associated with long-term use of moderate- or high-dose corticosteroids.
- Section 7.3.3 (Extent and Maintenance of Blinding): Removed text on the separate analysis of the 2 populations and added the shared timepoint for the primary efficacy analysis. Added text on blinding procedures after Week 26.
- Section 7.5.2 (Prohibited Medications and Treatments): Added requirements for corticosteroid, non-steroidal IST, and acetylcholinesterase inhibitor use. Added text to clarify that several medications allowed as continuous at study entry may not be allowed if newly prescribed during the study.
- Section 8.1 (Definitions): Added that the Investigator will determine the severity for events not listed in the CTCAE, and added respective severity descriptions (mild, moderate, severe, life-threatening, fatal) for Grades of 1 through 5.
- Section 9.1 (General Considerations): Removed text on the separate analysis of the 2 populations.
- Section 9.2 (Determination of Sample Size): Added the primary efficacy endpoint. Added rationale for the sample size of each population. Updated the study population numbers.
- Section 9.4 (Methods for Statistical Analyses): Removed text on the primary and supplemental estimands. Updated text on the composite strategy for binary and continuous efficacy endpoints. Added text to clarify study periods during which efficacy and safety endpoints may be summarized.
- Section 9.4.1 (Analysis of the Primary Efficacy Endpoint): Updated the primary efficacy endpoint. Updated text on the primary estimand and primary endpoint analysis.
- Section 9.4.2 (Analysis of Key Secondary Efficacy Endpoints): Updated the key secondary efficacy endpoints. Updated text on the primary estimand. Updated text on the estimate of treatment effect.
- Section 9.4.3 (Analysis of Other Secondary Efficacy Endpoints): Updated the additional secondary endpoints.
- Section 9.4.3.1 (Analyses of the proportion): Created new section. Added text on the primary estimand and revised text on the estimate of treatment effect.
- Section 9.4.3.2 (Analyses of the changes from baseline): Added text on the primary estimand and the estimate of treatment effect.

- Section 9.4.3.3 (Analyses for the time to first exacerbation): Added text on the primary estimand and revised text on hazard rate.
- Section 9.4.4 (Analysis of Exploratory Efficacy Endpoints): Updated the exploratory endpoints.
- Section 9.4.5 (Multiplicity control): Removed text on the separate analysis of the 2 populations. Updated text on type I error control and the hierarchical approach proposed. Updated text on secondary endpoints.
- Section 9.4.6 (Subgroup Analyses): Updated the list of subgroups to be analyzed.
- Section 9.4.7 (Safety Analysis): Removed text on the separate analysis of the 2 populations. Clarified study periods during which safety endpoints may be summarized, and added that the rate of AEs per 100 person-years at risk will be reported. Added that risk differences and corresponding 95% CI may also be presented, if applicable.
- Section 9.4.8 (Pharmacokinetics Analysis): Removed details of PK parameters to be analyzed.
- Section 9.5 (Planned Analyses): Updated text on the timing for the primary analysis. Added text on the study conduct for AChR-Ab+ subjects who haven't completed the RCP. Added text on blinding procedures. Revised text to state that the final analysis will be completed following study completion or early discontinuation by all subjects.
- In various sections, replaced "patient(s)" with "subject(s)" when describing participants in the study to be consistent with Version 6.0 changes.
- Additional minor revisions to text were made throughout the document for clarity.

13.4 Version 6.1

- Section 6.1.3 (Open-label Period): Day 792 corrected to Day 729.
- Section 6.2.5.2 (Collection of electronic Patient-reported Outcomes Assessments): Reference to paper collection was removed.
- Table 5 (Open-label Period Procedures for AChR-Ab+ and MuSK-Ab+ Populations): Day 730 corrected to Day 729.
- Table 5: Addition of OLP Day 15 C-SSRS at Day 15 (as this was erroneously removed from Protocol V6.0).
- Table 5: Removal of IP Administration at Day 1093 (± 20d) or EDV to provide consistency with verbiage in Section 6.1.3 and 6.1.4, respectively.
- Table 5, footnote "h" text separated into text for footnotes "h" and "i" as this was erroneously captured as 1 footnote instead of 2 in the previous version. Due to this update, previous footnotes "i" and "j" have been appropriately updated to "j" and "k", respectively.
- Table 5, Column "OLP Week 156, Day 1093 (±20d) or EDV", superscript letter "j" updated to "k" to corresponded to applicable footnote text.

- Section 13 (Protocol Changes): Changes under Version 6.0 updated to remove inaccurate changes: 1) deletion of change related to Section 6.3.2 title (as no change occurred); 2) deletion of change related to removal of [redacted] (as this remains included in the study).

13.5 Version 6.0

- Global change: The word "participant(s)" is changed to "subject(s)" for consistency.
- Global change: All brand names of the medications throughout the protocol have been removed for consistency.
- Title page: National Clinical Trial (NCT) number is added. Sponsor information and Responsible Medical Officer have been updated to reflect staff change.
- Sponsor Signature page: A new Sponsor page was included with Medical and Biostatistics Representative information.
- List of Appendices and Appendices: Updated to include listing of Opportunistic infections.
- List of Abbreviations page, Section 5.2 (Exclusion Criteria), and Section 7.5.2 (Prohibited Medications and Treatments): Updates are made to include neonatal fragment crystallizable (Fc) receptor blockers since it is a new stable IST treatment option for chronic therapy and rescue.

- Section 1 (Synopsis): Protocol number added as an independent row for consistency.
- Section 1 (Synopsis), Section 3.2.2 (Secondary Endpoints), Section 4.4 (Rationale for Endpoint Selection), and Section 9.4.2 (Analysis of Key Secondary Efficacy Endpoints): Key Secondary Endpoint number 2 has been updated to be maintain consistency with the primary analysis and to utilize more observed data.
- Section 1 (Synopsis), Figures 1, 2, and 3, Section 4.1 (Study Design), Section 6.1.3 (Open-label Period), Table 5 (Open-label Period Procedures for AChR-Ab+ and MuSK-Ab+ Populations [columns and footnote]), Section 6.3.1 (Discontinuation of Treatment), Section 6.3.2 (Withdrawal from Study), Section 6.5 (End of Study), and Table 6 (Description of Investigational Products and Dosing Regimens): Updated information on blinding and extension of OLP to allow long-term safety and efficacy data collection.

- Section 2.1.3 (Supportive Clinical Data for Inebilizumab) and 2.2 (Study Rationale): Updated information about inebilizumab to inform that it has been approved in other countries.
- Sections 3.2.2 (Secondary Endpoints), Section 4.4 (Rationale for Endpoint Selection), and Section 9.4 (Methods for Statistical Analyses): Key secondary endpoint updated to clarify timeline of rescue therapy use for AChR-Ab+ and MuSK-Ab+ subjects.
- Section 4.2 (Dose and Treatment Regimen Rationale): Updated to clarify there is no expected difference in inebilizumab PK between subjects with NMOSD and MG, the proposed dose regimen is expected to be well-tolerated and achieve similar PD effect in subjects with MG.
- Section 4.3 (Rationale for Study Population); Tables 3, 4 and 5 (Schedules of Study Assessment for AChR-Ab+ population, MuSK-Ab+ population and Open-label period and footnotes); Section 6.2.5.2 (Timing of Efficacy Assessments); and Section 9.4 (Methods for Statistical Analyses): The time was changed from 12 hours to 6 hours to allow for shorter time for subjects to hold acetylcholinesterase inhibitors while continuing to safeguard the collection of MG-ADL. Expanded Pyridostigmine to Acetylcholinesterase inhibitors. Clarified corticosteroid dose to include prednisone or its derivatives.
- Section 5.1 (Inclusion Criteria), Section 6.2.4 (Verification of Eligibility): Updated the MG-ADL scoring criteria to ensure adequate non-ocular scoring across a broad range of MG-ADL.
- Section 5.2 (Exclusion Criteria): Instruction to refer reader to Inclusion Criterion #7 in Exclusion Criterion #13 “b.” New drug class added under bullet point 11 and 12 to broaden the range of medications in these categories. Exclusion criterion was further clarified. 2 new exclusion criteria have been added to ensure that subjects entering the study are clinically and IST stable to ensure accurate baseline assessments. Hepatitis C exclusion criterion (Section 5.2, criterion #24) has been expanded to exclude subjects with a history of untreated hepatitis C infection or who have tested positive for HCV, unless the subject is considered to be cured following antiviral therapy.
- Section 6.1.1 (Screening Period), and footnote “c” of Table 2 (Screening Procedures [Visit 1]): Language updated to allow for the use of reference ranges provided by both labs used in the study. Clarified that re-screened subjects are not required to repeat serostatus testing as long as positive serostatus screening result within prior 6 months was done using cut-off points associated with the validated tests.
- Section 6.1.4 (Safety Follow-up Period): New section added to describe follow-up of subjects who do not enter OLP or discontinue IP during OLP. New Table 6: Safety Follow-up Period, was added to this section. This information is updated in Section 1 (Synopsis), Section 4.1 (Study Design), and Figure 2.
- Section 6.1.5.1 (Remote Visits and/or Procedures), Section 6.1.5.2 (Clinical Deterioration Visits), Section 6.1.5.3 (Unscheduled Visit), and Tables 3, 4, and 5 (Schedules of Study Assessment for AChR-Ab+ population, MuSK-Ab+ population and Open-label period

columns and footnotes): Have been added to clarify the difference between the Remote Visits and/or Procedures, Unscheduled Visit and the Clinical Deterioration visit.

- Section 6.1.5.3 (Unscheduled Visit): Updated to differentiate between Clinical Deterioration Visit and Unscheduled Visit.
- Section 6.1.5 (Special Visit Types) added to describe remote/home visits, clinical deterioration visits, and unscheduled visits. New table (Table 7: Procedures for Special Visit Types) was added to Section 6.1.5.
- Section 6.2.1 (Informed Consent): The section is updated to clarify that 2 separate ICFs need to be obtained, one each for the RCP and the OLP.
- Footnote I for Tables 3, 4, and 5 (Schedules of Study Assessment for aChR-Ab+ population, MuSk-Ab+ population and Open-label period): Updated to allow for flexibility of site dispensation of corticosteroids.
- Section 6.2.5.1 (Role of the Independent Rater): Split into 2 additional Sections 6.2.5.2 (Collection of Electronic Patient-reported Outcomes [ePRO] Assessments) and Section 6.2.5.3 (Timing of Efficacy Assessments), for clarity of the information presented. This addition of subsections caused re-organization of level 4 headers under the 6.2.5 level 3 header.

[redacted]

- Section 6.2.6.1 (Electrocardiogram): Added RR to include another interval for clarity of ECG information.
- Section 6.2.7 (Clinical Laboratory Assessments): Added Hepatitis C antibody under Viral Serology for consistency within the document.
- Section 6.3.1 (Discontinuation of Treatment): Updated to accommodate current study design.
- Section 6.3.2 (Withdrawal from Study): Updated information for clarity.
- Tables 3 (Randomized Controlled Period Schedule of Study Assessments for the AChR-Ab+ Population), 4 (Randomized Controlled Period Schedule of Study Assessments for the MuSK-Ab+ Population), and 5 (Open-label Period Procedures for aChR-Ab+ and MuSK-Ab+ Populations): Re-organized information regarding procedures and blood sampling into a new footnote h.
- Table 8 (Description of Investigational Products and Dosing Regimens): Updated manufacturer information.
- Section 7.1.1.1 (Investigational Product Inspection) and Section 7.1.3 (Reporting Product Complaints): Updated contact information of the Sponsor’s Quality Assurance.
- Table 10 (Randomized Controlled Period Prednisone Tapering Schedule): Study Day information updated for clarity.

- Section 7.2.1 (Oral Prednisone Taper) and Section 7.2.2 (Rescue Medication): Verbiage changed from study drug to IP for clarity.
- Section 7.3.2 (Randomization Strategy and Procedures): Language updated to clarify that stratification should be based on Day 1 QMG.
- Section 7.5.2 (Prohibited Medications and Treatments): B-Cell Depleting Therapies and Other immunosuppressive medications and monoclonal antibody medications were updated to clarify list of medications prohibited during the study.
- Section 8.3 (Reporting Adverse Events), Section 8.4.1 (Pregnancy), and Section 8.4.2 (Overdose or Misuse): Updated Sponsor's contact information for SAE form and safety reporting procedures.
- Section 8.5 (Adverse Events of Special Interest): Reference was added for Appendix 4. removed table to make easy reference by calling out Section 8.3 with contact information. Added IRR to the list of considered AESIs.
- Section 9.3 (Analysis Sets): Updated information in Per-protocol Analysis Set to better evaluate treatment effect in efficacy and safety data.
- Section 9.4 (Methods for Statistical Analyses): Updated to clarify the definition of primary estimand and supplemental estimands for the primary and key secondary endpoints.
- Section 10.1 (Regulatory and Ethical Considerations): Prior subtitle for this section was Good Clinical Practice. Added more details for more clarification.
- Section 11.3 (Audits): Language was updated for clarification.
- Section 14 (References): Updated per literature search.

13.6 Version 5.0

- Cover page – Responsible Medical Officer have been updated to reflect staff change.
- Section 1 (Synopsis), 4.1 (Study Design) and Figure 1 (Study Flow Diagram and Footnote): Approximate number of subjects in the study has been updated (up to additional 16 AChR-Ab+ subjects and 2 additional MuSK-Ab+ were added), in order to account for potential increased heterogeneity in baseline therapy in Japan. The total number represent upper estimated limit and may be reduced based on number of subjects enrolled in Japan.
- Section 1 (Synopsis), 3.3.2 (Exploratory Endpoints) and 6.2.8 (Pharmacokinetics, Pharmacodynamic, Immunogenicity, and Biomarker Evaluations): [redacted]
- Section 1 (Synopsis) and 4.1 (Study Design): Approximate number of sites have been updated.

- Section 2.1.5 (Anticipated Study Benefits and Risks), 4.1 (Study Design), 4.3 (Rationale for Study Population), 6.1.3 (Open-label Period), 7.5.1 (Immunosuppressive Medications During the Screening Period): Updated to include the allowance and guidelines for use of tacrolimus in Japan.

- Sections 4.1 (Study Design) and 7.3.2 (Randomization Strategy and Procedures): Stratification criteria for Japan were changed to align with the allowance of tacrolimus in Japan to maintain balanced randomization of Japanese subjects.
- Figures 2 and 3 (Randomization Schemes for AChR-Ab+ population and MuSK-Ab+ population): header of figures have been updated from “Randomization Scheme” to “Design Scheme” for a more accurate representation of what these figures depict.
- Section 5.1 (Inclusion Criteria 1): Guidance on consent in Japan where legal adult age is >18 have been rewarded to include general guidance for all countries where legal adult age is > 18. Additionally, this was moved from under Inclusion Criterion #1 to under Inclusion Criterion #2 where the informed consent is discussed.
- Section 5.1 (Inclusion Criteria 7c), 5.2 (Exclusion Criteria 12b), 7.5.1 (Immunosuppressive Medication During the Screening Period) and 7.5.2 (Prohibited Medications and Treatments): Updated to allow the use of tacrolimus in Japan only since tacrolimus in Japan is part of the standard of care for MG.
- Section 6.1.1 (Screening Period): Updated to allow screening extension to accommodate delays in study supplies (eg, lab kits supply delay from central lab).
- Section 6.1.1 (Screening Period) and Table 2 (Screening Procedures, footnote c): Guidelines were added for re-screened subjects regarding repeat serostatus testing.
- Section 6.1.2.1 (Remote Visits or Procedures): Section was added to accommodate exceptional circumstances under which particular study visits or procedures may be performed remotely (eg, due to COVID-19 restrictions) and with agreement of the medical monitor.
- Section 6.1.3 (Open-label Period): Updated to include guidance for subjects on tacrolimus in Japan.

- Section 6.2.1 (Informed Consent): Guidance for countries where legal adult age is > 18 years has been added. Additionally, Clarification was added that participation and informed consent forms for [redacted] and use of leftover blood samples for future research are only done if applicable in that country as not all countries will be participating in these optional substudies.
- Section 6.2.5.3 (Myasthenia Gravis Quality of Life-15, revised): Total score for MGQOL-15r was corrected from 45 to 30 and name of assessment was corrected from MG-QOL15r to MGQOL-15r throughout for consistency.
- Section 6.2.7 (Clinical Laboratory Assessments): Revised to state that in some cases, safety labs can be done locally if preapproved by the Sponsor Medical Monitor.
- Table 6 (Description of Investigational Products and Dosing Regimens): Legal name of DP manufacturer had changed and was therefore updated in the table.
- Section 7.1.1.3 (Dose Preparation): Clarification was added regarding total time allowed for room temperature storage.
- Section 7.1.1.4 (Dosing and Administration): Reference to new Table 7 was added and "approximately" was added to the duration under IP infusion instructions.
- Section 7.1.3 (Reporting Product complaints): Phone numbers have been removed since these may be subject to change.
- Table 7 (Predose IV Corticosteroid Dose Conversion): was added to the protocol to provide guidance on alternatives to IV methylprednisolone and the equivalent doses. Table numbers of previous tables 7, 8 and 9 have been updated accordingly.
- Table 9 (Corticosteroid Dose Conversion): Updated to include the equivalent dose of hydrocortisone. Table number was updated from 8 to 9.
- Section 7.2.2 (Rescue Medication): Updated to clarify that rescue therapies should be recorded on study's rescue therapy dedicated eCRF pages.
- Section 8 (Safety Assessment): Clarification was added to Adverse Event section that MG exacerbation are an endpoint in the study and therefore will not be recorded as AEs or SAEs (with the exception of exacerbations that involve myasthenic crisis or death).
- Section 8 (Safety Assessment): Serious adverse event definition for hospitalization was updated to remove the requirement for > 1 day or overnight length of hospital stay, based on request received from the Denmark regulatory authority.
- Section 8.4.2 (Overdose or Misuse): Language has been shortened and updated to include only IP and remove steroids and infusion premedication from overdose definition.
- Section 8.5 (Adverse Event of Special Interest): Updated to include reporting procedure for AESI.
- Section 9 (Statistical Considerations): Number of subjects have been updated to allow additional 16 AChR-Ab+ subjects and 2 additional MuSK-Ab+; additional subgroup analyses information was provided.

- Section 9.4.4 (Analysis of Exploratory Efficacy Endpoints): [redacted].
- Section 9.4.6 (Subgroup Analyses): Updated to clarify the detailed subgroups in the analyses; added a subgroup analysis of Racial/ethnic subgroups as needed for national/regional regulatory filings.
- Section 10.1 (Good Clinical Practice): Reference to the Declaration of Helsinki was removed as the current version of Declaration of Helsinki was not adopted by the FDA.
- Section 10.5 (Biological Specimens and Data): Updated to clarify that the mentioning of future use of leftover samples is only in applicable countries.
- Section 11.3 (Audits): Language was updated to include inspectors/inspections (in addition to auditors/audits).
- Section 11.4.3 (Record Retention): Revised to accurately capture ICH E6 wording.

13.7 Version 4.0 (China-specific Amendment)

- Section 1 (Synopsis) and 3.3.2 (Exploratory Endpoints): [redacted]
- Table 3 (Randomized Controlled Period Schedule of Study Assessments for the AChR-Ab+ Population), Table 4 (Randomized Controlled Period Schedule of Study Assessments for the MuSK-Ab+ Population), and Table 5 (Open-label Period Procedures for AChR-Ab+ and MuSK-Ab+ Populations): [redacted] (Tables 3 and 4 only) were removed from the tables, as these samples will not be collected in China. Footnotes were updated accordingly.
- Section 5.1 (Inclusion Criterion #1), Section 6.1.2 (Randomized Controlled Period), Table 3, and Table 4: Japan-specific procedures were removed from the China-specific protocol.

[redacted]

[redacted]

- Section 10.5 (Biological Specimens and Data): Reference to future use of biological samples was removed because that will not be performed in China.

13.8 Version 3.0

- Section 1 (Synopsis) and Section 3.1.2 (Primary Endpoint): "MG-ADL profile score" was changed to "MG-ADL score" to reflect the more commonly used name for the outcome.
- Section 2.1.4 (Risk Assessment for Inebilizumab): The summary of inebilizumab use during pregnancy was updated.
- Section 5.2 (Exclusion Criteria): Exclusion Criterion #11 was updated to change the CD19+ B-cell threshold for inclusion from one-half the lower limit of normal to ≥ 40 cells/μL for consistency with other exclusion criteria.
- Section 5.2 (Exclusion Criteria): Exclusion Criterion #27 was added to exclude subjects unable to read since subjects are required to read and complete PROs during the study.
- Section 5.2 (Exclusion Criteria): Exclusion Criterion #28 was added to exclude subjects with untreated active or latent TB. Section 6.1.1 (Screening Period), Table 2: QuantiFERON®-TB Gold blood test was added to the table of screening procedures. Section 6.2.7 (Clinical Laboratory Assessments): QuantiFERON®-TB Gold test was added to the list of laboratory assessments.
- Section 6.1.1 (Screening Period): Measurement of AChR and MuSK titers was removed from the Screening Visit since only serostatus will be determined.
- Section 6.1.1 (Screening Period), Section 6.1.2 (Randomized Controlled Period): The statements that patient questionnaires should be performed before other procedures were removed to allow sites to have more flexibility in the order of procedures.
- Section 6.1.2 (Randomized Controlled Period) and Tables 3 and 4: A requirement was added for Japanese sites to call study subjects every 2 weeks during the RCP to evaluate their clinical status. This was added at the request of the Japan Pharmaceuticals and Medical Devices Agency.
- Section 6.1.2 (Randomized Controlled Period), Tables 3 and 4 and Section 6.1.3 (Open-label Period), Table 5: It was clarified at which visits MGFA clinical classification and MGFA [redacted] procedures are to be performed.
- Section 6.1.2 (Randomized Controlled Period), Table 4: The order of procedures was changed to make it consistent with Table 3.
- Section 6.1.3 (Open-label Period): In the text and Table 5 it was clarified which procedures do and do not need to be repeated at OLP Day 1 if the visit is done within 14 days of the final RCP visit and the procedure was done at the final RCP visit.
- Section 6.2.3 (Confirmation of Myasthenia Gravis Antibody Status): Clarification was provided regarding procedures for measurement of AChR and MuSK antibodies in screening.
- Section 6.3.1 (Discontinuation of Treatment): International normalized ratio cut-off for discontinuation criteria for liver abnormalities was removed.

- Section 7.2.1 (Oral Prednisone Taper): It was specified that prednisolone can be used as an alternative to prednisone at the same dose. Allowance of prednisone 10 mg every other day as an alternative to prednisone 5 mg daily was added.
- Section 7.2.2 (Rescue Medications): Information on the statistical treatment of rescue therapy was removed and will be included in the SAP.
- Section 9.4 (Methods for Statistical Analysis): Information on the statistical treatment of subjects who use corticosteroids used above the baseline dose was removed and will be included in the SAP.
- Some minor changes were made to improve wording.

13.9 Version 2.0

- Title page: The EudraCT number was added.
- Section 2.1.4 (Risk Assessment for Inebilizumab): Additional information was added based on an update to the IB.
- Section 2.1.5 (Anticipated Study Benefits and Risks): This section was newly added.
- Section 3.2.2 (Secondary Endpoints): Change in Patient Global Impression of Change at the end of the RCP was added as a secondary endpoint, and a description was added in Section 6.2.5.4.
- Section 3.2.2 (Secondary Endpoints), Section 3.3.2 (Exploratory Endpoints): [redacted].
- Section 4.1 (Study Design): Clarification was added for why the QMG was used instead of the MG-ADL to quantify baseline disease severity for purposes of stratification of randomization.
- Section 4.1 (Study Design), Section 4.3 (Rationale for Study Population), Section 5.1 (Inclusion Criteria): Protocol was altered to require use of immunosuppression to enter the study. Section 4.3 (Rationale for Study Population); Section 5.2 (Exclusion Criteria), #13, Section 7.2.1 (Oral Prednisone Taper): The maximum allowed dose of prednisone at study entry was changed from 60 mg daily or 80 mg every other day to 40 mg daily or 80 mg every other day.
- Section 5.1 (Inclusion Criteria), #1: Clarification was added for Japan subjects < 20 years old requiring consent of a parent or other legally authorized representative, as the current adult age in Japan is 20.
- Section 5.1 (Inclusion Criteria), #6: The minimum QMG score for enrollment was decreased from 12 to 11.
- Section 5.1 (Inclusion Criteria), #9: The laboratory value for the postmenopausal range for FSH was added.
- Section 5.2 (Exclusion Criteria): The exclusion criterion for thymoma was changed to allow enrollment of those with benign thymoma that was resected > 1 years prior to screening. Malignant thymoma was allowed if resected > 5 years prior to screening with no evidence of active disease and no therapy received over the previous 5 years.
- Section 5.2 (Exclusion Criteria): Exclusion Criterion #22d was updated from < one-half the lower limit of normal to < 40 cells/µL to provide the actual number.

- Section 5.2 (Exclusion Criteria): As a prohibited medication, methotrexate was changed from requiring no washout to requiring a 4-week washout before Day 1.
- Section 6.1.2 (Randomized Controlled Period): [redacted] was removed from the Day 57, Day 85, Day 225, and Day 267 timepoints in Table 3 and the Day 57 and Day 85 timepoints in Table 4. A Day 29 timepoint for [redacted]
- Section 6.1.2.1 (Unscheduled Visit), Tables and 4: A description of procedures for an Unscheduled Visit was added.
- Section 6.1.3 (Open-label Period): The requirement to taper corticosteroids and non-steroidal immunosuppressants during the OLP was removed. Tapering of non-steroidal immunosuppressants was recommended per standard of care. Further tapering of corticosteroids was left to the discretion of the Investigator.
- Section 6.1.3 (Open-label Period): The duration of the OLP was increased from 12 to 18 months to allow a longer period of observation after the last dose of inebilizumab is given. The timing of visit was updated to make the intervals between visits consistent.
- Section 6.1.3 (Open-label Period), Table 5: C-SSRS testing was added to the OLP visits.
- Section 6.2.5 (Efficacy Assessments) and Section 6.2.6 (Safety Assessments): The location of where to record data of various efficacy assessments was added (ePRO system vs eCRF).
- Section 6.2.5.1 (Role of the Independent Rater): It was clarified that the independent rater performing the physical examination portion of the MGC should be physician, physician-assistant, nurse practitioner, physical therapist, or other healthcare provider who is experienced with neurological examination. It was clarified that the QMG can be performed by any independent rater who is experienced in performing the QMG and has completed the protocol training on QMG performance.
- Section 6.2.5.1 (Role of the Independent Rater), Section 6.2.5.2 (Myasthenia Gravis Activities of Daily Living): The MG-ADL was changed from the data being entered directly by the subject to being entered by a member of the site staff based on questions answered by the subject. This change was made to make the instrument used in the way that it was validated.
- Section 6.2.5.4 (Patient Global Impression of Change), Tables 3, 4, and 5: A description of the PGIC was added.

[redacted]

- Section 6.3.1 (Discontinuation of Treatment): A discontinuation criterion was added: Platelet count $< 50 \times 10^3/\mu L$ that does not improve to $\geq 50 \times 10^3/\mu L$ within 14 days as agreed upon following consultation with the medical monitor.
- Section 6.3.1 (Discontinuation of Treatment): A discontinuation criterion was added: use of prednisone > 10 mg/day for more than 8 consecutive weeks in the OLP.
- Section 6.3.1 (Discontinuation of Treatment): A discontinuation criterion was added: unblinding of the treatment assignment while the subject is in the RCP.

- Section 6.3.1 (Discontinuation of Treatment), Section 6.3.2 (Withdrawal from Study): The duration of follow-up after discontinuation of IP in the OLP was changed from 6 to 12 months and "until OLP Day 547" was added.
- Section 6.3.2 (Withdrawal from Study): It was clarified that subjects who discontinue IP but remain in the study should continue to have all study-related assessments except those directly related to dosing and OLP subjects should remain in the study until 12 months after last dose of IP or until OLP Day 547.
- Section 6.6 (Data Monitoring Committee): It was clarified that the DMC will evaluate study data for monitoring safety of the study.
- Section 7.2.1 (Oral Prednisone Taper): The corticosteroid taper was adjusted to make the taper slower for those entering at higher baseline prednisone doses. The corticosteroid taper in the OLP was changed from being mandatory to optional.
- Section 7.2.2 (Rescue Medications): Clarification was added regarding when rescue therapy can be used. High-dose corticosteroids were removed as an option for rescue therapy. The following statement was deleted: "Rescue medications will be considered standard of care and will not be provided or reimbursed by the Sponsor" and replaced by "Rescue therapy is considered standard of care treatment; information about Sponsor coverage of out-of-pocket costs incurred by subjects treated with rescue therapy will be included in the site contract."
- Section 7.3.2 (Randomization Strategy and Procedure): Stratification criteria were changed to align with changes to inclusion criteria of QMG score and requirement of immunosuppression.
- Section 7.3.3 (Extent and Maintenance of Blinding): Language was added to clarify that B-cell counts and [redacted] after the OLP Day 15 visit will not be considered unblinding.
- Section 8.1 (Safety Assessment Definitions): Clarification was added regarding the definition of Inpatient Hospitalization for SAE purposes.
- Section 9.4 (Methods for Statistical Analysis): Additional detail on estimands and intercurrent events was added.
- Section 13 (Protocol Changes): Section 13.1 Version 2.0 was added and subsequent sections were renumbered.

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15 APPENDICES

15.1 Appendix 1 Guidance for Anaphylaxis Diagnosis

The National Institute of Allergy and Infectious Disease and Food and Allergy Anaphylaxis Network define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (Category 1) to > 95% of all cases of anaphylaxis (for all 3 categories). Their clinical criteria for diagnosing anaphylaxis are:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND AT LEAST 1 OF THE FOLLOWING

   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)
   b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. 2 or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):

   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that subject (minutes to several hours):

   a. Infants and children: low systolic BP (age specific) or > 30% decrease in systolic BP
   b. Adults: systolic BP of < 90 mmHg or > 30% decrease from that person's baseline.

Reference

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15.2 Appendix 2 Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law (HL). It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study, the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets Potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with the Sponsor's clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug-Induced Liver Injury (DILI) caused by the IP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting adverse events (AEs) and serious adverse events (SAEs) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law

Aspartate aminotransferase (AST) or Alanine aminotransferase (ALT) ≥ 3 × upper limit of normal (ULN) together with total bilirubin (TBL) ≥ 2 × ULN at any point during the study following the start of IP, irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law

AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN, where no other reason, other than the IP, can be found to explain the combination of increases; eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL, the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of Potential Hy's Law Cases

In order to identify cases of PHL, it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

The Investigator will, without delay, review each new laboratory report and if the identification criteria are met will:

- Notify the Sponsor study representative.
- Determine whether the subject meets PHL criteria by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

Follow-up

Potential Hy's Law Criteria Are Not Met

If the subject does not meet PHL criteria, the Investigator will:

- Inform the Sponsor representative that the subject has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria Are Met

If the subject does meet PHL criteria, the Investigator will notify the Sponsor study representative who will then inform the central study team. The medical monitor contacts the Investigator to provide guidance, discuss and agree on an approach for the study subject's follow-up and the continuous review of data. Subsequent to this contact, the Investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.
- If at any time (in consultation with the medical monitor) the PHL case meets serious criteria, report it as a SAE using standard reporting procedures.

Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the medical monitor will contact the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IP. The medical monitor and safety physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

If the alternative explanation is not an AE, record the alternative explanation on the appropriate eCRF.

If the alternative explanation is an AE/SAE, record the AE/SAE in the eCRF accordingly and follow the Sponsor standard processes.

If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the IP:

Report a SAE (report term "Hy's Law") according to Sponsor standard processes.

- The "Medically Important" serious criterion should be used if no other serious criteria apply
- As there is no alternative explanation for the HL case, a causality assessment of "related" should be assigned

If there is an unavoidable delay of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

Report a SAE (report term "Potential Hy's Law") applying serious criteria and causality assessment as per above.

Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

FDA Guidance for Industry (issued July 2009) "Drug-induced liver injury: premarketing clinical evaluation":

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

15.3 Appendix 3 Investigator's Agreement

INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials related to Study VIB0551.P3.S1 (20230049) and agree to the following:

- To conduct this study as described by the protocol and any accessory materials
- To protect the rights, safety, and welfare of the subjects under my care
- To provide oversight to all personnel to whom study activities have been delegated
- To control all IPs provided by the Sponsor and maintain records of the disposition of those products
- To conduct the study in accordance with all applicable local and national regulations, the requirements of the ethics committee of record for my clinical site, and Good Clinical Practices as outlined by International Council for Harmonisation E6(R2)
- To obtain approval for the protocol and all written materials provided to subjects prior to initiating the study at my site
- To obtain informed consent – and updated consent in the event of new information or amendments – from all subjects enrolled at my study site prior to initiating any study-specific procedures or administering IPs to those subjects
- To maintain records of each subject's participation and all data required by the protocol

Name	**Title**	**Institution**
Signature		**Date**

15.4 Appendix 4 Study-Specified Opportunistic Infections that Meet Exclusion Criteria and Require Discontinuation of Investigational Product

Definite [a,b] Opportunistic Infection	Probable [c] Opportunistic Infection
Pneumocystis jirovecii	Paracoccidioides infections
BK virus disease including polyomavirus-associated nephropathy	*Penicillium marneffei* (Talaromyces)
Cytomegalovirus disease	Sporothrix schenckii
Posttransplant lymphoproliferative disorder (EBV)	Cryptosporidium species (chronic disease only)
Progressive multifocal leukoencephalopathy	Microsporidiosis
Bartonellosis (disseminated disease only)	Leishmaniasis (visceral only)
Blastomycosis	Trypanosoma cruzi infection (Chagas's disease) (disseminated disease only)
Toxoplasmosis	Campylobacteriosis (invasive disease only)
Coccidioidomycosis	Shigellosis (invasive disease only)
Histoplasmosis	Vibriosis (invasive disease due to *Vibrio vulnificus*)
Aspergillosis (invasive disease only)	HCV progression
Candidiasis (invasive disease or pharyngeal)	
Cryptococcosis	
Other invasive fungi: Mucormycosis (zygomycosis) (Rhizopus, Mucor and Lichtheimia), *Scedosporium/Pseudallescheria boydii*, *Fusarium*)	
Legionellosis	
Listeria monocytogenes (invasive disease only)	
Tuberculosis	
Nocardiosis	
Non-tuberculous mycobacterium disease	
Salmonellosis (invasive disease only)	
HBV reactivation	
Herpes simplex (invasive disease only)	
Herpes zoster (any form)	
Strongyloides (hyperinfection syndrome and disseminated forms only)	

EBV = Epstein-Barr virus; HBV = hepatitis B virus; HCV = hepatitis C virus.

a Generally does not occur in the absence of immunosuppression and whose presence suggests a severe alteration in host immunity.

b Can occur in subjects without recognized forms of immunosuppression, but whose presence indicates a potential or likely alteration in host immunity.

c Published data is currently lacking, but expert opinion believes that risk is likely elevated in the setting of biologic therapy.

Source: Winthrop KL, Novosad SA, Baddley JW, Calabrese L, Chiller T, Polgreen P, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. Ann Rheum Dis. 2015;74(12):2107-16.

Additional infections may be considered to be exclusionary and to require discontinuation of IP according to the judgment of the Investigator. Investigators can also exercise discretion in recording opportunistic infections as AESIs that are not specified in Appendix 4.

Approval Signatures

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