CLINICAL STUDY PROTOCOL

NCT Number: NCT04159805

Study Title: A Phase 2, Randomized, Placebo-Controlled Study to Evaluate Safety, Tolerability, and Efficacy of TAK-079 in Patients With Generalized Myasthenia Gravis

Study Number: TAK-079-1005

Protocol Version and Date:

Version 4.0: 03-Feb-2021

PROTOCOL

A Phase 2, Randomized, Placebo-Controlled Study to Evaluate Safety, Tolerability, and Efficacy of TAK-079 in Patients With Generalized Myasthenia Gravis

Safety, Tolerability, and Efficacy of TAK-079 in Patients With Generalized Myasthenia Gravis

Sponsor:	Millennium Pharmaceuticals, Inc.* 40 Landsdowne Street Cambridge, MA 02139 USA Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium," "sponsor," or "Takeda".
Study Number:	TAK-079-1005
EudraCT Number:	2019-003383-47
Compound:	TAK-079
Date:	02 February 2021 Version/Amendment Number: 4

Amendment History:

Date	Amendment Number	Type	Region
02 February 2021	Amendment 4	Substantial	Global
28 September 2020	Amendment 3	Substantial	Global
05 March 2020	Amendment 2	Substantial	Global
18 October 2019	Amendment 1	Nonsubstantial	Global
05 September 2019	Initial Protocol	Not applicable	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event and pregnancy reporting information is presented in Section 10.0, as is information on reporting product complaints.

Takeda Development Center–sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each patient.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

The names and contact information for the medical monitor and responsible medical officer are in the study contact list.

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical study disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

[redacted], MD, PhD Date
[redacted]
[redacted] Autoimmune Diseases

[redacted], PhD Date
[redacted], Biostatistics
Statistical and Quantitative Sciences

[redacted], PhD (or designee) Date
[redacted]
Quantitative Clinical Pharmacology

1.3 Protocol Amendment 4 Summary of Changes

Rationale for Amendment 4

This section describes the changes in reference to the protocol incorporating Amendment 4. The primary reason for this amendment is to clarify the intent of Exclusion Criterion No 1. Other minor changes and clarifications to the protocol are summarized in the table below.

Protocol Amendment 4		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 1.2 Approval	Change name of Biostatics approver from [redacted] to [redacted].	To update study personnel.
Section 2.0 STUDY SUMMARY Section 6.1 Overview of Study Section 9.5 Study Procedures Section 9.5.4 Medical/Surgical History Section 9.5.5 Concomitant Medications and Procedures Section 9.5.7 Height and Weight Appendix A Schedule of Events	Increase the length of the screening period from 21 days 28 days.	To lengthen the screening period by 1 week due to COVID-19-related shipping delays.
Section 2.0 STUDY SUMMARY Section 6.3 Number of Patients	Increase number of study centers from 40 to 50.	To mitigate the delayed enrollment caused by COVID-19.
Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	Exclusion Criterion No 1: Changed from: "history of thymoma or other thymic neoplasms" to read: "Presence of a thymoma (previous history of a fully encapsulated thymoma removed ≥12 months before screening is allowed) or history of invasive thymic malignancy unless deemed cured by adequate treatment with no evidence of recurrence for ≥5 years before screening."	To clarify that the intent is to exclude subjects with a current thymoma and not a previous history of a fully encapsulated thymoma (removed ≥12 months before screening) and to provide further detail regarding other malignancies of the thymus.

Protocol Amendment 4		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 2.0 STUDY SUMMARY Section 5.2.2 Secondary Endpoints Section 5.2.3 Exploratory Endpoints Section 13.1.3 Efficacy Analysis	Secondary Endpoint: The MG-QoL15r scale has been removed as one of the MG clinical impairment scales to assess the percentage of patients meeting minimal clinically important difference criteria. Exploratory Endpoint: The MG-QoL15r scale has been removed as one of the MG clinical impairment scales to assess the duration of a clinically meaningful effect on MG disease severity.	To remove the MG-QoL15r scale from this analysis as it does not have an established cutoff of clinically meaningful change.
Section 8.1 Study Drug Administration	Changed "...the Week 1 dose will be administered by giving each SC injection 30 minutes apart" to read: "the Week 1 dose will be administered by giving each SC injection 30 minutes apart (±10minutes)..."	To provide a 10 minute window to the 30-minute intervals between injections.
Section 8.1.2 Postdose Medication Appendix A Schedule of Events, footnote v	Modify timing of medication following the first dose of study drug from: "Considering the timing of the greatest pharmacologic effect of TAK-079, postdose medication should be given after the first dose and 1 day after the first dose of study drug." to read: Considering the timing of the greatest pharmacologic effect of TAK-079, postdose medication should be given 2 hours (±15 minutes) after the first injection of the first dose and 1 day after the first dose of study drug in the morning."	To provide more detailed guidance on the administration of postdose medication.
Section 9.5.6 Physical Examination Appendix A, footnote g	The following sentence has been added: "Women of childbearing potential should be asked about their menstrual history at each visit. A serum pregnancy test should be conducted for delayed menses (see Section 9.5.10)."	To ensure a woman is not pregnant before study drug administration.

Protocol Amendment 4		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 9.5.8 Vital Signs Appendix A Schedule of Events, footnote i.	A window of ±10 minutes has been added to 2 hour timeframe for assessing vital signs postdose after the first and second administration of study drug.	To provide a 10-minute window for obtaining vital signs after administration of study drug In addition, footnote "i" in Appendix A was revised to remove unclear wording about which vital signs are to be taken during the visits.
Section 9.5.10 Pregnancy Test Appendix A Schedule of Events, footnote j	Text has been revised to indicate that if the subject reports delayed menses, a serum pregnancy test should be completed and a negative result obtained before dosing with the study drug.	To ensure a woman is not pregnant before study drug administration.
Section 9.5.10.1 Definition of Women of Childbearing Potential	• Removed: "Has not been naturally postmenopausal (amenorrhea after cancer therapy does not rule out childbearing potential) for at least 24 consecutive months, ie, has had menses at any time in the preceding 24 consecutive months." • Clarified the definition of postmenopausal.	To remove confusing wording from template language that does not apply to this protocol.
Section 9.5.13.5 MG-QoL 15r	Revised total score range from "0 to 60" to read: "0 to 30." Removed last sentence that read: A reduction by 7 to 8 points in the total MG-QoL15r score is considered a clinically meaningful improvement.	To correct the total score of the MG-QoL15r scale. Removed criteria for clinically meaningful improvement as this pertained to the MG-QoL15 scale, not the revised MG-QoL15r scale.
Section 9.12 Coronavirus Disease 2019-Related Procedural Changes Appendix A Schedule of Events, footnote s	Added text: "The assessment of forced vital capacity for the QMG test may be omitted for COVID-19-related reasons."	To allow added flexibility for sites with varying policies and procedures due to COVID-19.
	Date of FDA guidance on COVID-19 changed from 02 July 2020 to 04 December 2020.	To update date of most recent FDA guidance on COVID-19.

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the investigator's brochure (IB), prescribing information, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and to protect the rights, safety, privacy, and well-being of study patients in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- ICH, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.0 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator (Appendix B).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix E of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

2.0 STUDY SUMMARY

Name of Sponsor: Millennium Pharmaceuticals, Inc	**Compound: TAK-079**
Title of Protocol: A Phase 2, Randomized, Placebo-Controlled Study to Evaluate Safety, Tolerability, and Efficacy of TAK-079 in Patients With Generalized Myasthenia Gravis	**EudraCT No.**: 2019-003383-47
Study Number: TAK-079-1005	Phase: 2

Study Design:

This is a phase 2, randomized, double-blind, placebo-controlled study designed to assess the safety, tolerability, and efficacy of TAK-079 in patients with generalized myasthenia gravis (MG) in combination with standard background therapy.

It is expected that approximately 36 patients will be randomized into the study. After a screening period of up to 28 days, eligible patients will be randomized in a 1:1:1 ratio to one of the following treatment groups:

- TAK-079 300 mg added to stable standard background therapy.
- TAK-079 600 mg added to stable standard background therapy.
- Matching placebo added to stable standard background therapy.

The study will be divided into 3 sequential periods: a dosing period (8 weeks), a safety follow-up period (SFP; 8 weeks), and a long-term follow-up period (LFP; 16 weeks).

During the 8-week dosing period, TAK-079/matching placebo will be administered via subcutaneous (SC) injection once weekly for 8 weeks. Patients will be premedicated with an antipyretic (such as acetaminophen) and an antihistamine (such as diphenhydramine) 1 to 3 hours before TAK-079 administration.

Safety assessment, including safety laboratory tests, will be performed each week before subsequent dosing. Patients may have study drug (TAK-079/placebo) doses modified (eg, withheld or delayed) for safety reasons.

After completing the 8-week dosing period, patients will enter an 8-week blinded SFP, completing safety and efficacy assessments every 2 weeks. After completion of the Week 16 visit in the SFP, patients will be unblinded before entering the LFP visit at Week 20.

Patients randomized to TAK-079 will be followed every 4 weeks from Week 20 through to Week 32 of the LFP for MG clinical activity scores and autoantibody levels; the end-of-study visit will take place at Week 32 of the LFP. For patients randomized to placebo, the end-of-study visit will take place at Week 20 of the LFP.

Adverse events (AEs) ongoing at the Week 16 visit of the SFP (including unresolved clinical/laboratory parameters) should be monitored through the LFP until they are resolved, return to baseline, or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). Study drug–related AEs/serious adverse events (SAEs) with onset after the SFP will be collected through the LFP. Overall, the maximum follow-up period is approximately 24 weeks after the last dose of study drug.

Patients will be permitted to receive rescue medication, as determined by the investigator, eg, intravenous immunoglobulin (IVIg), high dose corticosteroids, or plasmapheresis/plasma exchange. If the patient receives rescue therapy during the dosing period, they will automatically enter the SFP.

Primary Objective:

To evaluate the safety and tolerability of TAK-079 in patients with generalized MG who are receiving stable background therapy for MG.

Secondary Objective:

To assess the effects of TAK-079 on MG disease activity using clinical rating scales and autoantibody levels.

Patient Population: Generalized MG positive anti–acetylcholine receptor (AChR) or anti–muscle-specific tyrosine kinase (MuSK) antibodies, class II to IV disease according to the Myasthenia Gravis Foundation of America (MGFA), and a Myasthenia Gravis-Activities of Daily Living (MG-ADL) score of 6 or higher.	
Number of Patients: 36 patients	**Number of Sites**: Approximately 50 sites
Dose Level: TAK-079 300 mg, 600 mg, or matching placebo administered once weekly for 8 weeks.	**Route of Administration**: TAK-079/matching placebo: SC injection
Duration of Treatment: Dosing period: maximum of 8 weeks.	**Period of Evaluation:** From first dose of TAK-079 until last LFP visit.

Main Criteria for Inclusion:

Each patient must meet all the following inclusion criteria to be randomized to treatment:

1. Aged 18 years or older.
2. Diagnosis of MG supported by a positive serologic test for anti-AChR or anti-MuSK antibodies at screening.
3. MGFA clinical classification class II to IV at screening.
4. MG-ADL total score of 6 or greater at screening, with at least 4 points of this score attributed to nonocular items.
5. If receiving immunosuppressive drugs (ie, mycophenolate mofetil, methotrexate, cyclosporine, tacrolimus, cyclophosphamide), therapy must be ongoing for at least 6 months, with a stable dosing ongoing for at least 3 months before screening. Patients receiving azathioprine must be on a stable dose for at least 6 months before screening.
6. If receiving oral corticosteroids, therapy must be ongoing for at least 3 months, with a stable dose at least 1 month before screening. Corticosteroids, including dexamethasone, must be given as oral, daily or every-other-day therapy, as opposed to pulse therapy.
7. If receiving cholinesterase inhibitors, therapy with a stable dose is required at least 2 weeks before screening.
8. The doses of concomitant standard background therapy must be expected to remain stable throughout the study unless dose reduction is required due to toxicities. Allowed background therapy is defined as no more than a cholinesterase inhibitor ± corticosteroid ± 1 steroid-sparing immunosuppressive drug (limited to azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, tacrolimus, or cyclophosphamide). Patients must be on at least 1 allowed background medication.
9. Female patients of childbearing potential are required to have a negative pregnancy test. Both male and female patients must practice an effective, reliable and approved contraceptive regimen during the study and for up to 90 days or 5 half-lives, whichever is longer, after discontinuation of treatment.
10. Patients must be able and willing to comply with study procedures.

Main Criteria for Exclusion:

Patients meeting any of the following exclusion criteria are not to be randomized to treatment:

1. Presence of a thymoma (previous history of a fully encapsulated thymoma removed ≥12 months before screening is allowed) or history of invasive thymic malignancy unless deemed cured by adequate treatment with no evidence of recurrence for ≥5 years before screening.
2. History of thymectomy within 12 months before screening.
3. MGFA class I or V.
4. Received IVIg, SCIg (subcutaneous immunoglobulin), or plasmapheresis/plasma exchange within 4 weeks before screening, or an expectation that any therapy besides the patient's standard background therapies may be used for treatment of MG (eg, a rescue therapy) between screening and dosing.
5. Chronic obstructive pulmonary disease (COPD) or asthma with a pre-bronchodilatory forced expiratory volume in 1 second (FEV_1) <50% of predicted normal.
   Note: FEV_1 testing is required for patients suspected of having COPD or asthma.
6. Received rituximab, belimumab, eculizumab, or any monoclonal antibody for immunomodulation within 6 months before first dosing. Patients with prior exposure to rituximab must have CD19 counts within the normal range at screening.
7. Known autoimmune disease other than MG that would interfere with the course and conduct of the study.

8. Received a live vaccine within 4 weeks before screening or has any live vaccination planned during the study.
9. Any medical condition that, in the opinion of the investigator, might interfere with the patient's participation in the study (such as significant cardiovascular, pulmonary, hematologic, gastrointestinal, endocrinologic, hepatic, renal, neurologic, malignancy, or infectious disease), poses added risk for the patient, or could confound the assessment of the patient.
10. Pregnancy or lactation during the screening period or on Day 1 before first dose of study drug.
11. Participation in any other investigational drug study or exposure to other investigational agent within 4 weeks or 5 half-lives, whichever is longer, before Day 1.
12. An opportunistic infection ≤12 weeks before initial study dosing or is currently receiving treatment for a chronic opportunistic infection, such as tuberculosis (TB), pneumocystis pneumonia, cytomegalovirus, herpes simplex virus, herpes zoster, or atypical mycobacteria. A mild, localized herpes simplex infection within 12 weeks of study dosing is allowed, as long as the lesion has resolved without systemic therapy before Day 1.
13. Inadequate organ and bone marrow function:
    a) Alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal (ULN).
    b) Total bilirubin >1.5 times ULN (Note: Patients with a confirmed and documented diagnosis of Gilbert syndrome are not excluded based on this criterion).
    c) Platelets <75,000/mm^3.
    d) Absolute neutrophil count <1500/mm^3.
    e) Hemoglobin <8 g/dL.
    f) IgG <5 g/L (500 mg/dL).
    g) Lymphocyte count <500/mm^3.
14. A positive T-cell interferon-γ release assay (TIGRA) (result through QuantiFERON-TB Gold test or T-Spot/Elispot) at the screening visit, noting the following;
    a) A purified protein derivative (PPD) skin test may be used if TIGRA testing is not available.
    b) Patients with an indeterminate TIGRA result must meet the following criteria:
        i. Negative PPD skin test (defined as <5 mm induration).
        ii. At low risk of acquiring TB (eg, avoids close contact with TB-positive individual[s]) and/or chest x-ray ≤6 months before the screening visit that is consistent with no evidence of latent or active TB.
15. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
16. A positive test result for hepatitis B surface antigen, or hepatitis B core antibody, hepatitis C antibody, or HIV antibody/antigen, at screening. However, an individual who has a known history of chronic hepatitis C and has been treated and fully cured of the disease, confirmed with a negative hepatitis C virus RNA polymerase chain reaction test at screening, is not excluded on the basis of positive hepatitis C antibody alone.
17. A history of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in the TAK079/placebo formulation.

Main Criteria for Evaluation and Analyses:

Primary: Percentage of patients with treatment-emergent adverse events**,** including Grade 3 or higher events, SAEs, and AEs leading to TAK-079 discontinuation.

Secondary:

1. Score change from baseline in the following:
   a) MG Activities of Daily Living (MG-ADL) score.
   b) Quantitative Myasthenia Gravis (QMG) score.
   c) Myasthenia Gravis Composite (MGC) score.
   d) Revised 15-item Myasthenia Gravis Quality of Life scale (MG-QoL15r).
2. Change from baseline in anti-AChR antibody or anti-MuSK antibody levels
3. Percentage of patients meeting minimal clinically important difference criteria in the respective MG clinical impairment scales (MG-ADL, QMG, MGC).

Exploratory:

1. Serum concentration-time profile of TAK-079 PK parameters will include, but are not limited to, observed concentration at the end of a dosing interval (C_{trough}) over time.
2. Change in serum immunoglobulin levels.
3. Pharmacodynamic analysis of the presence and changes of immune cells in peripheral blood before and during therapy.
4. Score change from baseline in the Myasthenia Gravis Impairment Index (MGII) score.
5. Duration of a clinically meaningful effect on MG disease severity (in all clinical disease impairment scales: MG-ADL, QMG, MGC, MGII).
6. Percentage of patients meeting minimal clinically important difference criteria in the MGII scale.
7. Frequency and proportion of patients requiring rescue therapy.
8. Immunogenicity assessment of TAK-079 in peripheral blood, including antidrug antibody (ADA).
9. Biomarkers of disease activity such as complement levels (C3, C4, complement split products); specific markers of CD38 pathway modulation may also be evaluated.
10. Change in levels of the following vaccine-protective antibodies: measles, mumps, rubella, diphtheria, and tetanus.

Statistical Considerations:

Safety Analysis

The safety analysis set will include all patients who have received at least 1 dose of study drug.

Safety will be evaluated by the frequency of AEs, severity and types of AEs, and by changes from baseline in patients' vital signs, weight, and clinical laboratory results using the safety analysis set. Exposure to study drug and reasons for discontinuation will be tabulated.

TEAEs that occur after administration of the first dose of study drug and through to the end of the SFP period will be tabulated.

AEs will be tabulated according to the Medical Dictionary for Regulatory Activities, and data will be summarized using Preferred Term and primary System Organ Class. All safety analyses will be performed using the safety analysis population

Efficacy Endpoint Analyses: The analysis of the efficacy endpoints will be performed on the full analysis set, defined as all randomized patients who had baseline and at least 1 postbaseline efficacy assessment. Efficacy endpoints will be summarized by descriptive statistics and presented by treatment groups. Where appropriate, efficacy endpoints may be analyzed with the following methods:

- Binary endpoints will be analyzed using a Fisher's exact test.
- Changes from baseline endpoints measured repeatedly over time will be analyzed using a mixed-model repeated-measures analysis, which includes treatment, visit, and (treatment × visit) interaction terms as the

factors, with baseline values as covariates.

All tests of treatment effects will be conducted at a 2-sided α level of 0.05, and 95% CIs for the differences in proportions and least square means will be provided. No inferential hypothesis was tested in these endpoints, so CIs and p-values are not adjusted for multiplicity.

Sample Size Justification:

Approximately 36 patients are planned to be randomized to treatment in a ratio of 1:1:1 (TAK-079 300 mg, TAK-079 600 mg, or placebo). This study is exploratory and not powered to address any predefined hypothesis.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities except for those identified in the clinical supplier list in the study manual/binder. The identified vendors will perform specific study-related activities either in full or in partnership with the sponsor.

3.2 Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research, and study participation. The signatory coordinating investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

AChR	acetylcholine receptor
ADA	antidrug antibody
AE	adverse event
AUC	area under the plasma concentration-time curve
C_{max}	maximum observed plasma concentration
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRO	contract research organization
CRS	cytokine release syndrome
C_{trough}	observed concentration at the end of a dosing interval
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration (US)
FEV_1	forced expiratory volume in 1 second
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
hCG	human chorionic gonadotropin
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
Ig	immunoglobulin
IRB	institutional review board
IRR	infusion-related reaction
ISR	injection site reaction
IV	intravenous(ly)
IVIg	intravenous immunoglobulin
IXRS	interactive voice/web response system
LFP	long-term follow-up period
MedDRA	Medical Dictionary for Regulatory Activities
MG	myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living
MGC	Myasthenia Gravis Composite
MGFA	Myasthenia Gravis Foundation of America
MGII	Myasthenia Gravis Impairment Index
MG-QoL15r	revised 15-item Myasthenia Gravis Quality of Life scale

MHRA	Medicines and Healthcare products Regulatory Agency
MuSK	muscle-specific tyrosine kinase
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
NMJ	neuromuscular junction
NOAEL	no-observed-adverse-effect level
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PPD	purified protein derivative
PTE	pretreatment event
QMG	Quantitative Myasthenia Gravis
RBC	red blood cell
RRMM	relapsed and/or refractory multiple myeloma
SAE	serious adverse event
SC	subcutaneous(ly)
SFP	safety follow-up period
SLE	systemic lupus erythematosus
SOE	schedule of events
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TIGRA	T-cell interferon-γ release assay
TNF-α	tumor necrosis factor alpha
UK	United Kingdom
ULN	upper limit of the normal range
US	United States
WHO	World Health Organization

3.4 Corporate Identification

Millennium	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited

4.0 INTRODUCTION

4.1 Disease Background

Myasthenia gravis (MG) is a rare autoimmune disorder in which autoantibodies target the neuromuscular junction (NMJ) and postsynaptic membrane and interfere with neuromuscular transmission, which leads to progressive weakness of skeletal muscles. The estimated annual incidence of MG in the United States (US) is 5.3 per million, with a prevalence of approximately 77.7 per million [1-4].

Characteristically for MG, the skeletal muscle weakness and fatigability worsens with physical activity and improves with rest [5]. In some cases, muscle weakness can lead to respiratory and cardiac dysfunction [6]. The disease remains life-threatening; in a myasthenic crisis, the muscles that control breathing become too weak, which can result in death due to paralysis of the respiratory muscles.

MG is caused by pathogenic autoantibodies that are produced by plasma cells. Most patients (80%-90%) with MG produce immunoglobulin (Ig)G1 and IgG3 autoantibodies against the acetylcholine receptor (AChR), while the remaining patients either produce IgG4 autoantibodies against muscle specific tyrosine kinase (MuSK; ~5% of patients), IgG1-3 antibodies against the low-density lipoprotein receptor-related protein 4 (~1% of patients), or produce no detectable autoantibodies [7]. The binding of autoantibodies to proteins in the NMJ ultimately leads to damage of the postsynaptic membrane [5].

Reducing the levels of pathogenic autoantibodies is challenging. The autoantibody-producing plasma cells are resistant to many conventional pharmacologic strategies because they are not actively cycling and express relatively few surface antigens.

The current standard of care for MG consists of a combination of symptomatic therapy (acetylcholinesterase inhibitors, to increase the levels on acetylcholine in the synapse) and immunosuppression. Immunosuppressive or immunomodulatory therapies (such as corticosteroids, azathioprine, methotrexate, cyclosporine, tacrolimus, cyclophosphamide, plasmapheresis/plasma exchange, and intravenous immunoglobulin [IVIg]) are given to patients who do not have satisfactory results with symptomatic therapy alone. Nevertheless, approximately 10% of patients have treatment-refractory disease, and up to 80% of patients fail to reach a complete stable remission [8]. Immunosuppressive medications have several drawbacks, including limited efficacy and severe dose-limiting toxicities. Furthermore, these drugs do not directly affect autoantibody production.

Autoantibody levels can be lowered by targeting the B-cell progenitors of plasma cells. Rituximab (an anti-CD20 antibody) targets these plasma cell progenitors, thereby indirectly decreasing autoantibody production by preventing the replenishment of autoreactive plasma cells. However, rituximab's efficacy in MG has been limited, likely because the long-lived plasma cells that are thought to be primarily responsible for anti-AChR antibody production do not express CD20 and are therefore not targeted by rituximab [5].

There are some therapeutic options available to lower the antibody levels by increasing the clearance of pathogenic autoantibodies, eg, plasmapheresis/plasma exchange, administration of IVIg, or neonatal Fc receptor (FcRn) antagonists. Plasmapheresis and IVIg are mostly used until other medications take effect, before surgery, or for myasthenic crisis because of their fast but short-lived impact. An alternative approach to increase the clearance of autoantibodies may be achieved by blocking the FcRn, and several FcRn antagonists are currently in clinical development. These drugs decrease pathogenic IgG by accelerating their clearance via inhibiting FcRn-mediated IgG recycling. None of these 3 therapeutic strategies inhibit IgG production, and the duration of the effect is relatively short; consequently, most likely chronic administration would be required to maintain low levels of pathogenic autoantibodies [9].

Another therapeutic strategy in MG that does not eliminate the root cause of the disease is to reduce the complement-mediated damage of the postsynaptic membrane at the NMJ. This can be achieved with eculizumab, a monoclonal antibody against complement protein C5. While showing moderate efficacy, eculizumab therapy is related to increased risks of meningococcal infections and thereby is restricted by risk evaluation and mitigation strategies [10].

In conclusion, there is a need for novel therapies in MG that can provide deeper and sustained responses with a favorable safety profile, to help decrease use of corticosteroids and to improve patients' quality of life. Targeting CD38, a cell surface molecule whose expression is restricted to subsets of hematopoietic cells and that is highly expressed on plasmablasts, short-lived plasma cells, and long-lived plasma cells, is an attractive therapeutic strategy in MG. TAK-079 could eliminate the production of autoantibodies by depleting plasma cells, thus providing effective and more durable disease control, with a favorable safety and tolerability profile.

4.2 Rationale for the Proposed Study

TAK-079 is a fully human recombinant monoclonal antibody directed against CD38, an antigen that is highly expressed on plasma cells, plasmablasts, and natural killer (NK) cells and is induced on activated T cells and B cells. TAK-079 administration results in depletion of cells expressing high levels of CD38 through a mechanism that involves apoptosis, antibody-dependent cell-mediated cytotoxicity, and complement-dependent cytotoxicity [11]. TAK-079 depletes the cells that produce the pathogenic autoantibodies (plasmablasts, plasma cells, and especially long-lived plasma cells). A reduction in plasmablasts and long-lived plasma cells by TAK-079 is expected to result in a reduction in the levels of pathogenic autoantibodies, thereby improving the autoantibody-mediated pathology in MG, eg, reducing damage at the NMJ and improving the reversible neuromuscular deficits in these patients.

TAK-079 is therefore being proposed as a potential treatment for generalized MG in adult patients.

The pharmacodynamic effects of TAK-079 have been confirmed experimentally in vitro and in vivo and have also been shown in human clinical studies. In an in vitro study, TAK-079 reduced both short- and long-lived plasma cells isolated from bone marrow aspirates or blood from healthy control subjects and patients with systemic lupus erythematosus (SLE) (TKD-BCS-00416-R1). TAK-079 also reduced the number of cells producing autoantibodies, including VH4-34 (9G4) (reduced in 71% of samples) and anti-Ro (reduced in 58% of samples) in SLE patient samples.

These effects on autoantibodies corresponded to comparable reductions in total IgG-producing cells, indicating that total IgG could be used as a surrogate biomarker for autoantibodies, in the absence of autoantibody data.

An in vivo study in a monkey collagen-induced arthritis model of autoimmune disease demonstrated the therapeutic efficacy of TAK-079 (TAK-079-10032). Treatment of arthritic monkeys with TAK-079 (3 mg/kg intravenously [IV] weekly) was well tolerated and reduced disease progression. Arthritis scores and joint swelling were significantly lower than with the vehicle control and were accompanied by decreases in blood levels of C-reactive protein, alkaline phosphatase, and NK, B, and T cells. Histopathology, morphometry, and radiology revealed significantly less joint damage in animals treated with TAK-079 or dexamethasone (0.1 mg/kg oral gavage daily) compared with vehicle control animals, illustrating potential disease-modifying activity of TAK-079. These data indicate that depletion of CD38-expressing cells could be a therapeutic mechanism for treating autoimmune diseases.

In a study in healthy subjects (TAK-079_101), a single subcutaneous (SC) injection of 0.6 mg/kg TAK-079 led to >90% reduction in peripheral blood plasmablasts. The cells reverted to pretreatment levels within 50 days. The levels of immunoglobulins (IgM, IgA and IgG) were reduced by 15% to 60% and did not fully return to prestudy baseline by the end of the study (78 days). These data indicate that TAK-079 may reduce autoantibody levels for a comparable duration, which is unique among therapeutics in clinical development for MG.

Preliminary data from the ongoing clinical study in patients with relapsed and/or refractory multiple myeloma (RRMM; TAK-079-1501) confirm the expected pharmacodynamic profile of TAK-079. Peripheral blood samples and bone marrow biopsies from patients dosed at 45, 135, 300, and 600 mg demonstrated target occupancy and reduction of target cells (ie, plasmablasts, short- and long-lived plasma cells) in the target organ, ie, bone marrow. Reductions in IgA, IgG, and IgM levels were also observed. Maximal pharmacodynamic effects were observed in the bone marrow of patients dosed at $\geqslant$300 mg.

In conclusion, TAK-079 reduced levels of autoantibodies in SLE patient samples, an effect that was mirrored by corresponding reductions in total IgG production. Similar reductions in total IgG were observed in healthy subjects after a single SC dose of TAK-079 and in patients with multiple myeloma receiving multiple SC doses. It is therefore hypothesized that similar SC dosing in MG patients with TAK-079 will reduce levels of AChR and MuSK antibodies because they are components of the total IgG profile. TAK-079 has a unique mechanism of action that inhibits production of autoantibodies and total IgG, one that could include sustained efficacy in patients with MG, and suggests that TAK-079 may have the potential to address the unmet needs of patients suffering from autoantibody-mediated diseases such as MG.

4.3 Dose Rationale

The criteria for selecting doses and a regimen of TAK-079 for treating patients with MG was based upon identifying safe and well-tolerated doses that demonstrate pertinent pharmacodynamic activity.

The clinical experience to date has demonstrated that TAK-079 is safe and well-tolerated in 3 different populations (ie, healthy subjects, patients with RRMM, and patients with SLE) and across a broad range of doses (≤600 mg), vascular concentrations, and exposures.

In healthy subjects, single doses of TAK-079 up to 0.06 mg/kg IV and 0.6 mg/kg SC were well tolerated: adverse events (AEs) were mild to moderate in intensity, with most of the AEs being mild. There were no serious adverse events (SAEs) or deaths reported in the study, and no AEs led to either study or visit discontinuation. No remarkable findings for laboratory tests, electrocardiograms (ECGs), vital signs, or physical examinations were reported that were related to TAK-079 treatment (see TAK-079 Investigator's Brochure [IB]).

As of June 2019, 31 patients have been enrolled in the ongoing RRMM study across 4 dose escalation cohorts (4 patients in 45 mg; 3 patients in 135 mg; 12 patients in 300 mg; and 12 patients in 600 mg). The maximum duration of exposure is 9 and 11 months for a patient continuing to receive 300 mg and 135 mg, respectively. The maximum tolerated dose has not been identified. At the IB data cutoff date (20 March 2019), the safety profile was comparable for all tested doses (45 mg [n = 4], 135 mg [n = 3], 300 mg [n = 6], and 600 mg [n = 6]). No patients have experienced dose-limiting toxicity, injection site reactions, or systemic infusion reactions. Drug-related SAEs, AEs that led to study discontinuation, or on-study deaths have not been reported. The most commonly reported (≥20% of all patients) treatment-emergent adverse events (TEAEs) by Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term regardless of causality at doses up to 600 mg include anaemia, decreased appetite, fatigue, headache, hypertension, and insomnia. All AEs have been Grade 1 or 2 other than 2 events reported as drug-related Grade 3 events (decreased neutrophil count and anaemia [in 1 patient each]), both of which were transient (see current TAK-079 IB for further details).

As of June 2019, 4 patients have been enrolled and treated with 45 mg TAK-079 or placebo (in a blinded manner) in the ongoing study in SLE. Data are still blinded, but 1 patient has reported 2 TEAEs: nausea and headache (both events Grade 1). No infusion reactions, cytokine release syndrome (CRS), or injection site reactions have been reported (see current TAK-079 IB [cutoff 20 March 2019] for further details).

There were 3 adverse effects observed in nonclinical 3-month, Good Laboratory Practice (GLP)-compliant toxicology studies in pharmacologically responsive monkeys. These adverse effects were dose-dependent thrombocytopenia, anemia, and/or leukopenia (associated with infection only at nontolerated doses). Thrombocytopenia set the nonclinical no-observed-adverse-effect level (NOAEL) at a dose of 0.3 mg/kg, which corresponded to a maximum observed concentration (C_{max}) of 8.1 µg/mL and an area under the concentration-time curve (AUC) of 28,875 day*ng/mL.

To further investigate the potential for anemia and thrombocytopenia in humans, a series of in vitro studies was performed. TAK-079 bound to CD38 on 11% to 17% of human platelets in platelet-rich plasma (1:8 platelet-rich plasma dilution, n = 2 healthy donors) with intensity 57% to 70% that of isotype control antibody at concentrations of 20 µg/mL (TKD-BCS-00327-R1 Amendment 1) (monkey platelets were not assessed because of technical limitations). Also, TAK-079 bound to CD38 on healthy human red blood cells (RBCs) (~10%-51%, n = 5) and

monkey RBCs (up to 19%, n = 1) with low intensity at concentrations 0.1 to 100 µg/mL in vitro (TKD-BCS-00064-R1-Report and TKD-BCS-00327-R1 Amendment 1) and did not induce hemolysis at ≤20 µg/mL, or hemagglutination at ≤1000 µg/mL, the highest concentrations tested (TKD-BCS-00327-R1 Amendment 1). TAK-079 also bound to human and monkey megakaryocyte and erythroid progenitors but did not induce direct cytotoxicity in these cells (TKD-BCS-00315-R1 and TKD-BCS-00407-R1). Lastly, TAK-079 bound to subsets of human and monkey leukocytes and depleted cells that express high densities of CD38, eg, plasma cells, plasmablasts, and NK cells (TAK-079-10010, TAK-079-10166, and TAK-079-1501). Importantly, despite binding activity observed in vitro, drug-related anemia or thrombocytopenia has not been observed in clinical studies to date, despite the current dosing regimens exceeding the associated nonclinical doses, concentrations, and exposures up to a maximum clinical dose of 600 mg (maximum individual concentration of 235 µg/mL and exposure of 698,070 day*ng/mL).

Two pharmacodynamic effects of TAK-079 are considered most pertinent to treating patients with MG. Changes in the level of serum Ig are used as a surrogate biomarker of anti-AChR and anti-MuSK antibodies because these autoantibodies are of the same IgG antibody class and are not present in healthy subjects, patients with RRMM, or patients with SLE. A single SC dose of TAK-079 at 0.1, 0.3, or 0.6 mg/kg to healthy subjects reduced serum mean IgA levels by 20% to 30%; IgG levels by 40% to 60%; and IgM by 10% to 25% (Figure 4.a). Similarly, weekly dosing of patients with RRMM with 45, 135, 300, or 600 mg generally reduced serum IgA to 30% to 95%, IgG to 5% to 60%, and IgM to 0% to 50% of baseline levels (Figure 4.b).

The second pharmacodynamic effect is a reduction in the level of plasma cells in bone marrow aspirates. The elimination of nonmalignant plasma cells in the bone marrow aspirates of patients in the RRMM study was examined as a surrogate for the elimination of pathogenic autoantibody-secreting plasma cells, as the bone marrow is a known site for autoantibody production in MG [12]. The desired 80% reduction in nonmalignant bone marrow plasma cells required dosing at 300 and 600 mg of TAK-079 (Figure 4.c). Reductions in nonmalignant bone marrow plasma cells generally appeared similar with exposure to 300 and 600 mg of TAK-079. Considering the small sample size, variability in pharmacokinetics (PK), and comparable safety profiles, selecting both doses for assessing potential efficacy is warranted.

The dosing schedule was estimated based on the desired effect of achieving autoantibody reductions that are correlated with clinical improvement in MG. While there is no accepted consensus for such an autoantibody reduction threshold, group-level clinical improvements in MG patients have been reported with reductions in the >50% range with rituximab [13] and efgartigimod [14]. In the absence of data characterizing TAK-079 activity on autoantibody levels in MG patients, changes in serum IgG were used as a surrogate. In patients with RRMM, a ~50% reduction in IgG was observed only after 8 weekly doses of TAK-079 (in the 300 mg and 600 mg cohorts, Figure 4.b). Based on these data, a schedule of 8 weekly doses was selected for the present study, with weekly monitoring of clinical laboratory values (CBC, immunoglobulin levels, see Section 8.4.1) to ensure the safety of this approach. Following the 8-week dosing period, a 6-month follow-up is planned for the continued monitoring of safety laboratory parameters and for evaluating the durability of any clinical benefit. Additionally, information will be obtained on the

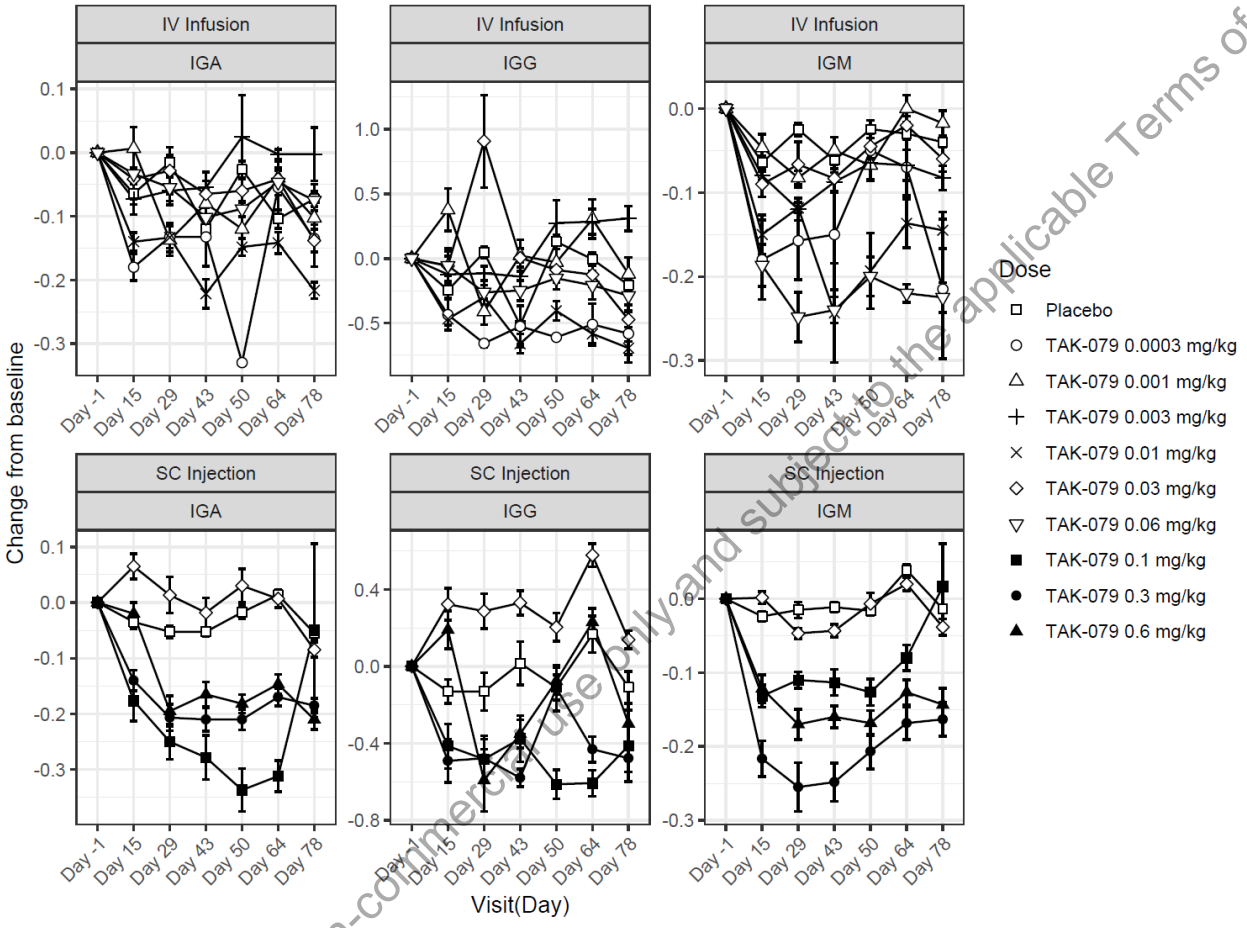
PK of TAK-079 and the reconstitution kinetics of IgG and autoantibody levels in MG patients to facilitate modeling for revised dosing regimens in subsequent studies.

The dose finding performed in patients with RRMM is relevant for dose selection in patients with MG because of similarities in target cell levels between these 2 populations. The mean levels of target cells in the target organ (bone marrow) are similar between patients with MG and the patients with RRMM studied in the 300 mg and 600 mg dose cohorts. In patients with MG, the mean level of plasma cells was reported to be 2.6% ± 1.9% of total mononuclear cells [15], while the mean levels of myeloma cells in the 300 and 600 mg cohorts were 2.3 ± 1.8% and 2.1% ± 2.6%, respectively. As we have selected the 300 and 600 mg doses based on safety, tolerability, and pharmacodynamic analyses (discussions above), the similarity in target cell levels between these patient groups provides reassurance that these analyses are translatable across the MG and RRMM indications.

Case reports exist of successfully treating antibody-driven diseases with anti-CD38 therapy using the same dose and schedule as in patients with multiple myeloma (daratumumab 16 mg/mL for ≥6 weekly doses), despite the absence of overall elevations in target plasma cells. For example, daratumumab was used to treat a patient with pure red cell aplasia (and otherwise normal bone marrow) from persistent anti–red blood cell antibodies after an ABO-mismatched allogenic bone marrow transplant for myelodysplastic syndrome [16]. Similarly, daratumumab was used successfully in a pediatric patient with anti–red blood cell antibodies after bone marrow transplantation [17]. Lastly, a case of antibody-mediated rejection after renal transplantation for postinfectious membranoproliferative glomerulonephritis was treated successfully with daratumumab after failure of bortezomib and rituximab therapy in a patient with normal bone marrow (less than 1% plasma cells) and concurrently treated with tacrolimus and prednisone [18]. No specific safety concerns of daratumumab therapy were reported. Together, these case reports indicate that the myeloma dose of anti-CD38 therapy was safe and effective in nonmyeloma patients who did not have any plasma cell tumor burden, had normal if not hypocellular bone marrow, and who had a critical need for removal of plasma cells secreting pathogenic antibodies.

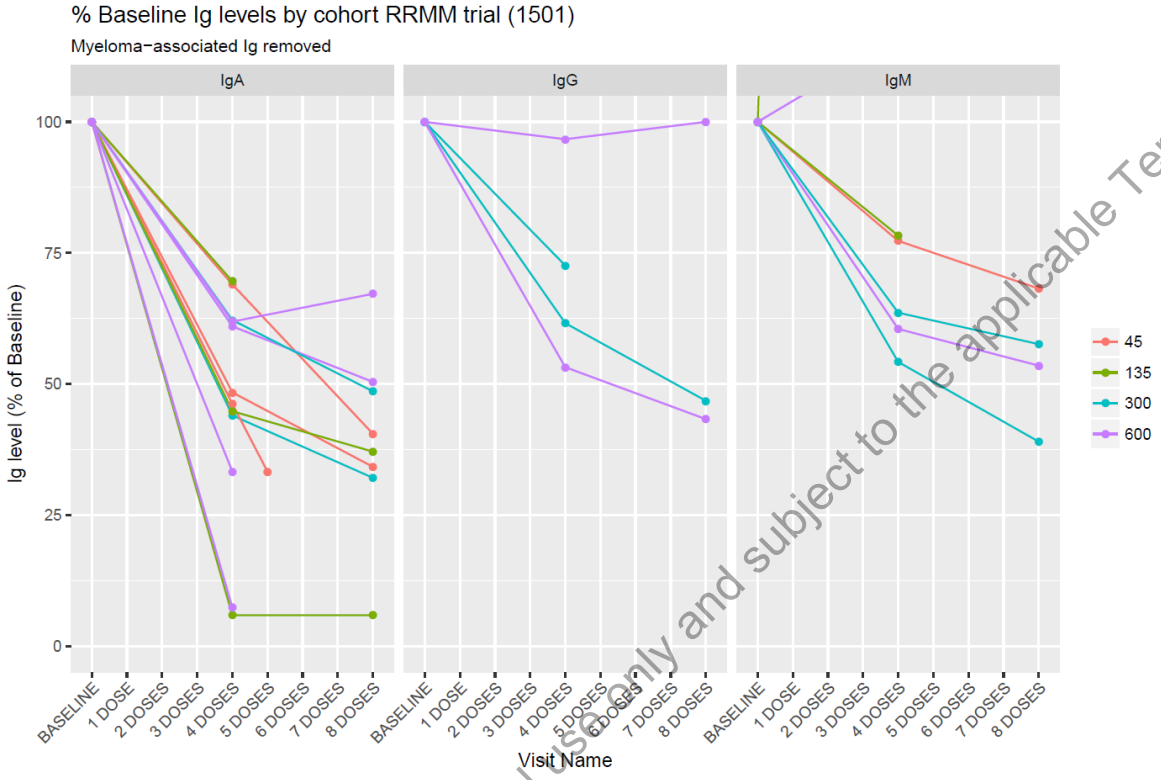
In conclusion, the collective safety, tolerability and pharmacodynamic profiles of TAK-079 in dose-escalation studies in healthy subjects, patients with RRMM, and patients with SLE indicate that the optimal doses and schedule of TAK-079 for patients with MG consist of 8 weekly doses of 300 or 600 mg.

Figure 4.a Change in Serum Baseline Levels of Total IgA, IgG, and IgM in Healthy Subjects



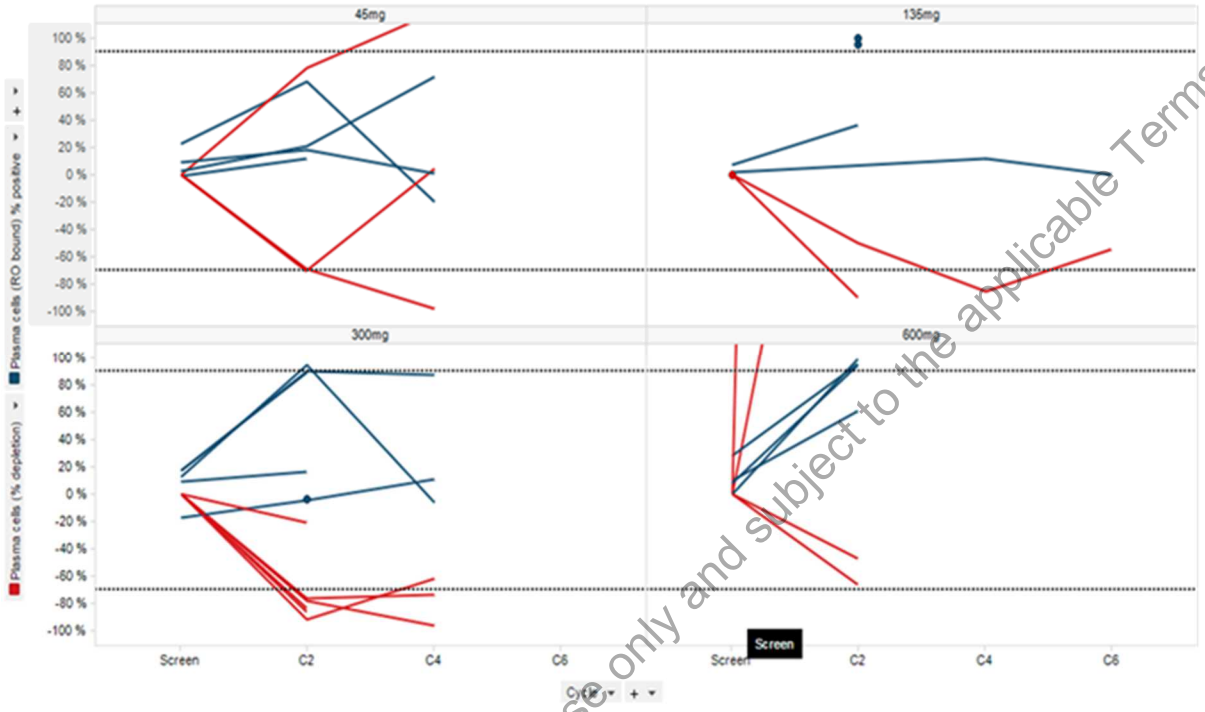
Ig: immunoglobulin; IV: intravenous; SC: subcutaneous; SEM: standard error mean.
Serum samples obtained after a single administration of TAK-079 or placebo, administered either as IV dosed 0.003 to 0.06 mg/kg or SC injection dosed 0.03 to 0.6 mg/kg.
Symbols represent the mean change for the cohort, and error bars represent the SEM.

Figure 4.b Serum Levels of Total IgA, IgG, and IgM in Patients With RRMM



Ig: immunoglobulin; LLD: lower limit of detection; RRMM: relapsed and/or refractory multiple myeloma.
Serum Ig levels (represented as percentage of baseline value for IgA, IgG, or IgM) for each subject obtained after TAK-079 subcutaneous dosing (45, 135, 300, or 600 mg) 1 week after the indicated number of doses. The myeloma-associated Ig is not shown. Ig profiles whose baseline values were already low (within 10% of the LLD of the assay) and subsequently dropped below the LLD are not shown.

Figure 4.c Pharmacodynamic Effects of TAK-079 on Plasma Cells in Bone Marrow Aspirate Samples From Patients With RRMM



RO: receptor occupancy (target occupancy); RRMM: relapsed and/or refractory multiple myeloma.

Target occupancy (blue lines, percentage of CD38 bound by TAK-079) and levels of plasma cells (red line, percent change from baseline level) in bone marrow aspirates from patients before treatment (screen) and then after 4 doses (Cycle 2), 12 doses (Cycle 4), and 14 doses (Cycle 6) of TAK-079 at 45, 135, 300, or 600 mg (dosed weekly for 8 weeks, followed by biweekly for 8 weeks, then every 4 weeks until disease progression). Target occupancy and plasma cell levels were quantified by flow cytometry, and the data represent individual patients.

4.4 Benefits and Risks Assessment

Because TAK-079 has not yet been tested in patients with MG, the overall clinical benefits and risks of TAK-079 in treating patients with MG have not been fully determined.

Potential benefits of TAK-079 in patients with MG are based on nonclinical and clinical data presented in Section 4.2. TAK-079 has been shown to reduce autoantibodies in an in vitro study of long-lived plasma cells from lupus patients, reduce inflammation in a monkey collagen-induced arthritis model, and reduce total immunoglobulin levels (a surrogate marker for autoantibodies) in a clinical study of healthy subjects and a clinical study of patients with RRMM. It is therefore hypothesized that TAK-079 can reduce the levels of pathogenic autoantibodies in patients with MG, thereby improving the muscle weakness caused by autoantibody-mediated inflammatory damage at the NMJ.

Risks of TAK-079 are based on clinical and nonclinical data presented in Section 4.3 and the intrinsic pharmacology of TAK-079 discussed in Section 8.6. Risks may include, but are not

limited to, injection site reactions (ISRs), CRS, hypersensitivity reactions, changes in hematologic parameters and infections. Patients will be monitored closely for these AEs in clinical studies with TAK-079.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

To evaluate the safety and tolerability of TAK-079 in patients with generalized MG who are receiving stable background therapy for MG.

5.1.2 Secondary Objectives

To assess the effects of TAK-079 on MG disease activity using clinical rating scales and autoantibody levels.

5.1.3 Exploratory Objectives

1. To determine the pharmacokinetics (PK) of TAK-079.
2. To determine the pharmacodynamic profile of TAK-079.
3. To explore the effects of repeated administration of TAK-079 on MG disease activity using a novel clinical disease assessment scale.
4. To explore the duration of a clinically meaningful effect on MG disease severity (using at least 1 MG clinical rating scale).
5. To explore the frequency and proportion of patients requiring rescue therapy.
6. To explore vaccine-induced protective antibodies.
7. To explore the effects of repeated administration of TAK-079 on exploratory biomarkers of disease activity.

5.2 Endpoints

5.2.1 Primary Endpoint

Percentage of patients with TEAEs, including Grade 3 or higher events, SAEs, and AEs leading to TAK-079 discontinuation.

5.2.2 Secondary Endpoints

1. Score change from baseline in the following:
   a) MG Activities of Daily Living (MG-ADL) score.
   b) Quantitative Myasthenia Gravis (QMG) score.

c) Myasthenia Gravis Composite (MGC) score.

d) Revised 15-item Myasthenia Gravis Quality of Life scale (MG-QoL15r).

2. Change from baseline in anti-AChR antibody or anti-MuSK antibody levels.
3. The percentage of patients meeting minimal clinically important difference criteria in the respective MG clinical impairment scales (MG-ADL, QMG, MGC).

5.2.3 Exploratory Endpoints

1. Serum concentration-time profile of TAK-079 PK parameters will include, but are not limited to observed concentration at the end of a dosing interval (C_{trough}) over time.
2. Change in serum immunoglobulin levels.
3. Pharmacodynamic analysis of the presence and changes of immune cells in peripheral blood before and during therapy.
4. Score change from baseline in Myasthenia Gravis Impairment Index (MGII) scores.
5. Duration of a clinically meaningful effect on MG disease severity (in all of the clinical disease impairment scales: MG-ADL, QMG, MGC, MGII).
6. Percentage of patients meeting minimal clinically important difference criteria in the MGII scale.
7. Frequency and proportion of patients requiring rescue therapy.
8. Immunogenicity assessment of TAK-079 in peripheral blood, including antidrug antibody (ADA).
9. Biomarkers of disease activity such as complement levels (C3, C4, complement split products); specific markers of CD38 pathway modulation may also be evaluated.
10. Change in levels of the following vaccine-protective antibodies: measles, mumps, rubella, diphtheria, and tetanus.

6.0 STUDY DESIGN

6.1 Overview of Study Design

This is a phase 2, randomized, double-blind, placebo-controlled study designed to assess the safety, tolerability, and efficacy of TAK-079 in patients with generalized MG in combination with standard background therapy.

It is expected that approximately 36 patients will be randomized into the study. After a screening period of up to 28 days, eligible patients will be randomized in a 1:1:1 ratio to one of the following treatment groups:

- TAK-079 300 mg added to stable standard background therapy.
- TAK-079 600 mg added to stable standard background therapy.

- Matching placebo added to stable standard background therapy.

Evaluation of intermediate doses and expansion of an existing dose level are all permissible after discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose-related toxicity, clinical activity, exposure, or pharmacodynamics of TAK-079.

The study will be divided into 3 sequential periods: a dosing period (8 weeks), a safety follow-up period (SFP; 8 weeks), and a long-term follow-up period (LFP; 16 weeks).

During the 8-week dosing period, TAK-079/matching placebo will be administered via SC injection once weekly for 8 weeks (see Section 8.1 for details on study drug administration).

Safety assessment, including safety laboratory tests (as listed in Appendix A), will be performed each week before subsequent dosing. Patients may have study drug (TAK-079/placebo) doses modified (eg, withheld or delayed) for safety reasons (see further details on dose modification/ stopping criteria in Table 8.d).

After completing the 8-week dosing period, patients will enter an 8-week blinded SFP, completing safety and efficacy assessments every 2 weeks. After completion of the Week 16 visit in the SFP, patients will be unblinded before entering the LFP visit at Week 20.

Patients randomized to TAK-079 will be followed every 4 weeks from Week 20 through Week 32 of the LFP for MG clinical activity scores and autoantibody levels; the end-of-study visit will take place at Week 32 of the LFP. For patients randomized to placebo, the end-of-study visit will take place at Week 20 of the LFP. The study schematic diagram is outlined in Figure 6.a.

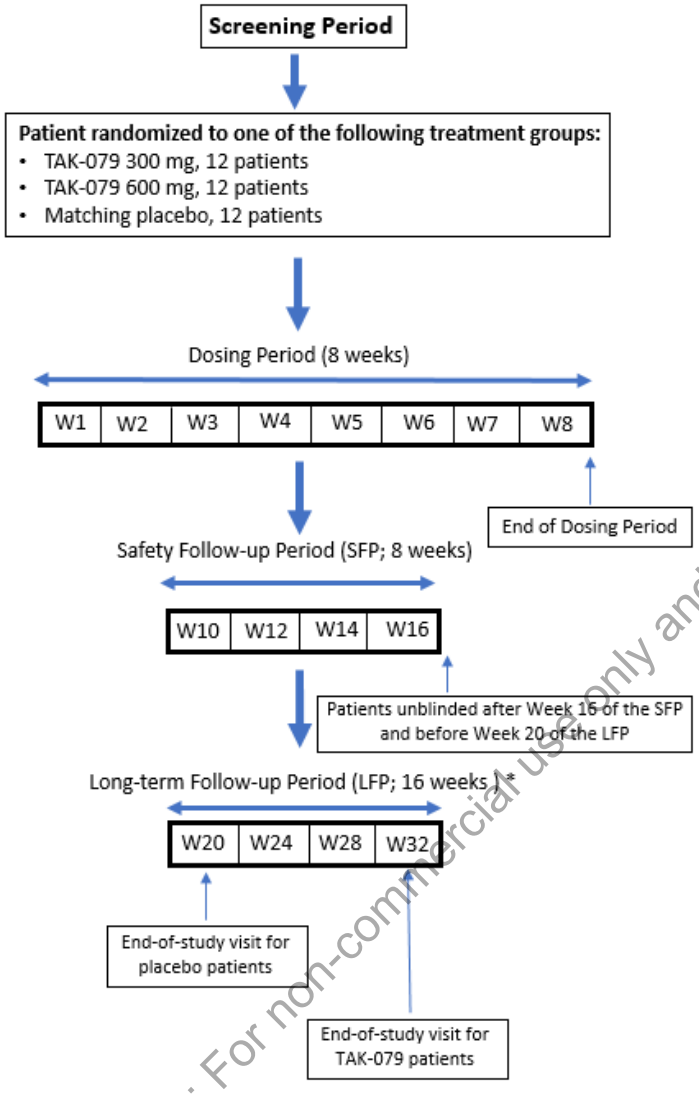
AEs ongoing at the Week 16 visit of the SFP (including unresolved clinical/laboratory parameters [see Section 9.6]) should be monitored through the LFP until they are resolved, return to baseline, or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). Study drug–related AEs/SAEs with onset after the SFP will be collected through the LFP.

Overall, the maximum follow-up period is approximately 24 weeks after the last dose of study drug.

Patients will be permitted to receive rescue medication (eg, IVIg, high dose corticosteroids, or plasmapheresis/plasma exchange) as determined by the investigator and described in Section 8.1.3. If the patient receives rescue therapy, they will automatically enter the SFP. Rescue therapy is defined as additional dosing of concomitant medications in accordance with institutional practices or the physician's best medical judgment to control and manage underlying MG conditions.

Study procedures and assessments, with associated time points, are presented in the schedule of events (SOE) table in Appendix A.

Figure 6.a Study Schematic



AE: adverse event; LFP: SAE: serious adverse event; W: week.
* Unresolved AEs as of Week 16 and related AEs/SAEs with onset after SFP will be collected through the LFP.

6.2 Safety and Disease Assessments

Safety evaluations will include monitoring of TEAEs per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03. Changes in clinical laboratory parameters (standard hematology and chemistry), vital signs, and ECGs that are judged by the investigator as clinically significant will be recorded on both the source documentation and in the electronic case report form (eCRF) as an AE.

Safety stopping rules are presented in Section 8.4.

Efficacy evaluations will include measurements of changes in MG disease activity using clinical rating scales and autoantibody levels.

Autoantibody levels will be measured at every visit, and MG clinical activity scores will be assessed throughout the study as shown in the SOE in Appendix A.

6.2.1 PK and Pharmacodynamic Assessments

Samples for PK, pharmacodynamic, and immunogenicity testing will be obtained at prespecified time points as described in the SOE in Appendix A.

6.3 Number of Patients

Approximately 36 patients with moderate to severe MG will be randomized from approximately 50 study sites in the US, Canada, and Europe.

6.4 Duration of Study

6.4.1 Duration of an Individual Patient's Study Participation

Study treatment duration will be a maximum of 8 weeks, followed by an 8-week blinded SFP.

Patients will be unblinded after Week 16 of the SFP and before Week 20 of the LFP. Patients randomized to TAK-079 will be followed every 4 weeks for 16 weeks in total in the LFP for continued monitoring of MG clinical activity scores and autoantibody levels. Patients randomized to placebo will attend an end-of-study visit at Week 20 of the LFP.

The total duration of an individual patient's study participation will be approximately 9 months.

6.4.2 End of Study/Study Completion Definition and Planned Reporting

The analyses for the clinical study report will be conducted after all patients randomized in the study have completed the end-of-study visit (ie, Week 20 for placebo patients or Week 32 for TAK-079 patients), as shown in Appendix A.

6.4.3 Time Frames for Primary and Secondary Endpoints to Support Disclosures

Refer to Section 15.4 for disclosure information for all primary and secondary endpoints.

6.4.4 Total Study Duration

It is anticipated that this study will end after all randomized patients have attended the end-of-study visit in the LFP (ie, Week 20 for placebo patients or Week 32 for TAK-079 patients) as shown in Appendix A. It is expected that the study will last for approximately 18 months (including enrollment, dosing period, SFP, and LFP).

7.0 STUDY POPULATION

7.1 Inclusion Criteria

Each patient must meet all the following inclusion criteria to be randomized to treatment:

1. The patient understands and agrees to study participation by providing a signed and dated written informed consent form (ICF) and any required privacy authorization before the initiation of any study procedures (as applicable, the patient's legally acceptable representative may provide written informed consent in accordance with local and regional regulatory requirements) and, in the opinion of the investigator, is capable of complying with protocol requirements.
2. Aged 18 years or older.
3. Diagnosis of MG supported by a positive serologic test for anti-AChR or anti-MuSK antibodies at screening.
4. Myasthenia Gravis Foundation of America (MGFA) clinical classification II to IV at screening.
5. MG-ADL total score of 6 or greater at screening, with at least 4 points attributed to nonocular items.
6. If receiving immunosuppressive drugs (ie, mycophenolate mofetil, methotrexate, cyclosporine, tacrolimus, cyclophosphamide), therapy must be ongoing for at least 6 months, with stable dosing ongoing for at least 3 months before screening. Patients receiving azathioprine must be on a stable dose for at least 6 months before screening.
7. If receiving oral corticosteroids, therapy must be ongoing for at least 3 months, with a stable dose at least 1 month before screening. Corticosteroids, including dexamethasone, must be given as oral, daily or every-other-day therapy, as opposed to pulse therapy.
8. If receiving cholinesterase inhibitors, therapy with a stable dose is required at least 2 weeks before screening.
9. The doses of concomitant standard background therapy must be expected to remain stable throughout the study unless dose reduction is required due to toxicities. Allowed background therapy is defined as no more than a cholinesterase inhibitor ± corticosteroid ± 1 steroid-sparing immunosuppressive drug (limited to azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, tacrolimus, or cyclophosphamide). Patients must be on at least one allowed background medication.
10. Female patients of childbearing potential are required to have a negative pregnancy test. Both male and female patients must practice an effective, reliable, and approved contraceptive regimen during the study and for up to 90 days or 5 half-lives, whichever is longer, after discontinuation of treatment (see Section 8.5.1).
11. Patients must be able and willing to comply with study procedures.

7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be randomized to treatment:

1. Presence of a thymoma (previous history of a fully encapsulated thymoma removed ≥12 months before screening is allowed) or history of invasive thymic malignancy unless deemed cured by adequate treatment with no evidence of recurrence for ≥5 years before screening.
2. History of thymectomy within 12 months before screening.
3. MGFA class I or V.
4. Received IVIg, SCIg (subcutaneous immunoglobulin), or plasmapheresis/plasma exchange within 4 weeks before screening, or an expectation that any therapy besides the patient's standard background therapies may be used for treatment of MG (eg, a rescue therapy) between screening and dosing.
5. Chronic obstructive pulmonary disease (COPD) or asthma with a pre-bronchodilatory forced expiratory volume in 1 second (FEV_1) <50% of predicted normal.

   Note: FEV_1 testing is required for patients suspected of having COPD or asthma.
6. Received rituximab, belimumab, eculizumab, or any monoclonal antibody for immunomodulation within 6 months before first dosing. Patients with prior exposure to rituximab must have CD19 counts within the normal range at screening.
7. Known autoimmune disease other than MG that could interfere with the course and conduct of the study.
8. Received a live vaccine within 4 weeks before screening or has any live vaccination planned during the study.
9. Any medical condition that, in the opinion of the investigator, might interfere with the patient's participation in the study (such as significant cardiovascular, pulmonary, hematologic, gastrointestinal, endocrinologic, hepatic, renal, neurologic, malignancy, or infectious disease), poses added risk for the patient, or could confound the assessment of the patient.
10. Pregnancy or lactation during the screening period or on Day 1 before first dose of study drug.
11. Participation in any other investigational drug study or exposure to other investigational agent within 4 weeks or 5 half-lives, whichever is longer, before Day 1.
12. An opportunistic infection ≤12 weeks before initial study dosing or currently receiving treatment for a chronic opportunistic infection, such as tuberculosis (TB), pneumocystis pneumonia, cytomegalovirus, herpes simplex virus, herpes zoster, or atypical mycobacteria. A mild, localized herpes simplex infection within 12 weeks of study dosing is allowed, as long as the lesion has resolved without systemic therapy prior to Day 1.

13. Inadequate organ and bone marrow function:
    a) Alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal (ULN).
    b) Total bilirubin >1.5 times ULN (Note: Patients with a confirmed and documented diagnosis of Gilbert syndrome are not excluded based on this criterion).
    c) Platelets <75,000/mm^3.
    d) Absolute neutrophil count <1500/mm^3.
    e) Hemoglobin <8 g/dL.
    f) IgG < 5 g/L (500 mg/dL)**.**
    g) Lymphocyte count <500/mm^3.
14. A positive T-cell interferon-γ release assay (TIGRA) (result through QuantiFERON-TB Gold test or T-Spot/Elispot) at the screening visit, noting the following:
    a) A purified protein derivative (PPD) skin test may be used if TIGRA testing is not available.
    b) Patients with an indeterminate TIGRA result must meet the following criteria:
        i. Negative PPD skin test (defined as <5 mm induration).
        ii. At low risk of acquiring TB (eg, avoids close contact with TB-positive individual[s]) and/or chest x-ray ≤6 months before the screening visit that is consistent with no evidence of latent or active TB.
15. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
16. A positive test result for hepatitis B surface antigen, or hepatitis B core antibody, or hepatitis C antibody, or HIV antibody/antigen, at screening. However, an individual who has a known history of chronic hepatitis C and has been treated and fully cured of the disease, confirmed with a negative hepatitis C virus RNA polymerase chain reaction test at screening, is not excluded on the basis of the positive hepatitis C antibody alone.
17. A history of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in the TAK-079/placebo formulation.

8.0 STUDY DRUG

8.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

After completion of all screening assessments and procedures and confirmation of eligibility, patients will report to the study site on Week 1 of the dosing period and be dosed with TAK-079

300 mg, TAK-079 600 mg, or matching placebo in accordance with their assigned treatment. Both the patient and physician will be blinded to treatment. Before TAK-079/placebo administration, patients will receive premedication as listed in Section 8.1.1 and will undergo safety assessments as outlined in Table 8.d and Appendix A.

Patients will receive study drug via SC injection, once weekly as outlined in Table 8.a and the SOE in Appendix A. The dosing period will last for 8 weeks. As dose levels (300 and 600 mg) will require multiple SC injections to administer the full dose, the Week 1 dose will be administered by giving each SC injection 30 minutes apart (±10 minutes) until the full scheduled dose has been administered. On all other drug administration days if the patient did not have a clinically significant infusion reaction per the investigator, the SC injections can be given at the same time without a waiting period.

Investigators will evaluate patients before each dose for the parameters outlined in Table 8.d. For the first dose, laboratory assessments in Table 8.d may be evaluated using results obtained at screening. Otherwise, laboratory results should be obtained on the day before or the day of dosing. In instances where clinical parameters do not meet criteria for continued dosing, the study drug must be temporarily withheld until parameters meet dosing levels, or discontinued, as outlined in Table 8.d or in accordance with the principal investigator's judgment. Dosing of TAK-079/placebo may not otherwise be reduced or escalated for any given patient.

Note: If study dosing is held for 2 consecutive doses because of safety concerns or conditions outlined in Table 8.d, the patient will be discontinued from study dosing and will advance to the SFP. If 2 or more patients discontinue study dosing based on the dose discontinuation criteria in Table 8.d, the Takeda clinician or designee will review available safety data to determine if adjustments to the treatment plan should be made.

Patients should remain on their stable dose of standard background therapy (as listed in Table 8.c), throughout the study unless dose reduction is required due to toxicities. Allowed background therapy is defined as no more than a cholinesterase inhibitor ± corticosteroid ± 1 steroid-sparing immunosuppressive drug (limited to azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, tacrolimus, or cyclophosphamide). Patients must be on at least one allowed background medication.

Excluded and permitted medications are summarized in Table 8.b and Table 8.c, respectively. Rescue therapy information is outlined in Section 8.1.3.

Table 8.a Summary of TAK-079/Placebo Dose Administration

Treatment Arm	Treatment [a]	Dose	Number of Patients
Arm 1	TAK-079	300 mg	12
Arm 2	TAK-079	600 mg	12
Arm 3	Matching placebo	Not applicable	12

[a] Patients will receive TAK-079 or matching placebo via subcutaneous administration once weekly over the course of 8 weeks, for 8 total doses.

8.1.1 Premedication

On each dosing day, 1 to 3 hours before TAK-079/placebo administration, patients are to be premedicated with an antipyretic (such as acetaminophen) and an antihistamine (such as diphenhydramine). The premedication regimen should be consistent with, but not limited to, the following:

- Antipyretic: oral acetaminophen (650-1000 mg).
- Antihistamine: oral or IV diphenhydramine (25-50 mg, or equivalent).

8.1.2 Postdose Medication

Patients will be closely monitored in the clinic for at least 2 hours after the first and second TAK-079/placebo dose; before discharge from the clinic, the possible signs and symptoms of anaphylactic reactions and CRS should be reviewed with patients.

After the first dose of study drug, patients will receive low-dose methylprednisolone (≤20 mg), or an equivalent, for the prevention of delayed injection-related reaction. Considering the timing of the greatest pharmacologic effect of TAK-079, postdose medication should be given 2 hours (±15 minutes) after the first injection of the first dose and 1 day after the first dose of study drug in the morning.

Postdose low-dose methylprednisolone (≤20 mg) is not mandated after subsequent doses of TAK-079/placebo (Weeks 2-8); however, it may be given if clinically indicated and under the discretion of the principal investigator.

NOTE: Patients with a higher risk of respiratory complications (eg, patients with a history of COPD and patients with asthma) may be administered the following, after each study dose (at the investigator's discretion):

a) An antihistamine (diphenhydramine or equivalent) on the first and second days after study dosing.

b) A short-acting β2-adrenergic receptor agonist, such as salbutamol (albuterol) aerosol.

c) Control medications for lung disease, such as the following:

   – Inhaled corticosteroids with or without long-acting β2 adrenergic receptor agonists for patients with asthma.

   – Long-acting bronchodilators, such as tiotropium or salmeterol, with or without inhaled corticosteroids, for patients with COPD.

The clinical site is responsible for sourcing treatments administered pre- or post–TAK-079/placebo administration.

On the basis of emerging data, the Takeda physician/designee may enhance treatments administered pre- or post–TAK-079/placebo injection to ensure patient safety.

8.1.3 Rescue Therapy

Rescue therapy is defined as additional dosing of concomitant medications in accordance with institutional practices or the physician's best medical judgment to control and manage underlying MG conditions. Rescue medications may include, but are not limited to, high-dose corticosteroids, IVIg, and plasmapheresis/plasma exchange. Protocol-restricted and permitted concomitant medications are outlined in Table 8.b and Table 8.c, respectively.

Patients should remain on their stable dose of immunosuppressive and corticosteroid therapies throughout the study (as aligned with protocol requirements in Table 8.b and Table 8.c). If the patient receives rescue therapy, they will automatically enter the SFP.

- Increasing, adding, or changing background immunosuppressive therapies, or adding a medication not otherwise within protocol limits, as deemed necessary by the principal investigator to treat manifestations of MG, should result in discontinuation of the patient from study dosing and advancement to SFP.

8.2 Excluded Concomitant Medications and Procedures

Excluded concomitant medications are provided in Table 8.b. If patients receive excluded medication, they will be discontinued from the dosing period and automatically enter the SFP.

Table 8.b Excluded Concomitant Medications

Category or Agent	Exclusion Criteria (Exclusion Criteria Must Be Upheld Throughout Study Participation, in Addition to the Time Points Indicated Below) [a]
Intravenous immunoglobulin [b]	Restricted from ≤4 weeks before the screening visit.
Plasmapheresis/plasma exchange [b]	Restricted from ≤4 weeks before the screening visit.
Subcutaneous immunoglobulin [b]	Restricted from ≤4 weeks before the screening visit.
Rituximab, belimumab, eculizumab, or any monoclonal antibody for immunomodulation	Restricted from ≤6 months before first dosing.
Live vaccinations	Restricted from ≤4 weeks before the screening visit.

AE: adverse event; MG: myasthenia gravis.
[a] Exceptions to excluded medications may be allowed for treatment of AEs, after discussion and agreement between the sponsor and principal investigator.
[b] Patients for whom any therapy (besides the allowed standard background therapies for MG) is reasonably expected between screening and dosing are excluded from study participation.

8.3 Permitted Concomitant Medications and Procedures

Permitted concomitant medications are summarized in Table 8.c.

Table 8.c Permitted Concomitant Medications

Medications	Criteria (Criteria Are to Be Maintained From Screening to Completion of Study Dosing Phase)
Immunosuppressants • Azathioprine [a] • Mycophenolate mofetil • Methotrexate • Cyclosporine • Tacrolimus • Cyclophosphamide	Therapy must be ongoing for at least 6 months with a stable dose for at least 3 months before the screening visit.
Oral corticosteroids	Therapy must be ongoing for at least 3 months with a stable dose at least 1 month before the screening visit.
Cholinesterase inhibitors	Therapy with a stable dose is required at least 2 weeks before the screening visit.

[a] Azathioprine dosing must be stable for at least 6 months before screening visit.

8.4 Study Stopping Rules

Takeda clinicians/designee will provide ongoing safety oversight and surveillance throughout the study dosing period, SFP, and LFP. As such, TAK-079 clinicians/designee are to receive and trend all reported SAEs and conduct a review of all safety data periodically throughout the study. On the basis of outcomes of the Takeda safety reviews and in accordance with predefined criteria, decisions about the dosing regimen are to be made and implemented.

8.4.1 Assessment and Criteria for Terminating Patient Dosing

Investigators will evaluate patients before each dose for the parameters outlined in Table 8.d. In instances where clinical parameters do not meet criteria for continued dosing, study drug dosing must be temporarily withheld until parameters meet dosing levels, or discontinued.

Patients whose clinical parameters meet dose discontinuation criteria, as outlined in Table 8.d, are to be permanently discontinued from study dosing and will advance to the SFP, completing all associated assessments listed in the SOE table in Appendix A.

In addition, patients should be permanently discontinued from study dosing if any of the following is experienced:

- An AE or other medical condition in which the principal investigator deems it is not in the best interest of the patient to continue study dosing.
- The patient receives rescue medication as described in Section 8.1.3.
- If study dosing is held for 2 consecutive doses because of safety concerns or conditions outlined in Table 8.d.

- The patient chooses to withdraw from study dosing.
- The patient has a confirmed pregnancy.

NOTE: Safety reviews of all AEs will be conducted in an ongoing manner (see details in Section 13.1.6). If the stopping bounds for general AEs or SAEs is met, an investigation of the safety profile will be conducted and a decision regarding accrual will be made. Further, if 2 or more patients discontinue study drug dosing on the basis of the dose discontinuation criteria in Table 8.d, the Takeda clinician/designee will review available safety data to determine if adjustments to the treatment plan should be made.

Immunoglobulin levels may be reduced with TAK-079; therefore, quantitative Ig levels (IgG, IgA, and IgM) will be evaluated during the treatment period at a central laboratory. If any of these are >50% below the lower limit of normal, the investigator should manage as clinically appropriate on the basis of signs and symptoms the patient is experiencing. If IgG levels are below the lower limit of normal and the patient is experiencing a severe infection, IVIg may be administered, as per physician discretion according to standard practice. If IVIg is given as a rescue treatment, as described in Section 8.1.3, the patient will be discontinued from the dosing period of the study and enter the SFP.

Table 8.d Summary of Subsequent Dosing Criteria

Safety Parameter	Dosing Criteria		
	Continue Dosing	**Dose Hold [a]**	**Dose Discontinuation [b]**
Laboratory Investigations			
Neutrophils	ANC ≥1500/mm^3	Total neutrophils ≥Grade 2 [c] ANC <1500/mm^3	
Platelets	Thrombocytopenia ≤Grade 2 [c] Platelets ≥50,000/mm^3	Thrombocytopenia ≥Grade 3 [c] Platelets <50,000/mm^3	
Total lymphocyte count	≥500/mm^3 or ≥90% of the baseline level	<500/mm^3 and <90% of the baseline level	
Hgb	≥8 g/dL	<8 g/dL	
Events of Clinical Interest			
Hypersensitivity (IRR, allergic reaction, or anaphylaxis) (See Section 8.6.1). **NOTE:** IRR, allergic reaction or anaphylaxis are each classified according to CTCAE v4.03. Anaphylaxis is diagnosed according to Sampson et al [19].	≤Grade 2 [c]		≥Grade 3[c] **or** any signs or symptoms of an anaphylactic reaction [19]
CRS (See Section 8.6.2) NOTE: CRS [d] is classified according to Lee et al [20].	Grade 1 with symptomatic treatment allowed in accordance with Lee et al [20].		≥Grade 2
Systemic infection		Grade 2 [c] Hold dosing until the infection is resolved.	≥Grade 3 [c] or infections requiring hospitalization

ANC: absolute neutrophil count; CRS: cytokine release syndrome; CTCAE: Common Terminology Criteria for Adverse Events; Hgb: hemoglobin; IRR: infusion-related reaction; MG: myasthenia gravis; NCI: National Cancer Institute; SFP: safety follow-up period.

[a] Patients whose clinical parameters meet dose-hold criteria will not receive the scheduled dose of TAK-079; patients instead return for reassessment and evaluation at next planned visit.

[b] Patients whose clinical parameters meet dose discontinuation criteria are to be permanently discontinued from study dosing; patients will advance to the SFP, completing all associated assessments. Standard background therapy for MG will be managed according to the principal investigator's discretion.

[c] Laboratory, IRR, allergic reactions, anaphylaxis and infection grading are based on CTCAE v4.03.

[d] A full cytokine panel is to be obtained for any suspected events, at any grade, of CRS; further information and suggested management of CRS is provided in the protocol.

8.5 Precautions and Restrictions

Patients will be closely monitored before all TAK-079/placebo administrations and for at least 2 hours after the administration of the first and second dose of TAK-079/placebo, with additional assessment and observations as necessary based on the principal investigator's best medical judgment, and as warranted by exhibited clinical signs or symptoms at each study clinic visit.

Postdose monitoring should include vital sign assessments as outlined in Section 9.5.8, and additional postdose medications for those with a history of asthma or COPD may be considered, as outlined in Section 8.1.2.

On each dosing day, patients should not drive, operate dangerous tools or machinery, or engage in any other potentially hazardous activity that requires full alertness and coordination if they experience sedation from any premedication listed in Section 8.1.1.

Patients are to be instructed to limit the use of alcohol while enrolled in this study.

8.5.1 Pregnancy, Lactation, and Contraception

TAK-079 has not been administered to women who are pregnant or lactating. No reproductive or developmental toxicity studies have been performed for TAK-079 to date; hence, the effects of TAK-079 on fertility and the developing fetus are not known at this time. There were no TAK-079–related findings (organ weight changes or microscopic findings) noted in the reproductive tract (cervix, epididymis, ovary, oviduct, testis, and vagina) of sexually immature male and female monkeys after administration for up to 13 weeks. Women of childbearing potential may be enrolled in clinical studies with appropriate precautions to prevent pregnancy.

The half-life of TAK-079 has not yet been determined. Based on conservative information in the literature regarding the half-life of IgG1 as well as other IgG1 human monoclonal antibodies [21,22], a conservative time frame to continue contraception would be 150 days.

TAK-079 should not be administered to women who are pregnant or breastfeeding.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR
- If they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception at the same time (Table 8.e), from the time of signing of the ICF through 90 days or 5 half-lives*, whichever is longer, after discontinuation of treatment, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient (periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together).

Table 8.e Highly Effective and Other Effective Methods of Contraception for Female Patients

Highly Effective Methods	Other Effective Methods (Barrier Methods)
IUD	Latex or nonlatex condom with or without a spermicidal agent
Hormonal (oral contraceptives, injectable contraceptives, contraceptive patches, or contraceptive implants)	Diaphragm with spermicide; cervical cap with a spermicide; sponge with a spermicide

IUD: intrauterine device.
It is recommended to combine a highly effective method with a barrier method. If one of the highly effective methods cannot be used, using 2 barrier methods at the same time is recommended.

Male patients, even if surgically sterilized (ie, status post-vasectomy), must agree to 1 of the following:

- Agree to practice effective barrier contraception (Table 8.f) during the entire study treatment period and through 90 days or 5 half-lives*, whichever is longer, after discontinuation of treatment, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.

Table 8.f Highly Effective and Other Effective Methods of Contraception for Male Patients

Highly Effective Methods	Other Effective Methods (Barrier Methods)
Vasectomy	Latex or nonlatex condom with or without a spermicidal agent Diaphragm with spermicide; cervical cap with spermicide; sponge with spermicide

It is recommended to combine the highly effective method with a barrier method. If the highly effective method cannot be used post-vasectomy, using 2 barrier methods at the same time is recommended.

- * Note that the half-life of TAK-079 has not yet been determined. Based on conservative information in the literature regarding the half-life of IgG1 as well as other IgG1 human monoclonal antibodies [21,22], a conservative time frame to continue contraception would be 150 days.

8.5.2 Drug Interactions

Nonclinical drug interaction studies have not been conducted with TAK-079. However, as a fully human IgG1 monoclonal antibody, the risk of drug-drug interactions is low.

8.5.3 Interference with Serological Testing

Anti-CD38 monoclonal antibodies have been reported to bind to CD38 on RBCs and results in a positive indirect Coombs test, which may persist for up to 6 months. The determination of a patient's ABO and Rh blood type are not impacted, but the RBC binding may mask detection of antibodies to minor antigens in the patient's serum [23,24]. It is possible TAK 079 may affect the results of these blood tests, this is being evaluated. Should a patient require a blood transfusion, blood transfusion centers should be informed of this interference with serological testing [24].

8.6 Management of Clinical Events

8.6.1 Hypersensitivity Reactions: Infusion Reactions

Because infusion reactions and other antibody-mediated hypersensitivity reactions have been reported with other biologic agents, similar AEs may be seen with TAK-079. Infusion reactions are potentially dose-limiting AEs, not uncommonly associated with IV administration of biologic agents, but are less frequently associated with SC injection of these therapies [20,25,26].

Symptoms of hypersensitivity may range from mild skin rash to more severe reactions, wheezing, hypotension, poor perfusion, respiratory arrest, and rarely death. Nonanaphylactic clinical hypersensitivity typically occurs within the first hour after dosing; however, delayed responses have been reported in literature with other biologic agents [27]. Symptoms of anaphylaxis, a potentially life-threatening condition, range from swelling, angioedema, and bronchospasm to respiratory distress and shock [27]. Hypersensitivity reactions in the literature often occur within a few hours following drug intake [20,27]. Based on outcomes from studies with daratumumab, patients who experience CRS and have preexisting COPD or asthma may be at particular risk for such respiratory complications as bronchospasm should an infusion reaction event occur. Therefore, patients whose FEV_1 is <50% of predicted normal will be excluded from study participation (see Section 7.2) [28]. Eligible patients with a history of COPD may require additional postdose medications to manage respiratory complications (see Section 8.1.2) [26].

To date, subjects administered TAK-079 have not exhibited anaphylactic symptoms. In the clinical study of healthy subjects (TAK-079_101), an infusion-related reaction (IRR) was defined as a TEAE occurring within 2 hours after the start of an infusion; there were no IRRs in this study, and no allergic or cytokine release reactions were observed within this time period (TAK-079 IB).

In this study:

- Patients with a history of severe allergic or anaphylactic reactions to recombinant proteins or excipients used in the TAK-079 formulation are not eligible and therefore will not be exposed to TAK-079.
- Premedication before each study dose, to prevent IRRs, is mandatory for all patients (as described in Section 8.1.1); postdose medication can be administered at the investigator's discretion.

- Patients who are treated with TAK-079/placebo will be carefully monitored in the clinic for 2 hours after the first 2 doses, and any AE will be managed in accordance with available guidelines or institutional standards of care [19,29].

NOTE: Additional blood pressure measurements should be assessed any time the patient complains of symptoms consistent with an IRR. If the patient experiences hypotension (with or without symptoms), intensive blood pressure monitoring according to local practice should be instituted. The patient should not be released from the site until blood pressure has returned to Grade 1 or baseline for at least 1 hour.

8.6.1.1 Management Recommendations for Hypersensitivity Reactions

Patients in clinical studies receiving TAK-079 are to be carefully monitored for signs and symptoms of systemic hypersensitivity reactions (including IRRs, allergic reactions, or anaphylaxis; management recommendations for CRS are discussed separately in Section 8.6.2.1). Signs and symptoms of systemic hypersensitivity reactions include rash, urticaria, fever, and/or bronchospasms. Depending on the severity of the reaction, management of hypersensitivity reactions may include discontinuation of SC administration of TAK-079 and/or the administration of appropriate medical therapy.

Recommendations for the management of hypersensitivity reactions [19] are as follows:

Grade 1

a) Study Management:

- If the full dose of TAK-079 has not yet been administered, hold dosing until symptoms resolve, at which time the remainder of TAK-079 dose may be administered.

b) Patient Support:

- Monitor closely until resolution of symptoms.

Grade 2

a) Study Management:

- If the full dose of TAK-079 has not yet been administered, hold dosing until symptoms resolve, at which time the remainder of TAK-079 dose may be administered.

b) Patient Support:

- Administer appropriate symptomatic and prophylactic medical care; consider postinjection medications as outlined in Section 8.1.2.
- For allergic reaction, provide symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, epinephrine) as medically appropriate and consider postinjection medications.

Grade 3 or Greater (including any diagnosis of anaphylaxis according to Sampson et al [19]).

a) Study Management:

- Patients are to discontinue study dosing and advance to the safety follow-up period of the study.

b) Patient Support:

- Provide symptomatic treatment, including epinephrine, until symptoms resolve.
- Consider hospitalization as appropriate.

8.6.2 Cytokine Release Syndrome

CRS represents an important infusion reaction often associated with the use of natural and bispecific monoclonal antibodies used in anti-inflammatory and antitumor therapies [20,30,31]. Onset of CRS may occur early in therapy, often after the first infusion of the drug [20,31,32], because of a high level of activation of the immune system and engagement and proliferation of T cells that can result in increased cytokine release.

An in vitro study with human lymphocytes demonstrated that TAK-079 has no agonist activity, suggesting that TAK-079 is unlikely to cause cytokine release due to cell activation. In repeated-dose toxicity studies in cynomolgus monkeys, there were no TAK-079–related increases in cytokines at 0.1 mg/kg. At ≥0.3 mg/kg, dose-related increases (up to 29.5-fold for any individual monkey) in tumor necrosis factor alpha (TNF-α) were observed 30 minutes after the first dose of TAK-079. These increases were considered small compared with elevations observed during a cytokine storm event, were not accompanied by changes in other cytokines, and did not translate into clinical manifestation of CRS. Increases in serum TNF-α may be related to TAK-079–mediated lyses of CD38+ lymphocytes.

In the first-in-human study, conducted in healthy subjects, rarely observed symptoms consistent with mild CRS were reported, particularly at higher doses; dose adjustment or interruption was not required. No CRS has been reported in the ongoing SLE and RRMM studies (TAK-079 IB).

The CRS hallmark is fever [20]. CRS also presents with rash, urticaria, headache, chills, fatigue, nausea, and/or vomiting [20,30]. Severe CRS is characterized by severe dyspnea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. The acute respiratory failure may be accompanied by such events as pulmonary interstitial infiltration or edema visible on a chest x-ray. The syndrome frequently manifests within 1 or 2 hours of initiating the first infusion [20,32,33]. Patients with a history of pulmonary insufficiency or those with pulmonary tumor infiltration may be at greater risk of poor outcome and should be treated with increased caution. On the basis of outcomes from studies of the anti-CD38 monoclonal antibody daratumumab, patients with preexisting COPD or asthma may be at particular risk for respiratory complications, such as bronchospasm, should an infusion reaction or CRS event occur [28]. Therefore, if the patient's FEV_1 is <50% of predicted normal, they will be excluded from study participation (see Section 7.2). Eligible patients with a history of COPD

may require additional postinjection medications to manage respiratory complications [26] (see Section 8.1.2).

8.6.2.1 Management Recommendations for CRS

Premedication before each study dose, to prevent infusion reaction, is mandatory for all patients as described in Section 8.1.1. Postdosing medication, to be administered at the investigator's discretion, is described in Section 8.1.2.

Immediate clinical assessment and management of symptoms is key to symptom management. Patients will be monitored in the clinic for at least 2 hours after the first 2 TAK-079 doses. Medical symptomatic treatment according to guidelines or institutional standard of care is recommended [20]. Before discharge from the clinic, the possible signs and symptoms of anaphylactic reactions and CRS should be reviewed with patients. Further, patients should receive information about what to do if emergency care is needed (see Appendix C for further details on clinical signs and symptoms associated with CRS and the CRS grading system [20]).

If a patient is exhibiting signs or symptoms possibly assessed as CRS by the investigator, a blood draw should be performed for central evaluation that could include, but need not be limited to, immune markers and cytokine markers. Additional guidance for study management and patient support for CRS by grade is as follows:

Grade 1 (defined as fever, constitutional symptoms)

a) **Study Management:**

- Hold study dosing until symptoms resolve; resume dose of TAK-079 at same dose level after symptom resolution.

b) **Patient Support:**

- Provide vigilant supportive symptomatic treatment, which may include antipyretics, analgesics, and antihistamines.

Grade 2 (defined as hypotension, hypoxia, organ toxicity)

a) **Study Management:**

- Discontinue study dosing and advance to SFP.

b) **Patient Support:**

- Provide vigilant supportive symptomatic treatment, which may include antipyretics, analgesics, and antihistamines, with or without tocilizumab.

Grade 3 (defined as hypotension, hypoxia, and severe organ toxicity)

a) **Study Management:**

- Discontinue study dosing and advance to SFP.

b) Patient Support:

- Provide vigilant supportive care, including but not limited to tocilizumab, antipyretics, analgesics, and antihistamines, as medically indicated [20].

8.6.3 Hematologic Effects

Reductions in platelets, lymphocytes, and RBCs occurred in nonclinical studies in some animals administered repeated doses of TAK-079 at ≥1 mg/kg, higher than the NOAEL of 0.3 mg/kg. In the first-in-human study, no decreases were seen in RBCs or platelets.

In the healthy subjects study (TAK-079-101), which is completed, and in the SLE study (TAK-079-2001), which is ongoing, hematologic parameters were monitored closely. There were no markedly abnormal hematologic values in any subject or any AEs related to thrombocytopenia or anemia in the healthy subjects study or, as of the TAK-079 IB clinical data cutoff (20 March 2019), in the SLE study. In the study in RRMM (TAK-079-1501), hematologic parameters were monitored according to standard practice. At doses up to 600 mg, no decreases in platelet counts below the lower limit of normal related to TAK-079 were seen (note: 1 event of Grade 3 thrombocytopenia was reported as related to progression of the underlying myeloma). Two events of Grade 3 anemia have been reported, with one reported as related to study drug and the other reported as not related to study drug but related to progression of the underlying myeloma. No events of lymphocytopenia (or decreased lymphocyte count) have been reported (TAK-079 IB).

Patients will be monitored closely, including testing of hematologic parameters throughout this clinical study as described in Section 9.5.12 and Appendix A. In instances where clinical parameters do not meet dosing criteria, study dosing must be temporarily or permanently withheld as outlined in Table 8.d. Medical interventions may be administered according to institutional guidelines.

8.6.4 Infections

In a GLP-compliant, 13-week toxicology study, bacterial and/or viral infection, secondary to immune suppression, was observed in cynomolgus monkeys at IV doses of 3, 30, and 80 mg/kg administered once every 2 weeks. The NOAEL dose of 0.3 mg/kg, administered IV once every week, was not associated with infections.

Mild infection, specifically nasopharyngitis, was reported across all SC dose levels in the healthy subjects study (TAK-079_101). As of the TAK-079 IB data cutoff (20 March 2019) in the study in patients with RRMM (TAK-079-1501), 4 of 19 patients treated at doses up to 600 mg reported an event in the infections and infestations System Organ Class; the most common AE reported was upper respiratory tract infection (n = 2); all were Grade 2, and only 1 was reported as related to study drug. No infections have been reported in the patients in the SLE study (TAK-079-2001) (TAK-079 IB).

Patients will be monitored for any signs and symptoms of infections throughout this clinical study (see Appendix A and Table 8.d). In instances where clinical parameters do not meet dosing criteria,

study dosing must be temporarily or permanently withheld as outlined in Table 8.d. Management of infections according to standard medical care is recommended.

8.6.5 Injection Site Reactions

Local injection site abnormalities have not been observed in monkey and rat nonclinical studies after SC and/or IV administration of TAK-079. In the clinical study of healthy subjects (TAK-079-101), mild injection site AEs were reported; most were Grade 1 and included primarily erythema or tenderness. All injection reactions resolved within a few days.

In the literature, ISRs with anti-CD38 monoclonal antibodies have been reported [34]. ISRs consisted of induration, erythema, injection site discoloration, and hematomas (all grade 16.7%) [34].

Mild injection site AEs, reported as erythema or tenderness with palpation, were mostly observed at the 2 lowest SC doses in the healthy subjects study. All reactions resolved within a few days. No oral medications, such as paracetamol (acetaminophen) or antihistamines, were needed to treat these mild ISRs. In the study in patients with RRMM at doses up to 600 mg (given with 3 SC injections), no ISRs have been reported (TAK-079 IB). Patients receiving TAK-079 SC will be closely monitored for any ISR and will be managed with standard medical care.

8.6.6 Antidrug Antibody Interactions

Antidrug antibody (ADA) responses were detected in most monkeys in the single-dose PK studies and the 4-week (non-GLP) and 13-week (GLP) toxicology studies. Stronger positive ADA responses were generally associated with lower serum concentrations of TAK-079, and this was especially notable in the 13-week repeated-dose toxicity studies and at lower doses. In the single-dose healthy subjects study (TAK-079-101), 5 of 54 TAK-079–treated subjects were positive for ADA (3 subjects with transient ADA and 2 subjects with persistent ADA). Of these, 1 subject was treated in the 0.06 mg IV cohort, and the remaining 4 subjects were treated with 0.03 mg/kg (2 subjects), 0.1 mg/kg (1 subject), or 0.6 mg/kg (1 subject) SC TAK-079. Immunogenicity was not associated with clinically significant AEs, even in the 2 subjects with persistent immunogenicity (TAK-079 IB).

8.6.7 Overdose

As outlined in Section 10.1.2, an overdose is defined as a known deliberate or accidental administration of investigational drug, to or by the study subject, at a dose above that which was assigned to that individual subject (ie, patient) according to the study protocol.

To date, there is no experience with overdose of TAK-079. If an overdose does occur, as defined in Section 10.1.2, close monitoring and supportive treatment, as medically required, are recommended. Events of overdose, with or without an associated AE, should be promptly reported to the study medical monitor and will be entered into the eCRFs as an AE.

8.7 Description of Investigational Agents

8.7.1 Study Drug: TAK-079

TAK-079 is a full-length, human IgG1 monoclonal antibody directed against human CD38. The antibody is composed of 2 light chains of the lambda subclass and 2 heavy chains linked together by 2 disulfide bridges.

The strength of the TAK-079 drug product for SC use in this study is 100 mg TAK-079 in 1 mL (100 mg/mL). TAK-079 drug product and matching placebo are supplied in aseptically filled, single-use, clear, type I, borosilicate glass vials with fluoropolymer-coated butyl rubber stoppers and aluminum crimp seals with flip-off caps.

8.7.1.1 Preparation, Reconstitution, and Dispensation

Refer to the pharmacy manual for detailed instructions regarding the preparation of TAK-079 study supply.

TAK-079 is a monoclonal antibody and caution should be exercised when handling TAK-079 as with other biologics.

8.7.1.2 Packaging and Labeling

Supplies of TAK-079 are labeled according to the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practices and include any locally required statements.

8.7.1.3 Storage, Handling, and Accountability

During shipping, vials are to be protected from light and maintained within temperatures provided in the pharmacy manual. Each TAK-079 shipment includes a packing slip listing the contents of the shipment, and any applicable forms. The investigator or designee must confirm that appropriate temperature conditions have been maintained for all TAK-079 received and that any discrepancies are reported and resolved before use.

Upon receipt of study medication, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, the medication is received within the labeled storage conditions, and is in good condition. If quantity and conditions are acceptable, the investigator or designee should acknowledge the receipt of the shipment by signing the bottom half of the packing list and faxing per instructions provided on the form. If there are any discrepancies between the packing list and the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file. The sponsor must be notified immediately of any temperature excursions and shipping and handling or storage discrepancies.

All clinical study material must be kept in an appropriate, limited access, secure location until used, destroyed, or returned to the sponsor or designee. TAK-079 must be stored according to the manufacturer's stipulation, as specified on the label (see the pharmacy manual for additional

information). Detailed dosage preparation instructions are provided in the Directions for Use section of the pharmacy manual. Complete receipt, inventory, accountability, reconciliation, and destruction records must be maintained for all used and unused study drug vials. Detailed instructions and the associated forms for these activities are in the pharmacy manual. Drug supplies will be counted and reconciled at the site before being returned to Takeda or designee or being destroyed.

The investigator or designee must ensure that the study medication is used in accordance with the approved protocol and is dispensed only to patients enrolled in the study. To document appropriate use of study medication (TAK-079), the investigator must maintain records of all study medication delivery to the site, site inventory, use by each patient, and return to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of clinical study material during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired clinical study material for return to the sponsor or its designee.

Further guidance and information are provided in the pharmacy manual.

8.7.2 Clinical Study Drug Blinding

The assignment of study patients to 1 of 3 study arms is maintained through a blinded randomization schedule, available in instances of medical emergencies to the principal investigator. Otherwise, site staff will remain blinded through Week 16 of the study, as described in Section 6.1. Details on maintaining the study blind, and unblinding procedures, are outlined in Section 8.7.4.

8.7.3 Randomization Code Creation and Storage

The randomization and medication schedule will be generated and maintained by an interactive voice/web response system (IXRS). All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.7.4 Clinical Study Blind Maintenance/Unblinding Procedure

To maintain the integrity of the study, all study personnel, including the investigators, site personnel, the contract research organization (CRO) medical monitor, study clinicians, and the sponsor, will be blinded to the treatment assignments during the treatment period. Treatment assignments will be obtained through the IXRS according to the procedures outlined in the study manual or relevant training materials. Information regarding the treatment assignments will be kept securely at Takeda or designee, per its standard operating procedures.

- Records of the patient number, the date the study drug was dispensed, and the treatment assignment will be maintained by the study site.

- Emergency unblinding, if necessary, will be conducted via the IXRS. The following are key factors to be considered regarding breaking the study blind:
  - If the treatment assignment must be revealed for the safety of the patient, to treat an AE, or to inform decisions for subsequent therapy, the investigator will contact the Takeda clinician or designee (in accordance to contact information and procedures outlined in the study manual or relevant training materials).
  - A decision to break the blind must be reached by the Takeda clinician and the investigator. The investigator, or designee, may break the blind through the IXRS independent of the Takeda clinician only if the investigator considers the situation to be an emergency and requires specific knowledge of the blinded study treatment to properly treat the AE/safety issue.
  - If the treatment of the AE/safety issue is anticipated to be the same regardless of study drug assignment, the blind should not be broken.
  - The event requiring breaking the blind must be documented in the eCRF, including the date the blind was broken.

After breaking the blind, the patient will be discontinued from further study drug administration in this study.

8.7.5 Destruction of Sponsor-Supplied Drugs

The investigator, institution, or head of the medical institution (where applicable) is responsible for TAK-079 accountability, reconciliation, and record maintenance, ie, receipt, reconciliation, and final disposition records.

The investigator must maintain 100% accountability for all study medication (TAK-079) received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date/retest date is provided to the investigator.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

Per standard clinical practice, a site representative, otherwise uninvolved with study conduct, will review the patient dosing log before Day 1 dosing and after dosing to ensure that all patients received the correct dose of study medication. This review will be documented at the site.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately. Empty, partially used, and unused TAK-079 will be disposed of, retained, or returned to the sponsor or designee, as directed by the sponsor or designee. The investigator must maintain a

current inventory (drug accountability log) of all sponsor-supplied study medication delivered to the site, inventory at the site, and patients' use records. This log must accurately reflect the drug accountability of the study medication at all times. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied medication, expiry/retest date, and amount dispensed including the initials of the person dispensing and the person receiving the study medication. The log should include all required information as a separate entry for each patient to whom study medication is dispensed.

Before site closure or at appropriate intervals, a representative from the sponsor or its designee will perform clinical study material accountability and reconciliation before clinical study materials are returned to the sponsor or its designee or destroyed at the site, as applicable. The investigator will retain the original documentation regarding clinical study material accountability, return, and/or destruction, and copies will be sent to the sponsor or designee.

Further guidance and information are provided in the pharmacy manual.

9.0 STUDY CONDUCT

This study will be conducted in compliance with the protocol, GCP, applicable regulatory requirements, and ICH guidelines.

9.1 Study Personnel and Organizations

Contact information for the project clinician, the central laboratory conducting the analysis of PK samples, coordinating investigator, interactive response technology provider, and CRO team may be found in the study manual/binder. The list of investigators is available in the sponsor's investigator database.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/ independent ethics committee (IEC).

9.3 Assignment of Randomization Numbers

At the time of randomization, after completion of all screening assessments and procedures and confirmation of eligibility, patients are assigned a 4-digit randomization sequence number. Randomization numbers are generated by the IXRS.

9.4 Treatment Group Assignments

Patients will be randomly assigned in a 1:1:1 ratio to 1 of the 3 treatment arms as outlined in Table 8.a at the completion of study screening and before dosing on study Day 1, in accordance with the randomization schedule as generated by the IXRS. Randomization information is stored in a secured area, accessible only by authorized personnel, and necessary site staff in instances of emergency unblinding.

9.5 Study Procedures

Refer to the SOE (Appendix A) for timing of assessments. Additional details are provided as necessary in the sections that follow.

The screening period for this study is 28 days (Day -28 to Day -1). Assessments and procedures should be performed on schedule, within the time frame and window allowance in Appendix A. Further time allowance for most study procedures and assessments is acceptable in extenuating circumstances (ie, holidays, vacations, and other administrative reasons) on approval by the medical monitor or delegate; however, these time extensions **should not deviate more than 7 days** from the scheduled procedural time.

9.5.1 Informed Consent

Each patient will be asked to provide written informed consent before any study-related procedures are conducted, unless those procedures are performed as part of the patient's standard care.

9.5.2 Inclusion and Exclusion

Eligibility criteria and associated screening study assessments must be confirmed during the screening period, after a patient has signed the ICF, and before receiving study drug.

Principal investigators must provide the Takeda clinician/study medical monitor a summary of key eligibility criteria for review so eligibility can be verified before randomizing each patient.

9.5.3 Patient Demographics

Patient demographics characteristics will be collected at screening and will include age, sex, race, and ethnicity (optional depending on country).

9.5.4 Medical/Surgical History

A complete medical history is compiled for each patient during the screening period (ie, ≤28 days before study Day 1) and includes assessment and documentation of prior medical history, comorbidities, and concomitant treatments. This includes assessments of current MG signs, symptoms, morbidities, as evaluated and scored by disease activity tools, and previous and current MG therapies.

9.5.5 Concomitant Medications and Procedures

Concomitant medications, blood products, and procedures from within 28 days before the first dose of TAK-079 through the end of the patient's participation in the study will be recorded in the eCRF. Trade name and international nonproprietary name (if available), indication, and start and end dates of the administered medication are to be recorded. Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF (see Sections 8.2 and 8.3 for a list of excluded and permitted concomitant medications).

9.5.5.1 Background MG Therapy

Eligible patients will have received MG background therapy (Table 8.c) before screening. Once randomized into the study, patients will remain on background therapy, as managed by their principal investigator, in accordance with local institutional practices, and in alignment with the study protocol, throughout study participation. Allowed background therapy is defined as no more than a cholinesterase inhibitor ± corticosteroid ± 1 steroid-sparing immunosuppressive drug (limited to azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, tacrolimus, or cyclophosphamide). Patients must be on at least one allowed background medication. Background MG therapy ongoing at the time of screening will be recorded in the eCRF, as well as any changes to this therapy.

9.5.6 Physical Examination

A complete physical examination as well as a symptom-directed physical examination with assessments for MG signs and symptoms will be completed in accordance with standard of care at the times specified in the SOE (Appendix A). Women of childbearing potential should be asked about their menstrual history at each visit. A serum pregnancy test should be conducted for delayed menses (see Section 9.5.10).

9.5.7 Height and Weight

Height will be measured during screening only (within 28 days before the first dose of TAK-079).

Weight will be measured during screening and at Weeks 10, 16, and 32 as outlined in Appendix A.

9.5.8 Vital Signs

Vital signs (body temperature, respiratory rate, heart rate, and blood pressure) will be evaluated at visits specified in Appendix A and recorded both on the source documentation and in the eCRF. In addition, vital signs should be assessed at any time it is clinically warranted, ie, patient exhibits signs or symptoms of ISR, CRS, or hypersensitivity reactions. As indicated in Appendix A, vital signs are to be assessed before each study dose and 2 hours (±10 minutes) postdose after the first and second TAK-079/placebo dose.

Clinically significant values, as determined by the principal investigator, must be documented as an AE and closely monitored for follow-up.

9.5.9 12-Lead ECG

A single 12-lead ECG is to be performed at the screening visit (for assessment of eligibility) and at Weeks 10 and 16 of the SFP, and 32 of the LFP and will be read locally. Additional ECGs may be done per investigator discretion.

Each ECG recording should be performed according to standard institutional practice.

NOTE: Any ECG finding that is judged by the investigator as clinically significant (except at the screening visit) is considered an AE; as such, clinically significant findings are to be recorded on

the source documentation and in the eCRF, and the patient should undergo continued monitoring as described in Section 10.1.2.

9.5.10 Pregnancy Test

A serum pregnancy (human chorionic gonadotropin [hCG]) test will be completed for all female patients; this test will be performed at screening and during the SFP and must be negative for the patient to be randomized and to continue in the study.

A urine pregnancy test will be completed for all female patients before the first dose of TAK-079/placebo and at Week 5 of the dosing period. If the subject reports delayed menses a serum pregnancy test should be completed and a negative result obtained before dosing with the study drug.

All study pregnancy testing may be conducted at a designated local laboratory as determined and confirmed by the sponsor, with appropriate laboratory documentation provided in advance of study testing.

9.5.10.1 Definition of Women of Childbearing Potential

A woman of childbearing potential is a sexually mature woman who:

- Has not undergone a hysterectomy or bilateral oophorectomy, or
- Is not postmenopausal. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

9.5.10.2 Timing of Pregnancy Testing

Women of childbearing potential must have pregnancy testing completed in accordance with the timing outlined as follows:

- *Before Initial Study Dosing*:
  - Screening period: a negative **serum** pregnancy test (hCG <5 mIU/mL).
  - Baseline: (Either Day 1 prior to initial study dosing, or 1 day before study dosing) a negative **urine** pregnancy test with a sensitivity of at least 50 mIU/mL. If the urine test is indeterminate, a serum pregnancy test is mandatory.
- *During Study Enrollment*:
  - At Week 5, before dosing (**urine** pregnancy test).
  - During SFP, and LFP as outlined in Appendix A (**serum** pregnancy test).
  - If a menstrual period is delayed (**serum** pregnancy test).
  - Additional pregnancy tests to be conducted as requested by the IRB and/or as required by local regulations.

9.5.11 AEs

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in Appendix A. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of AEs and SAEs.

9.5.12 Clinical Laboratory Evaluations

Hematology, serum chemistry, and serology assessments will be performed locally, with reference ranges provided in the electronic data capture (EDC) system. Clinical laboratory evaluations will be performed according to the SOE in Appendix A throughout the study.

Instructions for handling and shipping clinical laboratory samples are provided in the study laboratory manual.

9.5.12.1 Clinical Chemistry and Hematology

Blood samples for analysis of the clinical chemistry and hematology parameters shown in Table 9.a will be obtained as specified in the SOE (Appendix A).

Table 9.a Clinical Chemistry and Hematology Tests

Hematology	Serum Chemistry	
Hematocrit	Albumin	Chloride
Hemoglobin	Alkaline phosphatase (ALP)	Glucose
Leukocytes with differential	Alanine aminotransferase (ALT)	Lactate dehydrogenase (LDH)
Total lymphocyte count	Aspartate aminotransferase (AST)	Potassium
Neutrophils (ANC)	Bilirubin (total)	Sodium
Platelet (count)	Blood urea nitrogen (BUN)	
Coombs test (both direct and indirect)	Calcium	
	Carbon dioxide (CO_2)	
Serum pregnancy test	Creatinine	

ANC: absolute neutrophil count.

9.5.13 Disease Assessment

The study principal investigator or appropriately trained, delegated, study site staff will assess each patient for disease activity based on the following MG disease activity scales outlined in the following sections and in accordance with the SOE in Appendix A.

Further details for completing the disease assessment scales are provided in the rater manual and associated training materials.

9.5.13.1 MG-ADL Score

The MG-ADL is a validated, 8-question patient-reported outcome measure of MG symptoms [35,36]. The MG-ADL assesses relevant MG symptoms and their functional impact on the patient.

The patient will assess functional disability secondary to ocular (2 items), bulbar (3 items), respiratory (1 item), and gross motor or limb impairment (2 items). Each item is individually graded from 0 (normal) to 3 (severe). The total MG-ADL score ranges from 0 to 24 points, with higher scores indicating greater functional impairment and disability.

A 2-point reduction in the MG-ADL total score is considered a clinically meaningful improvement.

9.5.13.2 MGII Score

The MGII is a novel and validated measure of MG severity, with demonstrated feasibility, reliability, and construct validity [37,38]. The MGII score was developed using patient input and consists of 6 physician-examination and 22 patient-reported items. The MGII has less floor effect (ie, more dynamic range at the lower end of the scale) than other commonly used measures and is therefore more sensitive to detect change. The total score ranges from 0 to 84 (with higher scores indicating worse MG disease activity), and a group-level reduction by 8 points reflects the minimal clinically important difference.

9.5.13.3 MGC Score

The MGC scale is a validated patient- and physician-reported 10-item assessment tool for evaluating the signs and symptoms of MG. Physician assessment includes assessment for ptosis (upward gaze), double vision on lateral gaze, eye closure, neck flexion or extension, shoulder abduction, and hip flexion; patient assessment includes self-report of talking, chewing, swallowing, and breathing. Items are scored based on 4 potential levels of impact: normal, mild, moderate, or severe. The total score ranges from 0 to 50, with higher scores indicating a greater impact of MG on functional activities [39-41].

A 3-point reduction in the MGC total score is considered a clinically meaningful improvement.

9.5.13.4 QMG Score for Disease Severity

The QMG score is a physician-reported, validated, 13-item disease-severity assessment tool. The QMG score evaluates muscle strength based on quantitative testing of sentinel muscle groups: ocular (2 items), facial (1 item), bulbar (2 items), gross motor (6 items), axial (1 item), and respiratory (1 item). Each item is graded on a scale of 0 to 3, with 3 being the most severe. The total score ranges from 0 to 39, with higher scores representing a greater disease burden [42,43].

A 3-point reduction in the QMG total score is considered a clinically meaningful improvement.

9.5.13.5 MG-QoL15r

The MG-QoL15r is a validated tool containing 15 patient-reported items about the patient's perception of impairment and disability and the degree to which the patient tolerates disease manifestations [44-46]. The total score ranges from 0 to 30, with higher scores indicating worse MG disease activity.

9.5.13.6 Patient Global Impression of Change

The Patient Global Impression of Change (PGIC) is an anchor scale used to aid the interpretation of the above MG disease activity instruments (MG-ADL, MGII, MGC, QMG and MG-QoL15r). The PGIC may be used in analyses of meaningful change and other psychometric properties and performance characteristics of these instruments.

9.5.13.7 Patient Global Impression of Severity

The Patient Global Impression of Severity (PGIS) is an anchor scale used to aid the interpretation of the above MG disease activity instruments (MG-ADL, MGII, MGC, QMG and MG-QoL15r). The PGIS may be used in analyses of meaningful change and other psychometric properties and performance characteristics of these instruments.

9.5.13.8 Quantification of Ig

Serum samples for IgM, IgG, and IgA will be obtained at screening and throughout the study at the time points specified in Appendix A; testing will be performed at the central laboratory.

9.5.14 Biomarker, Pharmacodynamic, and PK Samples

Samples are collected by venipuncture or indwelling catheter at the time points detailed in the SOE (Appendix A) for the measurement of serum concentrations of TAK-079 and biomarker assessments. Samples will be tested at a central laboratory.

9.5.14.1 Primary Specimen Collection

Table 9.b Primary Specimen Collection

Specimen Name in Schedule of Procedures	Primary Specimen	Description of Intended Use	Sample Collection
Serum sample for autoantibodies	Serum	Antibody level	Mandatory
Blood sample for flow cytometry	Blood	CD19+ counts	Mandatory [a]
Blood sample for pharmacodynamics	Blood	Pharmacodynamic (changes in CD38+ cells)	Mandatory
Blood sample for immunoprofiling	Blood	Broad immune cell changes	Mandatory
Serum sample for circulating biomarkers	Serum	Biomarker measurements	Mandatory
Serum sample for quantitative IgA/IgM/IgG	Serum	Ig measurements	Mandatory
Serum sample for immunogenicity assessments	Serum	Immunogenicity assessments	Mandatory
Serum sample for TAK-079 PK	Serum	PK measurements	Mandatory
Serum sample for vaccine-induced protective antibodies	Serum	Vaccine-induced protective antibodies	Mandatory
Serum sample for HBV, HCV, and HIV	Serum	Study eligibility	Mandatory
Blood sample for HCV RNA PCR	Blood	Study eligibility	Mandatory [b]

HBV: hepatitis B virus; HCV: hepatitis C virus; Ig: immunoglobulin; PCR: polymerase chain reaction; PK: pharmacokinetics.

[a] CD19 evaluation to be performed only in patients with prior exposure to rituximab.

[b] To be performed only for patients who have received curative treatment for prior chronic HCV infection.

9.5.15 PK Measurements

Serum samples for the measurement of concentrations of TAK-079 will be collected at multiple time points as specified in the SOE in Appendix A.

The timing of samples may be modified during the study on the basis of emerging PK data if a change in the sampling scheme is considered necessary to better characterize the PK profile of TAK-079. Additional PK samples may be requested if deemed necessary by the medical monitor for specific events of clinical interest or AEs.

Details regarding the preparation, handling, and shipping of the PK samples are provided in the laboratory manual.

9.5.16 Pharmacodynamic/Biomarker Measurements

In this study, several biomarkers will be assessed to test for correlation with safety, PK, and, if possible, with efficacy. These biomarkers will be used to identify patients who have a higher probability of response or adverse reactions to TAK-079. The biomarker sample analysis will be

performed if or when required. Because new techniques continue to be developed, the method and laboratory that will be recommended for the biomarker analysis cannot be anticipated. Samples for pharmacodynamic measurements will be collected as detailed in Appendix A.

If a patient is exhibiting signs or symptoms possibly assessed as CRS by the investigator, a blood draw should be performed for central evaluation that could include, but is not limited to, immune markers and cytokine markers. Further details are provided in the laboratory manual.

9.5.16.1 Autoantibodies

Serum samples will be collected to detect anti-AChR and anti-MuSK antibodies as outlined in Appendix A and analyzed by a central laboratory.

9.5.16.2 Pharmacodynamics

Blood samples will be collected to analyze CD38+ expression and monitor changes in immune cells by flow cytometry before, during, and at the end of treatment. These evaluations will be performed at a central laboratory.

9.5.16.3 Circulating Biomarkers

Serum samples for cytokines/chemokines will be collected before, during, and at the end of treatment to help identify patients who have a higher probability of response or of experiencing adverse reactions to TAK-079.

9.5.16.4 Immunoprofiling

Blood samples for immunoprofiling will be collected for profiling of immune cells before, during, and at the end of treatment. These blood samples will be analyzed for the presence and changes of immune cells by flow or mass cytometry.

9.5.16.5 Vaccine-Induced Protective Antibodies

Serum samples for vaccine-induced protective antibodies (measles, mumps, rubella, tetanus, and diphtheria) will be collected before, during, and at the end of treatment.

9.5.17 Immunogenicity Sample Collection

Serum samples for the measurement of anti–TAK-079 antibody (antidrug antibody and ADA are exchangeable terms in this protocol) will be collected at multiple time points as specified in the SOE in Appendix A.

The samples must be taken before each dosing. Details regarding the preparation, handling, and shipping of the immunogenicity samples are provided in the laboratory manual. Positive ADA screening samples will be further tested for true positivity and titer by the study central laboratory.

9.6 End of Safety Follow-up Assessments

End of SFP clinical parameters, as outlined in Table 9.c, will be assessed at Week 16 of the SFP (see SOE in Appendix A). If clinical presentation and parameters do not meet the end of SFP criteria, and are deemed by the principal investigator as study related, the study-related parameters not meeting end-of-study criteria will continue to be assessed in the LFP until they normalize or return to baseline.

Table 9.c End of Safety Follow-Up Period Clinical Parameters

Safety Parameter Laboratory Investigations	End-of-Study Criteria	Continuation to Long-term Follow-up
Neutrophils	≥LLN or ≥study baseline levels, or abnormal levels that are not directly related to dosing of investigational product.	<LLN and <study baseline levels that are directly related to dosing of investigational product.
Platelets		
Total lymphocyte count		
Hgb		
IgG, IgA, and IgM levels		
Events of clinical interest		
TAK-079–related hypersensitivity reaction (IRR, allergic reaction, or anaphylaxis) (See Section 8.6.1).	Clinical symptoms related to hypersensitivity reaction resolved.	Clinical symptoms related to hypersensitivity reaction ongoing.
TAK-079-related CRS (See Section 8.6.2).	Clinical symptoms related to CRS reaction resolved.	Clinical symptoms related to CRS reaction ongoing.
Systemic infection		Any ≥Grade 2 [a] systemic infection that is not resolved.

CRS: cytokine release syndrome; CTCAE: Common Terminology Criteria for Adverse Events; Hgb: hemoglobin; Ig: immunoglobulin; IRR: infusion-related reaction; LLN: lower limit of normal; NCI: National Cancer Institute.
[a] Laboratory and infection grading are based on NCI CTCAE v4.03.

9.7 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed study treatment once they have completed the 8-week dosing period.

9.8 Completion of Study (for Individual Patients)

A patient will be considered to have completed the study once they have completed the dosing period and at completion of the Week 20 or Week 32 end-of-study visit of the LFP (for patients randomized to placebo or TAK-079, respectively).

9.9 Discontinuation of Treatment With Study Drug

Study drug must be permanently discontinued for patients meeting any of the following criteria:

- Withdrawal by patient.

- Pregnancy.

Treatment with study drug may also be discontinued for any of the following reasons:

- AE/SAE.
- Protocol deviation.
- Symptomatic deterioration.
- Unsatisfactory therapeutic response.
- Study terminated by sponsor.
- Lost to follow-up.
- Other.

Once study drug has been discontinued, all study procedures outlined for the end-of-treatment visit will be completed as specified in the SOE in Appendix A. The primary reason for study drug discontinuation will be recorded on the eCRF.

In addition, study drug should also be discontinued if the patient meets the criteria outlined in Section 8.4.1.

9.10 Withdrawal of Patients From Study

A patient will be withdrawn from the study for any of the following reasons:

- Death.
- Study terminated by sponsor.
- Withdrawal by patient.
- Lost to follow-up.
- Other.

The consequence of a patient withdrawing consent from further treatment and follow-up is that no new information will be collected from the withdrawn patient and added to the existing data or any database. However, every effort will be made to follow all patients for safety. Data collected during patient consent, however, must be included in the database.

9.11 Study Compliance

TAK-079/placebo will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

9.12 Coronavirus Disease 2019–Related Procedural Changes

The following information provides guidance regarding changes to the study procedures that could be implemented for study participants or study sites affected by the coronavirus disease 2019 (COVID-19) public health emergency. This guidance takes references from the Food and Drug Association (FDA) Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency - Guidance for Industry, Investigators, and Institutional Review Boards, March 2020, updated 04 December 2020, and the European Medicines Agency (EMA) Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic, Version 3 (28 April 2020).

As the COVID-19 pandemic may peak in different regions at different times and restrictions implemented by local laws and recommendations may vary, any decision on procedural changes should be made on a case-by-case basis by the principal investigator in consultation with the study team and the medical team as needed, while maintaining patient safety and confidentiality as the priority.

Procedural changes due to COVID-19 may include the following:

- Informed consent procedure: If necessary, informed consent from a potential or current trial participant may be obtained via electronic informed consent capabilities, or an electronic face-to-face consent interview when these individuals are unable to travel to the site.
- During the COVID-19 public health emergency, remote visits may be conducted by phone (eg, collection of AEs and safety monitoring), video conferencing (Telehealth with the physician or Telemedicine or other platform acceptable to the physician and patient) or site staff visiting the participant's residence. Local visits and Telemedicine must comply with national and local laws and regulations. The type of alternative visit must be recorded on the eCRF. The investigator may use their judgement to determine the appropriateness of a remote visit as an alternative visit in advance (for example, if no significant issues arise that may necessitate a hands-on physical exam).
- "Remote visits" via virtual communications may be performed as a safety check on the patient's well-being.
- For home healthcare visits, collection of clinical laboratory samples (blood specimen collection or other diagnostic tests) may be performed by the investigator, qualified site staff or qualified home healthcare provider who can visit the study participant's residence. These may be obtained the day before a scheduled visit (see Appendix A).
- ECG procedures: For home healthcare visits, ECGs may be performed by a qualified health care professional who is authorized/certified to perform such tests routinely.
- Patient visits at screening, Weeks 1-4, 8, 12, 16, 20, and 32 must be done with the patient present at the investigative site. Other visits may be conducted at the clinic or by optional home healthcare visits (or a hybrid of Telehealth/Telemedicine with home healthcare) to extend flexibility to patients during COVID-19 public health emergency. Home healthcare visits will be documented in the study records and eCRF. As per the investigator's judgment, if there are

no concerns raised by the symptom-directed physical, vital signs measurements will not be required to be collected at the Week14 visit during the COVID-19 pandemic. QMG, MGC and the physician examination portion of MGII may be omitted if performing a remote visit.

- For possible dosing visits at home, the investigator or qualified site staff must evaluate the patient either remotely or at the patient's residence prior to dose administration. A patient should have previously received 4 doses of study drug at the clinic site unless otherwise approved by the sponsor. Safety parameters for dosing decisions (Table 8.d) must be evaluated as in a regular in-clinic visit. Dose administration must be performed by a qualified healthcare provider.
- Safety labs (eg, complete blood count, chemistry, liver function tests) may be obtained at a clinic local to the patient's home with sponsor approval.
- Deviations from the protocol-specified procedures will be recorded as related to COVID-19.
- The assessment of forced vital capacity for the QMG test may be omitted for COVID-19-related reasons.
- Patients who discontinued from screening due to COVID-19–related factors but were otherwise qualified to participate in the trial may be rescreened if the sponsor's clinician agrees.
- Missed or delayed clinic visits or subject withdrawals due to COVID-19 must be recorded on the eCRF.
- Withdrawal: If a patient chooses to withdraw from study participation due to personal concerns related to the COVID-19 pandemic (other than a COVID-19–related AE), this should be specified as the reason for patient withdrawal in the eCRF.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

A pretreatment event (PTE) is any untoward medical occurrence in a patient who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AE Definition

AE means any untoward medical occurrence in a patient administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product.

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a preexisting condition. (Intermittent events for preexisting conditions or underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses versus signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters maybe considered AEs if they are judged to be clinically significant, ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation. A laboratory retest and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Preexisting conditions:

- A preexisting condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as a PTE or AE. A baseline evaluation (eg, laboratory test, ECG, x-ray) should NOT be recorded as a PTE unless related to a study procedure. However, if the patient experiences a worsening or complication of such a concurrent medical history condition, the worsening or complication should be recorded

appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). Investigators should ensure that the event term recorded captures the change in the condition, eg, "worsening of…".

- If a patient has a preexisting episodic condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an PTE/AE if the episodes become more frequent, serious, or severe in nature; that is, investigators should ensure that the AE term recorded captures the change from baseline in the condition, eg "worsening of…".
- If a patient has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent than that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition, eg, "worsening of…".

Worsening of AEs:

- If the patient experiences a worsening or complication of a PTE after the first administration of study medication or a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition, eg, "worsening of…".

Changes in severity of AEs:

- If the patient experiences a change in the severity of an AE that is not associated with a change in study medication, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled before signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) because of worsening of the preexisting condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the patient's medical condition should not be recorded as AEs but should be documented in the patient's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

- An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study patient, at a dose above that which is assigned to that individual patient according to the study protocol.
- All cases of overdose (with or without associated AEs) are to be documented on the Overdose page of the eCRF to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on the AE CRF(s) according to Section 10.5.

- SAEs of overdose should be reported according to the procedure outlined in Section 10.2.
- If an overdose does occur, close monitoring and supportive treatment as medically required.

10.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of an existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly/birth defect.
- Is a medically important event that satisfies any of the following:
  - May require intervention to prevent items 1 through 5 above.
  - May expose the patient to danger, even though the event is not immediately life-threatening or fatal or does not result in hospitalization.
  - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant Adverse Event List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
	Acute liver failure
Torsade de pointes/ventricular fibrillation/ventricular tachycardia	Anaphylactic shock
	Acute renal failure
Malignant hypertension	Pulmonary hypertension
Convulsive seizures	Pulmonary fibrosis
Agranulocytosis	Confirmed or suspected endotoxin shock
Aplastic anemia	Confirmed or suspected transmission of infectious agent by a medicinal product
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Neuroleptic malignant syndrome/malignant hyperthermia
	Spontaneous abortion/stillbirth and fetal death

- Note: Some clinical centers may only be able to provide certain rescue therapies (eg, IVIg) via inpatient hospitalization. Therefore, the hospital admission itself (in an otherwise clinically

stable patient) specifically for access and administration of rescue therapy does not count automatically as an SAE, unless there are other circumstances that fulfill SAE criteria.

AEs that fulfill 1 or more of the serious criteria above are to be considered SAEs and should be reported and followed up in the same manner.

As there is no MG or neurologic specific grading scale, in this study intensity for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE, version 4.03, effective 27 November 2017 [47]. Use of the CTCAE criteria scale is aligned with the international consensus guidance for the management of MG [48] which is supported by the American Academy of Neurology (aan/Guidelines/home/GuidelineDetail/823 Accessed 21 Aug 2019) and the Myasthenia Gravis Foundation of America (myastheniagravisnews/2018/02/01/panel-of-myasthenia-gravis-experts-propose-guidelines-for-treatment-and-care/ Accessed 21 Aug 2019). Especially at lower grades of toxicity, laboratory parameters are similar between the CTCAE and WHO toxicity criteria; note in this study the threshold for holding study drug is at a low grade (see Table 8.d); therefore either scale could be applicable. The CTCAE criteria, however, also allows for more precise grading of severity of AEs reported with biologics such as infections and infusion related reactions (hypersensitivity and anaphylaxis) as compared to the WHO toxicity grading scale where criterion for these are lacking. In addition, the CTCAE criteria has very thorough criteria for Neuro and Neuromuscular AEs which again is quite sparse in the WHO criteria. For these reasons, rather than try to use 2 separate scales, the CTCAE criteria will be used in this study.

Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4) because the terms *serious* and *severe* are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as a single comprehensive event.

Regardless of causality, SAEs must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee within 24 hours of becoming aware of the event. This will be done by transmitting an electronic data capture (EDC)

SAE report. If transmission of an EDC SAE report is not feasible within 24 hours, then a facsimile of the completed Takeda paper-based SAE form should be sent (please see fax numbers below). In case of fax, site personnel need to confirm successful transmission of all pages and include an email address on the fax cover sheet so that an acknowledgment of receipt can be returned via e-mail within 1 business day. Email submission of SAE forms with an attachment in portable document format should only be used in the case where fax is not possible and EDC is not feasible within 24 hours of receiving the event. In case of email, site personnel need to confirm successful transmission by awaiting an acknowledgment of the receipt via email within 1 business day. If SAEs are reported via fax or by email, EDC must be updated as soon as possible with the appropriate information.

The SAE form should be transmitted within 24 hours to the attention of the contact listed as follows:

SAE Reporting Contact Information
Cognizant
United States and Canada Toll-free fax #: 1-800-963-6290
Rest of World fax#: +1-202-315-3560
Email: takedaoncocases@cognizant.com

If information not available at the time of the first report becomes available at a later date, then the investigator will transmit a follow-up EDC SAE report (or a paper-based SAE form if an EDC SAE report is not feasible) or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the study are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study; eg, surgery was performed earlier or later than planned.

For both serious and nonserious AEs, the investigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study drug administration.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 4.03, effective 27 November 2017 [47].

Relationship of the event to study drug administration (ie, its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: Is there a reasonable possibility that the AE is associated with the study drug?

10.3 Monitoring of AEs and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the signing of informed consent through the SFP and recorded in the eCRF. AEs ongoing at the Week 16 visit of the SFP should be monitored through the LFP until

they are resolved, return to baseline, or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). Study-drug related AEs/SAEs with onset after the SFP will be collected through the LFP.

- SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the signing of informed consent through the SFP and recorded in the eCRF. After this period, during the LFP, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by sending a completed pregnancy form to the Takeda Global Pharmacovigilance department or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10.5 Procedures for Reporting Including Overdose

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on the AE eCRF. SAEs of overdose should be reported according to the procedure outlined in Section 10.2.

10.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and IRBs and IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited reports within 7 days for fatal and life-threatening events and within 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the study. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

In accordance with Takeda standard operating procedures, each clinical trial is evaluated to determine whether a data safety monitoring board (DSMB) should be convened. Applicable regulation and guidance (including the guidance set forth by the US FDA as described in the Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees, fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf, Accessed 24 July 2019) are used to evaluate each trial in terms of potential confounding factors that complicate evaluation of the study safety and/or efficacy data, and potential risks of the study design or treatment to study participants.

A DSMB is not indicated at this time for this study given that Takeda's standards and processes, which include continuous review and evaluation of safety data reported from all participating sites through the conduct of the study, are appropriate for the ongoing monitoring of patient safety and data integrity (see Section 6.2). However, the decision to convene a DSMB could be made at any time during the conduct of Study TAK-079-1005.

Though a formal DSMB will not be formed, internal reviews of available safety information will be conducted. Key safety data will be reviewed and evaluated by sponsor representatives for possible study conduct recommendation(s). The sponsor representatives will make decisions regarding dosing and/or scheduling, which will be discussed with investigators for decision for alignment.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the data management plan. If selected for coding, AEs, medical history, and concurrent conditions will be coded using the MedDRA. Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each patient who signs an ICF.

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, CRO partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designee) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for the change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor (or designee) will be permitted to review the patient's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating patients, medical records, temporary media such as thermal-sensitive paper, source worksheets, all original signed and dated ICFs, patient authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copies of eCRFs including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and the sponsor (or designees). Any source documentation printed on degradable thermal-sensitive paper should be photocopied by the site and filed with the original in the patient's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the clinical study site agreement between the investigator and sponsor.

Refer to the clinical study site agreement for the sponsor's requirements for record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

13.1.1 Analysis Sets

Full analysis set: all enrolled patients. In efficacy analyses, only patients with both baseline and at least 1 valid postbaseline value will be included.

Safety analysis set: patients who have received at least 1 dose of study drug.

PK analysis set: patients who have received at least 1 dose and have at least 1 measurable TAK-079 serum concentration.

Pharmacodynamic analysis set: patients who have a baseline and at least 1 postbaseline sample assessment.

Immunogenicity analysis set: patients from the safety population who have a baseline and at least 1 postbaseline immunogenicity sample assessment.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Patient demographic and baseline characteristics will be summarized descriptively. Variables to be analyzed include sex, age, race, medical history, prior medications/therapies, ECG findings, and other parameters as appropriate. For continuous variables, descriptive statistics (number, mean, standard deviation, median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented as needed.

13.1.3 Efficacy Analysis

Efficacy is not the primary endpoint for this study. Secondary efficacy measures will include:

- Score change from baseline for the following:
  - MG-ADL score
  - QMG score
  - MGC score
- Change from baseline in anti-AChR antibody or anti-MuSK antibody levels.
- Percentage of patients meeting minimal clinically important difference criteria in the respective MG clinical impairment scales (MG-ADL, QMG, MGC).

Exploratory efficacy measures will include:

- Score change from baseline in the MGII score.
- Duration of a clinically meaningful effect on MG disease severity (in all the clinical disease impairment scales: MG-ADL, QMG, MGC, MGII).
- Percentage of patients meeting minimal clinically important difference criteria in the MGII scale.
- Frequency and proportion of patients requiring rescue therapy

Efficacy endpoints will be summarized by descriptive statistics and presented by treatment group. Where appropriate, efficacy endpoints may be analyzed with the following methods:

- Binary endpoints will be analyzed using a Fisher's exact test.

- Change from baseline endpoints measured repeatedly over time will be analyzed using a mixed-model repeated-measures analysis, which includes treatment, visit, and (treatment × visit) interaction terms as the factors, with baseline values as covariates.

All tests of treatment effects will be conducted at a 2-sided α level of 0.05, and 95% CIs for the differences in proportions and least squares means will be provided. No inferential hypothesis was tested in these endpoints, so CIs and p-values are not adjusted for multiplicity.

All efficacy analyses will be performed using the full analysis set.

13.1.4 PK Analysis

Descriptive summary of the concentration-time profile of serum TAK-079 will be provided. PK parameters will include C_{trough}. Data permitting, additional parameters eg, C_{max}, AUC after last dose, and half-life may be reported. A population PK model may be developed. If developed, the population PK model will be reported separately. PK/pharmacodynamic analyses of selected pharmacodynamic and/or efficacy measures may be conducted as data permit. Any population PK/pharmacodynamic analysis if conducted will be reported separately.

13.1.5 Immunogenicity Analyses

TAK-079 immunogenicity status (ADA incidence) will be analyzed and summarized using descriptive statistics, as applicable, and using the immunogenicity analysis set. The effect of immunogenicity on PK, pharmacodynamics, safety, and efficacy may be explored. Immunogenicity analyses will be based on available data from patients with a baseline assessment and at least 1 postbaseline immunogenicity assessment.

13.1.6 Safety Analysis

Safety will be evaluated by the frequency of AEs, severity and types of AEs, and by changes from baseline in patients' vital signs, weight, and clinical laboratory results using the safety analysis set. Exposure to study drug and reasons for discontinuation will be tabulated.

TEAEs that occur after administration of the first dose of study drug and through the end of the SFP period will be tabulated.

AEs will be tabulated according to the MedDRA, and data will be summarized using Preferred Term and primary System Organ Class. All safety analyses will be performed using the safety analysis population.

In this study, Grade 2 or greater medication related toxicities will be monitored starting from the first 12 safety-evaluable patients and then every 12 safety-evaluable patients. If the stopping bounds of ≥3/12, and ≥5/24 have been achieved, accrual to the study will be suspended to allow for a blinded investigation of the safety profile. After consideration by the study team, which could include the safety management team as appropriate, especially if case unblinding is necessary, a decision will be made as to whether accrual can be resumed. The AE grading limits are based on the International Consensus Guidelines for the Management of Myasthenia Gravis where the aim is no more than grade 1 CTCAE medication side effects [48]. The statistical bounds are based on a

Bayesian strategy to monitor outcomes in clinical trials. If the stopping rule is met, there is 80% probability that the true toxicity rate is greater than 10% with a prior beta distribution with parameters 0.2 and 1.8 for the binomially distributed toxicity rate [49].

Takeda clinicians will conduct reviews of SAEs and related clinical parameters to ensure consistency with an acceptable benefit-risk ratio throughout the study. If >2 patients experience the same SAE, the study will be suspended to allow for a blinded investigation by the study team which may include the safety management team as noted above; after which a decision will be made to whether accrual can be resumed.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

Approximately 36 patients are planned to be randomized to treatment in a ratio of 1:1:1 (TAK-079 300 mg, TAK-079 600 mg, or placebo). This study is exploratory and not powered to address any predefined hypothesis.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic, alternative monitoring approaches such as remote source data verification or telephone contact may be used to ensure data quality and integrity and maintain patient safety. Alternative monitoring approaches should be used only where allowed by applicable local regulations and permitted by the IRB/IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee including, but not limited to, the investigator's binder, study medication, patient medical records, informed consent documentation, documentation of patient authorization to use personal health information (if separate from the ICFs), and eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study patients. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or

designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the patient's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the patient, or confound interpretation of the primary study assessment.

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a patient or the reliability and robustness of the data generated, it may be reported to regulatory authorities as a serious breach of GCP and the protocol.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, US FDA, the United Kingdom [UK] Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, patients) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonized Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the responsibilities of the investigator that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. American sites unwilling to provide names and titles of all members because of privacy and conflict of interest concerns should instead provide a Federalwide Assurance number or comparable number assigned by the US Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the IB, a copy of the ICF, and, if applicable, patient recruitment materials and advertisements and other documents required by all applicable laws and regulations must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and patient informed consent must be obtained and submitted to the sponsor or designee before commencement of the study, ie, before shipment of the sponsor-supplied drug or study-specific screening activity. The IRB or IEC approval must refer to the study by its exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor will ship drug once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from the competent authority to begin the study. Until the site receives notification, no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by patients, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor (or designee).

Patient incentives should not exert undue influence for participation. Payments to patients must be approved by the IRB or IEC and sponsor.

15.2 Patient Information, Informed Consent, and Patient Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the patient's personal and personal health information for purposes of conducting the study. The ICF and the patient information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, and the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and, if applicable, the patient authorization form. The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The ICF, patient authorization form (if applicable), and patient information sheet (if applicable) must be written in a language fully comprehensible to the prospective patient. It is the

responsibility of the investigator to explain the detailed elements of the ICF, patient authorization form (if applicable), and patient information sheet (if applicable) to the patient. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. If the patient is not capable of rendering adequate written informed consent, the patient's legally acceptable representative may provide such consent for the patient in accordance with applicable laws and regulations.

The patient, or the patient's legally acceptable representative, must be given ample opportunity to (1) inquire about details of the study and (2) decide whether to participate in the study. If the patient, or the patient's legally acceptable representative, determines that he or she will participate in the study, then the ICF and patient authorization form (if applicable) must be signed and dated by the patient, or the patient's legally acceptable representative, at the time of consent and before the patient enters into the study. The patient or the patient's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ink. The investigator must also sign and date the ICF and patient authorization (if applicable) at the time of consent and before the patient enters into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, patient authorization form (if applicable), and patient information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the patient signs the informed consent in the patient's medical record. Copies of the signed ICF, the signed patient authorization form (if applicable), and patient information sheet (if applicable) shall be given to the patient.

All revised ICFs must be reviewed and signed by relevant patients or the relevant patient's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the patient's medical record, and the patient should receive a copy of the revised ICF.

15.3 Patient Confidentiality

The sponsor and designees affirm and uphold the principle of the patient's right to protection against invasion of privacy. Throughout this study, a patient's source data will be linked to the sponsor's clinical study database or documentation only via a unique identification number. As permitted by all applicable laws and regulations, limited patient attributes, such as sex, age, or date of birth, and patient initials may be used to verify the patient and accuracy of the patient's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, US FDA, UK MHRA, Japan PMDA), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the patient's original medical records (source data or documents) including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a patient's study participation, and autopsy reports. Access to a patient's original medical records requires the specific authorization of the patient as part of the informed consent process (see Section 15.2).

Copies of any patient source documents that are provided to the sponsor must have certain identifying personal information removed, eg, patient name, address, and other identifier fields not collected on the patient's eCRF.

15.4 Publication, Disclosure, and Clinical Study Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the clinical study site agreement. In the event of any discrepancy between the protocol and the clinical study site agreement, the clinical study site agreement will prevail.

15.4.2 Clinical Study Registration

To ensure that information on clinical studies reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Takeda will, at a minimum, register interventional clinical studies it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites on or before start of study, as defined by Takeda policy/standards. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

As needed, Takeda and investigator/site contact information may be made public to support participant access to studies via registries. In certain situations/registries, Takeda may assist participants or potential participants in finding a clinical study by helping them locate study sites closest to their homes by providing the investigator name, address, and phone number via email/phone or other methods preferred by callers requesting study information. Once patients receive investigator contact information, they may call the site requesting enrollment into the study. The investigative sites are encouraged to handle the study inquiries according to their established patient screening process. If the caller asks additional questions beyond the topic of study enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Study Results Disclosure

Takeda will post the results of clinical studies on ClinicalTrials.gov, and other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda policy/standards, applicable laws, and/or regulations.

15.4.4 Data Sharing

The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving patient care. Qualified independent researchers will be permitted to use data collected from patients during the study to conduct additional scientific research, which may be unrelated to the study drug or the patient's disease. The data provided to external researchers will not include information that identifies patients personally.

15.5 Insurance and Compensation for Injury

Each patient in the study must be insured in accordance with the regulations applicable to the site where the patient is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study patients. Refer to the clinical study site agreement regarding the sponsor's policy on patient compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

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Appendix A Schedule of Events

Study Procedures [a]	**Screening**	**Treatment Period**								**Safety Follow-up Period (SFP)**				**Long-term Follow-up Period (LFP)**			
Period		**Length: 8 weeks**															
Week [b]	**Days -28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**14**	**16** [c]	**20** [d]	**24**	**28**	**32**
Window		**±2 days**								**±2 days**				**±2 days**			
Informed consent [e]	X																
Eligibility criteria [f]	X																
Demographics	X																
Complete medical history, including prior therapy	X																
Complete physical examination	X												X				X
Symptom-directed physical examination [g]		X	X	X	X	X	X	X	X	X	X	X		X	X	X	
12-lead ECG [h]	X									X			X				X
Vital signs [i]	X	X	X	X	X	X	X	X	X	X	X	X	X				
Investigator predosing criteria assessment			X	X	X	X	X	X	X								
Height (cm)	X																
Weight (kg)	X									X			X				X
Blood type assessment	X																
Laboratory Assessments																	
Serum pregnancy test [h]	X									X			X				X
Urine pregnancy test [h,j,m]		X				X											
Hematology [h,k,m]	X	X	X	X	X	X	X	X	X	X	X	X	X				X
Clinical chemistry [h,k,m]	X					X			X				X				X
Direct/indirect Coombs test [h,m]		X				X				X			X				

Appendix A Schedule of Events

Study Procedures [a]	Screening	Treatment Period								Safety Follow-up Period (SFP)				Long-term Follow-up Period (LFP)			
Period		Length: 8 weeks															
Week [b]	Days -28 to -1	1	2	3	4	5	6	7	8	10	12	14	16 [c]	20 [d]	24	28	32
Window		±2 days								±2 days				±2 days			
T-cell interferon-γ release assay (TIGRA)	X																
Serum sample for anti-AChR or anti-MuSK antibodies [h,l,m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for immunoprofiling [h,m]		X			X				X		X		X				X
Blood sample for CD19 assay [n]	X																
Serum sample for circulating biomarkers [h,m,o,p]		X			X				X		X		X				X
Serum sample for quantitative IgA/IgM/IgG [h,m,q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum sample for TAK-079 PK [h,m,p]		X	X	X	X	X	X	X	X		X		X		X		X
Blood sample for pharmacodynamic biomarkers [h,m]		X			X				X		X		X				X
Serum sample for immunogenicity (eg, ADA) [h,m]		X	X		X		X		X		X		X		X		X
Serum sample for vaccine-induced protective antibodies [h, m]	X				X				X				X				X
Samples for HBV, HCV, and HIV assessment	X																

Appendix A Schedule of Events

Study Procedures [a]	Screening	Treatment Period								Safety Follow-up Period (SFP)				Long-term Follow-up Period (LFP)			
Period		Length: 8 weeks															
Week [b]	Days -28 to -1	1	2	3	4	5	6	7	8	10	12	14	16 [c]	20 [d]	24	28	32
Window		±2 days								±2 days				±2 days			
Disease Assessment tests [h]																	
MG-ADL score	X	X			X		X		X	X	X	X	X	X	X	X	X
MGII score [r]		X			X		X		X	X	X	X	X	X	X	X	X
MGC score [s]		X			X		X		X	X	X	X	X	X	X	X	X
QMG score [s]		X			X		X		X	X	X	X	X	X	X	X	X
MG-QoL15r		X			X		X		X	X	X	X	X	X	X	X	X
PGIS		X			X		X		X	X	X	X	X	X	X	X	X
PGIC										X			X				X
Study Therapy Administration																	
Premedication dosing [t]		X	X	X	X	X	X	X	X								
TAK-079, SC [u]		X	X	X	X	X	X	X	X								
Postdose medication [v]		X															
AE reporting [w]	New onset AEs recorded from the signing of the ICF through the SFP; SAEs collected from the signing of the ICF through the SFP; unresolved AEs/SAEs as of Week 16 and study drug-related AEs/SAEs with onset after SFP collected through the LFP																
Concomitant medications/ procedures monitoring	Recorded from signing of the ICF through SFP													Recorded only for concomitant medications/procedures related to underlying disease			

AChR: acetylcholine receptor; ADA: antidrug antibodies; AE: adverse event; CRS: cytokine release syndrome; COVID-19: coronavirus disease 2019; ECG: electrocardiogram; eCRF: electronic case report form; HBV: hepatitis B virus; HCV: hepatitis C virus; ICF: informed consent form; Ig: Immunoglobulin; IRB: institutional review board; IVIg: intravenous immunoglobulin; LFP: long-term follow-up period; MG: myasthenia gravis; MG-ADL: Myasthenia Gravis-Activities of Daily Living; MGC: Myasthenia Gravis Composite; MGII: Myasthenia Gravis Impairment Index; MG-QoL15r; Myasthenia Gravis Quality of Life Scale; MuSK: muscle-specific tyrosine kinase; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PK: pharmacokinetic; QMG:

Appendix A Schedule of Events

Study Procedures [a]	Screening	Treatment Period								Safety Follow-up Period (SFP)				Long-term Follow-up Period (LFP)			
Period		Length: 8 weeks															
Week [b]	Days -28 to -1	1	2	3	4	5	6	7	8	10	12	14	16 [c]	20 [d]	24	28	32
Window		±2 days								±2 days				±2 days			

Quantitative Myasthenia Gravis; SAE: serious adverse event; SC: subcutaneous; SFP: safety follow-up period; TEAE: treatment-emergent adverse event.

[a] Patients may undergo additional laboratory assessments and observations as necessary based on the principal investigator's best medical judgment, and as warranted by exhibited clinical signs or symptoms at each study clinic visit.

[b] Patient visits at screening, Weeks 1-4, 8, 12, 16, 20, and 32 must be done with the patient present at the investigative site. Other visits may be conducted at the clinic or by optional home healthcare visits (or a hybrid of Telehealth/Telemedicine with home healthcare) to extend flexibility to patients during COVID-19 public health emergency. Home healthcare visits will be documented in the study records and eCRF.

[c] Patients will be unblinded after Week 16. Clinical parameters below the levels in Table 8.d for continued dosing, including ongoing drug-related AEs, at Week 16 should be monitored until the parameters/AEs are resolved, return to baseline, or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

[d] The Week 20 visit of the LFP will be the end-of-study visit for patients randomized to placebo. Patients randomized to placebo will require only a symptom-directed physical examination at this visit.

[e] Informed consent must be documented before initiating any screening procedures associated with the study.

[f] Screening period is 28 days (ie, Day -28 to Day -1). Confirmation of patient eligibility by a Takeda project clinician or designee is required before enrollment and before receiving study drug. See Section 9.5 for additional time allowance for extenuating circumstances, to include but not be limited to, need for screening retesting, as granted on approval by Takeda or designee.

[g] Physical examinations are to be symptom- and MG disease–directed with significant clinical findings noted as AEs. In LFP, needed only if there were ongoing drug-related AEs at the Week 16 assessment. Women of childbearing potential should be asked about their menstrual history at each visit. A serum pregnancy test should be conducted for delayed menses (see Section 9.5.10).

[h] Assessments may be performed on the day before or the day of the indicated visit before dosing.

[i] Vital signs (temperature, blood pressure, respiratory rate, and heart rate) are measured before all TAK-079 administrations and 2 hours (±10 minutes) postdose after the first and second TAK-079/placebo dose. In addition, vital signs should be assessed at any time it is clinically warranted. As per the investigator's judgment, if there are no concerns raised by the symptom-directed physical, vital signs measurements will not be required to be collected at the Week14 visit during the COVID-19 pandemic.

[j] The results of urine pregnancy tests must be available and negative before TAK-079 is administered. A serum pregnancy test should be completed if the patient's menstrual period is delayed, or if the IRB requests, and a negative result obtained before dosing with the study drug (see Section 9.5.10). Serum pregnancy testing

Appendix A Schedule of Events

Study Procedures [a]	Screening	Treatment Period								Safety Follow-up Period (SFP)				Long-term Follow-up Period (LFP)			
Period		Length: 8 weeks															
Week [b]	Days -28 to -1	1	2	3	4	5	6	7	8	10	12	14	16 [c]	20 [d]	24	28	32
Window		±2 days								±2 days				±2 days			

may be used in place of urine pregnancy testing with prior permission from the sponsor.

[k] Hematology and chemistry laboratory samples will be collected locally. Local laboratory evaluations may be done more frequently at the investigator's discretion (eg, for acute management of TEAEs) and may be used for dosing decisions.

[l] Clinical laboratory evaluations for disease assessments (anti-AChR and anti-MuSK antibodies) will be tested centrally.

[m] Samples collected before TAK-079 administration.

[n] CD19 evaluation to be performed only in patients with prior exposure to rituximab; CD19 counts must be within the normal range at screening to be eligible.

[o] Circulating biomarkers may include assessment of complement C3 and C4 levels. Sample is also drawn for cytokine markers. Additional samples of cytokine markers are to be drawn if CRS is suspected.

[p] Additional PK and biomarker sampling may be requested.

[q] Quantitative immunoglobulins will be tested at a central laboratory; thus, results will not be available before each weekly dose. However, per standard medical practice, investigators should review the results once available and take appropriate clinical action, which may include but is not limited to withholding study drug and treatment with IVIg, for example, in the setting of a severe infection.

[r] Physician examination portion of this assessment may be omitted if performing a remote visit.

[s] Procedure may be omitted if performing a remote visit. The assessment of forced vital capacity for QMG test may be omitted for COVID-19-related reasons (see Section 9.12).

[t] Premedication and postdose medication before and after TAK-079 administration as outlined in Section 8.1.

[u] Time and anatomical site should be recorded for each injection. Patients will be closely monitored in the clinic for at least 2 hours after the first and second TAK-079 dose; before discharge from the clinic, the possible signs and symptoms of anaphylactic reactions and CRS should be reviewed with patients.

[v] Postdose medication should be given 2 hours (±15 minutes) after the first injection of the first dose and 1 day after the first dose of study drug in the morning. Postdose medication may be given with subsequent doses if clinically indicated and under the discretion of the principal investigator (see Section 8.1.2).

[w] Assessments for AEs are to include a symptomatic examination per standard medical practice.

Appendix B Clinical Signs and Symptoms of Cytokine Release Syndrome

Organ System	Symptoms
Constitutional	Fever with or without rigors, malaise, fatigue, anorexia, myalgias, arthralgia, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Coagulation	Elevated D-dimer, hypofibrinogenemia with or without bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Headache, mental status changes, confusion, delirium, word-finding difficulty or frank aphasia, hallucinations, tremor, dysmetria, altered gait, seizures

Source: Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124(2):188-95 [20].

Appendix C Grading System for Cytokine Release Syndrome

Grade	Toxicity
Grade 1	Symptoms are not life-threatening and require symptomatic treatment only, eg, fever, nausea, fatigue, headache, myalgias, malaise)
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement <40%, or Hypotension responsive to fluids or low dose of 1 vasopressor, or Grade 2 organ toxicity
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement ≥40%, or Hypotension requiring high dose or multiple vasopressors, or Grade 3 organ toxicity, or Grade 4 transaminitis
Grade 4	Life-threatening symptoms Requirements for ventilator support, or Grade 4 organ toxicity (excluding transaminitis)
Grade 5	Death

Source: Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124(2):188-95 [20].

Grades 2 to 4 refer to the Common Terminology Criteria for Adverse Events, version 4.03 grading.

Appendix D Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the Statement of Investigator (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform study-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.
4. Ensure that study-related procedures, including study-specific (nonroutine/nonstandard panel) screening assessments, are NOT performed on potential patients before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to patients. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each patient who participates in the study, and document the date of consent in the patient's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a patient authorization section that describes the uses and disclosures of a patient's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a patient authorization, then the investigator must obtain a separate patient authorization form from each patient or the patient's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should

contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix E Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of the investigator, including his or her name, address, and other identifying personal information. In addition, the investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the UK, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

The investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of the investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details, and results on publicly accessible clinical study registries, databases, and websites.

The investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in the investigator's own country.

The investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix F MG-ADL Score

MG Activities of Daily Living (MG-ADL) profile

Appendix G MGII Score

Myasthenia Gravis Impairment Index (MGII) ™

ID: _____

Date: _____

Please answer the following questions regarding your symptoms. Only consider those that you think are related to myasthenia. Check the answer that best describes your symptoms over the past 2 weeks.

Ocular

1)

Have you experienced episodes of double vision? If yes, at what time do they occur **(on average)**?	No Double Vision ☐ 0	Episodes only in the evenings ☐ 1	Episodes starting in the afternoons ☐ 2	Constant or present most of the day ☐ 3

2)

Have you experienced double vision with activities such as reading, driving, watching TV or using a computer? If yes, how long does it take **(on average)** before the double vision occurs?	No Double Vision ☐ 0	After more than 1 hour ☐ 1	After less than 1 hour, but not immediately ☐ 2	Constant double vision or it starts immediately ☐ 3

3)

Have you experienced double vision? If yes, how severe has it been **(at your worst)**?	No Double Vision ☐ 0	Mild: it doesn't affect my daily activities ☐ 1	It affects my activities but no need to cover one eye ☐ 2	I need to cover one eye to be able to function ☐ 3

4)

Have you experienced drooping of your eyelid(s)? If yes, when does it occur **(on average)**?	No eyelid drooping ☐ 0	Only in the evenings ☐ 1	Drooping starts in the afternoons ☐ 2	Constant drooping or present most of the day ☐ 3

5)

Have you experienced drooping of your eyelid(s) with activities such as reading, driving, watching TV or using a computer? If yes, how long does it take **(on average)** before the drooping occurs?	No eyelid drooping ☐ 0	After more than 1 hour ☐ 1	After less than 1 hour, but not immediately ☐ 2	Constant drooping or it starts immediately ☐ 3

6)

Have you experienced drooping of your eyelids? If yes, how severe has it been **(at your worst)?**	No eyelid drooping ☐ 0	Mild: it doesn't affect my vision ☐ 1	It affects my vision but no need to lift my eyelid ☐ 2	I need to lift my eyelid or tilt my head to be able to see ☐ 3

Impairment Index (MGII) ™

ID: _____

PROBLEMS EATING: Please answer regarding the past 2 weeks.

7. Difficulty swallowing

Have you experienced difficulty swallowing? How severe has it been **(at your worst**)?	No swallowing problems	Occasional episodes of choking/coughing with food or liquids	Liquids return through my nose, but no problems with solid food	Difficulty swallowing hard food, requiring a change in diet	Unable to swallow or using a feeding tube
	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

8. Chewing different types of food

Have you experienced difficulty chewing? How severe has it been **(at your worst**)?	No difficulty chewing	Difficulty chewing hard foods (e.g. steak, raw carrots)	Difficulty chewing soft foods (e.g. hard boiled egg)	Unable to chew (eating only liquids or feeding tube)
	☐ 0	☐ 1	☐ 2	☐ 3

9. Chewing tiredness/fatigue

At your worst, how long does it take to develop fatigue or tiredness in your jaw?	No difficulty chewing	Difficulty chewing at the end of the meal	Difficulty chewing from the beginning of the meal	Unable to chew (eating only liquids or feeding tube)
	☐ 0	☐ 1	☐ 2	☐ 3

PROBLEMS SPEAKING AND BREATHING: Please answer regarding the past 2 weeks.

10. Voice changes through the day

Have you experienced episodes of nasal, hoarse or weak voice? When do they occur **on average**?	No voice changes	Voice changes only in the evenings	Voice changes starting in the afternoons	Constant voice changes or present most of the day
	☐ 0	☐ 1	☐ 2	☐ 3

11. Voice changes with prolonged conversation

How long can you talk **(on average)**, before developing voice changes, such as nasal, hoarse or weak voice? (Normal conversation, with pauses for other speakers)	No voice changes	Voice changes after more than 30 minutes	Voice changes after less than 30 minutes, but not immediately	Constant voice changes or they start immediately (less than 1 minute)
	☐ 0	☐ 1	☐ 2	☐ 3

12. Severity of voice changes

At your worst, how severe have your voice changes been? (Nasal, hoarse, weak voice)	No voice changes	Mild changes: my voice is mostly clear	Moderate changes: it can be hard to understand me	Severe changes: it is impossible to understand me
	☐ 0	☐ 1	☐ 2	☐ 3

Myasthenia Gravis Impairment Index (MGII) ™

ID: _____

PROBLEMS SPEAKING AND BREATHING (Cont.): Please answer regarding the past 2 weeks.

13. Speech clarity through the day

Have you experienced difficulty pronouncing words or slurred speech? When does it occur **on average**?	No episodes of slurred speech ☐ 0	Slurred speech only in the evenings ☐ 1	Slurred speech starting in the afternoons ☐ 2	Constant slurring, or present most of the day ☐ 3

14. Speech clarity with prolonged conversation

How long can you talk **(on average)**, before developing slurred speech? (Normal conversation, with pauses for other speakers)	No episodes of slurred speech ☐ 0	Slurred speech after 30 minutes ☐ 1	Slurred speech after less than 30 minutes, but not immediately ☐ 2	Constant slurring, or it starts immediately (less than 1 minute) ☐ 3

15. Severity of speech changes

At your worst, how severe have your speech changes been? (Slurring, difficulty pronouncing words)	No episodes of slurred speech ☐ 0	Mild slurring: It is easy to understand me ☐ 1	Moderate slurring: There are some difficulties understanding me ☐ 2	Severe slurring: it is impossible to understand me ☐ 3

16. Difficulty breathing

Have you experienced shortness of breath that is caused by myasthenia? (i.e. not caused by asthma, or other lung/heart disease) If yes, when has it occurred **(at your worst)**?	No shortness of breath (except for strenuous exercise) ☐ 0	With moderate effort (e.g. walking several blocks at my own pace) ☐ 1	With minimal effort (e.g. getting dressed, walking inside the house) ☐ 2	At rest or when lying on my back ☐ 3	Requiring assisted ventilation ☐ 4

GENERALIZED SYMPTOMS: Please answer regarding the past 2 weeks.

17. Overall physical tiredness

Have you experienced overall physical tiredness caused by myasthenia gravis? (i.e. not by sleeplessness, depression or other medical conditions)	No physical tiredness ☐ 0	Overall physical tiredness in the evenings ☐ 1	Overall physical tiredness starting in the afternoons ☐ 2	Constant physical tiredness, or present most of the day ☐ 3

Myasthenia Gravis Impairment Index (MGII) ™

ID: _____

GENERALIZED SYMPTOMS: Please answer regarding the past 2 weeks.

18. Arm weakness severity

Have you experienced weakness in your arms? If yes, how severe has it been **(at your worst)**?	No arm weakness ☐ 0	Mild weakness (e.g. difficulty lifting heavy objects) ☐ 1	Moderate weakness (e.g. difficulty lifting arms above the shoulders, but I can do it) ☐ 2	Severe weakness (unable to lift arms above the shoulders) ☐ 3

19. Arm weakness with prolonged use

Have you experienced weakness in your arms after prolonged use? When does it happen **(on average)**?	No arm weakness ☐ 0	Weakness when keeping arms up for long (e.g. washing or drying my hair) ☐ 1	Weakness with prolonged activities at shoulder level (organizing objects on a shelf, holding a phone to the ear) ☐ 2	Weakness with minimal effort (e.g. desk work, chopping vegetables) ☐ 3

20. Leg weakness severity

Have you experienced weakness in your legs? If yes, how severe has it been **(at your worst)?**	No leg weakness ☐ 0	Mild weakness (e.g. difficulty standing from a squat or from tying my shoes) ☐ 1	Moderate weakness (e.g difficulty standing from a chair, I need to push up with my arms) ☐ 2	Severe weakness (e.g unable to stand from a chair without assistance) ☐ 3

21. Leg weakness with prolonged use

Have you experienced weakness in your legs after prolonged use? When does it happen **(on average)**?	No leg weakness ☐ 0	Weakness when walking more than 10 blocks at my own pace ☐ 1	Weakness when walking less than 10 blocks at my own pace ☐ 2	Constant weakness or with minimal effort (standing, walking inside the house) ☐ 3

22. Neck weakness

Have you experienced weakness in your neck? When does it happen **(on average)**?	No neck weakness ☐ 0	Weakness only in the evenings ☐ 1	Weakness starting in the afternoons ☐ 2	Constant weakness or present most of the day ☐ 3

MG Impairment Index (MGII) - Examination

ID:_____
Date:_____

This sheet refers to the physical examination. Detailed instructions are found in the instruction manual. You will need a stopwatch.

	0	1	2	3	Score
E1. Diplopia	No Diplopia	Diplopia in only 1 direction.	Diplopia in 2 directions.	Diplopia in ≥3 directions OR in primary gaze.	
E2. Ptosis	No ptosis	Ptosis between 10-60 seconds.	Spontaneous ptosis or in less than 10 seconds.		
E3. Lower Facial Strength	Normal strength	Can resist with cheeks, but air escapes through lips.	Unable to seal lips or provide resistance with cheeks.		
E4. Arm Endurance	Holds arms for 180 seconds.	Holds arms for 91-179 seconds.	Holds arms for 30-90 seconds.	Holds arms for < 30 seconds.	
E5. Leg Endurance	Holds leg for 90 seconds.	Holds leg for 40-89 seconds.	Holds leg for 16-39 seconds.	Holds leg for ≤ 15 seconds.	
E6. Neck Endurance	Holds head for 60 seconds.	Holds head for 35-59 seconds.	Holds head for 11-34 seconds.	Holds head for ≤ 10 seconds.	

Appendix H MGC Score

MG composite scale

Ptosis, upward ease (physician examination)	>45 seconds = 0	11-45 seconds = 1	1-10 seconds = 2	Immediate = 3
Double vision on lateral Gaze, left or right (physician examination)	>45 seconds = 0	11-45 seconds = 1	1-10 seconds = 3	Immediate = 4
Eye closure (physician examination)	Normal = 0	Mild weakness (can be forced open with effort) = 0	Moderate weakness (can be forced open easily) = 1	Severe weakness (unable to keep eye closed) = 2
Talking (patient history)	Normal = 0	Intermittent slurring or nasal speech = 2	Constant slurring or nasal but can be understood = 4	Difficult to understand speech = 6
Chewing (patient history)	Normal = 0	Fatigue with solid food = 2	Fatigue with soft food = 4	Gastric tube = 6
Swallowing (patient history)	Normal = 0	Rare episode of choking or trouble swallowing = 2	Frequent trouble swallowing, for example necessitating change in diet = 5	Gastric tube = 6
Breathing (thought to be caused by MG)	Normal = 0	Shortness of breath with exertion = 2	Shortness of breath at rest = 4	Ventilator dependence = 9
Neck flexion or extension (weakest) (physician examination)	Normal = 0	Mild weakness = 1	Moderate weakness (i.e., ~50% weak, ±15%) = 3	Severe weakness = 4
Shoulder abduction (physician examination)	Normal = 0	Mild weakness = 2	Moderate weakness (i.e., ~50% weak, ±15%) = 4	Severe weakness = 5
Hip flexion (physician examination)	Normal = 0	Mild weakness = 2	Moderate weakness (i.e., ~50% weak, ±15%) = 4	Severe weakness = 5
TOTAL				_____

Note: Please note that “moderate weakness” for neck and limb items should be construed as weakness that equals roughly 50% ± 15% of expected normal strength. Any weakness milder than that would be “mild,” and any weakness more severe than that would be classified as “severe.”

Appendix I QMG Score

QMG form

Test Item	None	Mild	Moderate	Severe	Score	
Grade	**0**	**1**	**2**	**3**	**Raw**	**Scale**
Double vision on lateral gaze Right or left (circle one), secs	61	11-60	1-10	Spontaneous		
Ptosis (upward gaze)	61	11-60	1-10	Spontaneous		
Facial muscles	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete		
Swallowing 4 oz water (1/2 cup)	Normal	Minimal coughing or throat clearing	Severe coughing/choking or nasal regurgitation	Cannot swallow (test not attempted)		
Speech after counting aloud from 1 to 50 (onset of dysarthria)	None at 50	Dysarthria at 30-49	Dysarthria at 10-29	Dysarthria at 9		
Right arm outstretched (90 degrees sitting), seconds	240	90-239	10-89	0-9		
Left arm outstretched (90 degrees sitting), seconds	240	90-239	10-89	0-9		
Forced Vital Capacity	$\geq$ 80	65-79	50-64	<50		
Rt- hand grip, kg Men Women	 $\geq$ 45 $\geq$ 30	 15-44 10-29	 5-14 5-9	 0-4 0-4		
Lt- hand grip, kg Men Women	 $\geq$ 35 $\geq$ 25	 15-34 10-24	 5-14 5-9	 0-4 0-4		
Head lifted (45 degrees supine seconds	120	30-119	1-29	0		
Right leg outstretched (45 degrees supine), seconds	100	31-99	1-30	0		
Left leg outstretched (45 degrees supine), seconds	100	31-99	1-30	0		
				TOTAL QMG SCORE :		

Appendix J MG-QoL15r

Patient ID #: _____
Date: _____

Please indicate how true each statement has been (over the past few weeks).

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

Total MGOOL-R score

Appendix K PGIC

Appendix L PGIS

PGIS Questionnaire

Patient ID:_____
Date:_____

How much has your myasthenia gravis affected your functioning **in the past 7 days?**

✓*one box only*

- ☐ **Not at all**
- ☐ **A little bit**
- ☐ **Somewhat**
- ☐ **Quite a bit**
- ☐ **Very much**

Appendix M Protocol History

Date	Amendment Number	Type	Region
02 February 2021	Amendment 4	Substantial	Global
28 September 2020	Amendment 3	Substantial	Global
05 March 2020	Amendment 2	Substantial	Global
18 October 2019	Amendment 1	Nonsubstantial	Global
05 September 2019	Initial Protocol	Not applicable	Global

Protocol Amendment 3 Summary and Rationale

The primary reason for this amendment was to add contingency plans for the coronavirus disease 2019 (COVID-19) pandemic by incorporating flexibility for study participants and investigators, while continuing to maintain patient safety and study integrity as per local site regulations. Other minor changes and clarifications to the protocol are summarized below.

Protocol Amendment 3		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 2.0 STUDY SUMMARY	Statistical Considerations: Updated text in the synopsis for the primary endpoint analysis to be consistent with the body of the protocol.	To harmonize the analysis of the safety data between the synopsis and body of the protocol.
Section 2.0 STUDY SUMMARY Section 5.2.3 Exploratory Endpoints	Amended the wording for the exploratory endpoint of pharmacokinetics (PK) from "PK of TAK-079 in combination with the background therapy. PK parameters include but are not limited to C_{max}, AUC, and t_{max} (time of first occurrence of C_{max}) to read: "Serum concentration-time profile of TAK-079 PK parameters will include, but are not limited to C_{trough} over time."	Clarify PK endpoint.
	Added exploratory endpoint: Change in serum immunoglobulin levels.	The reduction in immunoglobulin levels is an important pharmacodynamic indicator of TAK-079 effect.
	Added antidrug antibody (ADA) as an immunogenicity assessment and removed ADA as a biomarker.	To clarify that ADA is an immunogenicity assessment and not a biomarker of disease activity.

Protocol Amendment 3		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	Exclusion Criterion #4: Revised to exclude patients if there is an expectation that any rescue therapy may be needed between screening and dosing.	To clarify that a patient's underlying MG should be stable enough that the need for rescue therapy is not expected before dosing.
Section 2.0 STUDY SUMMARY Section 13.1.3 Efficacy Analysis	Statistical Considerations: Changed "Secondary Efficacy Endpoints" to read: "Efficacy Endpoint Analyses." Revised text to specify how different types of secondary efficacy endpoints (binary vs continuous) will be analyzed.	To clarify statistical analyses.
Section 13.1.4 PK Analysis	PK analysis description made clearer and more concise.	To clarify the PK analysis to better reflect the information that will be obtained from the PK sampling schedule in this study.
Section 2.0 STUDY SUMMARY Section 13.3 Determination of Sample Size	Amended the sample-size justification to remove the statement describing a power calculation for the secondary efficacy endpoints.	To further clarify that this study is an exploratory study and not powered to test any predefined statistical hypothesis at a formal α level. Statistical tests will be not be inferential and will not be adjusted for multiplicity.
Section 4.4 Benefits and Risks Assessment	New section added summarizing the potential risks and benefits of TAK-079.	Added in response to a health authority request.
Section 5.1.3 Exploratory Objectives	Removed "in combination with background therapy" from the exploratory objectives of the PK and pharmacodynamics of TAK-079.	To clarify that the PK and pharmacodynamics of TAK-079 will be determined regardless of background therapy received.
Section 8.1 Study Drug Administration	Added clarifying statements that first dose assessments detailed in Table 8.d may be satisfied by screening.	To clarify that on Day 1 of dosing, these laboratory studies would have been recently obtained in the absence of recently administered study drug. For other doses, the window is expanded to allow obtaining labs the day before (rather than restricted to 24 hours before the study visit) for flexibility in obtaining laboratory results, especially in light of operational complexities due to coronavirus disease 2019 (COVID-19).

Protocol Amendment 3		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 8.1.2 Postdose Medication	The dose of methylprednisone was corrected from <20 mg to read ≤20 mg.	To correct typographical error.
Section 8.2 Excluded Concomitant Medications and Procedures, Table 8.b Excluded Concomitant Medications	Added footnote b to the categories of intravenous immunoglobulin, plasmapheresis/plasma exchange, and subcutaneous immunoglobulin: "Patients for whom any therapy (besides the allowed standard background therapies for MG) is reasonably expected between screening and dosing are excluded from study participation."	To align with text in Exclusion Criterion No 4.
	Corrected exclusion criteria for dosing of rituximab, belimumab, eculizumab, or any monoclonal antibody for immunomodulation restricted from ≤6 months "before the screening visit" to read "before the first dosing."	To align with text in Exclusion Criterion No 6.
Section 8.4.1 Assessment and Criteria for Terminating Patient Dosing, Table 8.d Summary of Subsequent Dosing Criteria	Safety Parameter: Total lymphocyte count: Continue Dosing: Corrected "≥500/mm^3" to read: "≥500/mm^3 or ≥90% of the baseline level." Dose Hold: Corrected "<500/mm^3" to read:" <500/mm^3 and <90% of the baseline level."	Allows for minor fluctuations in the cell counts for patients on background therapy who may also have low baseline values. This criterion is based on emerging information from ongoing clinical studies with TAK-079.

Protocol Amendment 3		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
	Amended footnote c from "Laboratory grading is based on CTCAE v4.03" to read: "Laboratory and infection grading are based on CTCAE v4.03. Added footnote c to: row labeled "Platelets" for Thrombocytopenia ≤Grade 2[c] and Thrombocytopenia ≤Grade 3[c]; row labeled "Hypersensitivity (allergic reaction or anaphylaxis)[e]" for ≤Grade 2[c], and row labeled "Systemic infection" for Grade 2[c] and ≥Grade 3[c] Removed footnote f from Systemic infection Grade 2[c] and ≥Grade 3[c].	To clarify that all laboratory and infection grades listed in the table are based on Common Terminology Criteria for Adverse Events (CTCAE) v4.03 criteria.
Section 8.5.1 Pregnancy, Lactations, and Contraception	Changed Section heading to include "Contraception" and added Table 8.e (methods of contraception for female patients) and Table 8.f (methods of contraception for male patients) to match with contraception method recommendations provided in the informed consent form.	Text added in response to a request from a health authority.
Section 8.6.1.1 Management Recommendations for Hypersensitivity Reactions	First sentence: Change ISR to IRR.	Correct typo.
	Add "Signs and symptoms of systemic hypersensitivity reactions include rash, urticaria, fever, and/or bronchospasms."	To describe the clinical presentation of an infusion reaction.
	Remove examples of Grade 1, Grade 2, and Grade 3 hypersensitivity reactions. Add text in parenthesis after Grade 3 or greater: "(including any diagnosis of anaphylaxis according to Sampson [24])."	To avoid confusion with definition of CTCAE v4.03 grades and criteria for diagnosis of anaphylaxis.

Protocol Amendment 3		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Table 8.d Summary of Subsequent Dosing Criteria	Table 8.d: Revised wording: Hypersensitivity (IRR, allergic reaction, or anaphylaxis (See Section 8.6.1). NOTE: IRR, allergic reaction, and anaphylaxis are each classified according to CTCAE v4.03. Anaphylaxis is diagnosed according to Sampson et al [19]. Continue Dosing: ≤Grade 2 Dose Discontinuation: ≥Grade 3 or any signs or symptoms of an anaphylactic reaction [19]. CRS (See Section 8.6.2) NOTE: CRS is classified in accordance with Lee et al [20]. Continue Dosing: Grade 1 with symptomatic treatment allowed in accordance with Lee et al [20]. Dose Discontinuation: ≥Grade 2. Remove Table footnotes e and f as information is redundant with information provided in table.	Make dosing criteria for hypersensitivity and CRS in table consistent with text in Section 8.6.1 and Section 8.6.2
Section 9.12 COVID-19 Related Procedural Changes	Added new section (Section 9.12) and text regarding contingency plans for the COVID-19 pandemic ongoing during the clinical study.	New section to mitigate the impact of the COVID-19 pandemic to ensure the rights, safety, and well-being of patients, the safety of clinical trial staff, maintain compliance with Good Clinical Practice, maintain study integrity, and patient privacy.
Section 9.5.10.2 Timing of Pregnancy Testing	Changed timing of pregnancy testing before initial study dosing at baseline from "within 24 hours before the start of study drug" to read: "Either Day 1 prior to initial study dosing, or 1 day before study dosing."	To clarify the timing of pregnancy testing at baseline.

Protocol Amendment 3		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 9.6 End of Safety Follow-up Period Assessments, Table 9.c End of Safety Follow-Up Period Clinical Parameters	Table 9.c: Revised criteria for neutrophils, platelets, total lymphocyte count, and Hgb as follows: **End-of-Study Criteria:** ≥LLN or ≥study baseline levels, or abnormal levels that are not directly related to dosing of investigational product. **Continuation to Long-term Follow-up:** <LLN and < study baseline levels that are directly related to dosing of investigational product.	To clarify the end-of-study criteria and long-term follow-up parameters by correcting errors and unclear wording.
	TAK-079-related hypersensitivity reaction (IRR, allergic reaction, or anaphylaxis) (See Section 8.6.1) **End-of-Study Criteria:** Clinical symptoms related to hypersensitivity reaction resolved. **Continuation to Long-term Follow-up**: Clinical symptoms related to hypersensitivity reaction ongoing.	
	TAK-079-related CRS (See Section 8.6.2) **End-of-Study Criteria:** Clinical symptoms related to CRS reaction resolved. **Continuation to Long-term Follow-up:** Clinical symptoms related to CRS reaction ongoing.	
	Revised criteria for systemic infection as follows: **Continuation to Long-term Follow-up:** Any ≥Grade 2 [b] systemic infection that is not resolved.	
	Footnote a: added "see Section 8.6.2 for details" for definitions of CTCAE grades.	

Protocol Amendment 3		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 10.1.3 SAE Definition	Added: Note: Some clinical centers may only be able to provide certain rescue therapies (eg, IVIg) via inpatient hospitalization. Therefore, the hospital admission itself (in an otherwise clinically stable patient) specifically for access and administration of rescue therapy does not count automatically as an SAE, unless there are other circumstances that fulfill SAE criteria.	Added clarification that inpatient stay for rescue therapy does not automatically count as a serious adverse event (SAE).
Section 13.1.1 Analysis Sets	The definition of the PK analysis set has been clarified to read "Patients who have received at least 1 dose and have at least 1 measurable TAK-079 serum concentration."	Clarification.
Section 13.1.5 Immunogenicity Analyses	Added "pharmacodynamics" to the statement that reads: The effect of immunogenicity on PK, pharmacodynamics, safety, and efficacy may be explored.	Correction.
Section 14.1 Study-Site Monitoring Visits	Added 2nd paragraph of text regarding contingency plans for Study-Site Monitoring Visits conducted during the COVID-19 pandemic.	Text added per Sponsor's COVID-19 guidelines.
Appendix A Schedule of Events	Removed serum sample collection for immunogenicity (eg, ADA) at Weeks 3, 5, and 7.	Serum samples do not need to be collected every week.
	Reordered all footnotes due to the addition of 4 footnotes (b, h, r, and s).	N/A
	Added footnote b to table row labeled "Week" to allow for remote visits at certain time points.	Added per COVID-19 guidelines to allow flexibility for remote visits.

Protocol Amendment 3		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Appendix A *continued...*	Added footnote letter h to table rows labeled: 12-lead ECG; serum pregnancy test; urine pregnancy test; hematology; clinical chemistry; direct/indirect Coombs test; serum sample for anti-AChR or anti-MuSK antibodies; blood sample for immunoprofiling; serum sample for circulating biomarkers; serum sample for quantitative IgA/IgM/IgG; serum sample for TAK-079 PK; serum sample for immunogenicity (eg, ADA); serum sample for vaccine-induced protective antibodies; pharmacodynamic biomarkers; and Disease assessment tests.	To indicate that assessments may be performed on the day before or the day of the indicated visit before dosing.
	Added text to table footnote i to state that vital signs measurements will not be required at the Week 14 visit during the COVID-19 pandemic visit as long as there are no concerns raised by the symptom-directed physical.	Added per COVID-19 guidelines to allow flexibility for remote visits.
	Added text to footnote j and added footnote "j" designator to table row labeled urine pregnancy test to indicate that serum pregnancy testing may be used in place of urine pregnancy testing with prior permission from the sponsor.	To clarify that the intent of the protocol is not to exclude use of more accurate serum pregnancy tests if this is logistically feasible for a site.
	Added footnote letter m to table rows labeled: urine pregnancy test, hematology; clinical chemistry; direct/indirect Coombs test, and serum sample for vaccine-induced protective antibodies.	To ensure that samples are collected before TAK-079 administration
	Added footnote r to table row labeled Myasthenia Gravis Impairment Index (MGII) score to indicate that the Physician examination portion of the MGII score may be omitted if performing a remote visit.	Added per COVID-19 guidelines to allow flexibility for remote visits.

Protocol Amendment 3		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
	Added footnote s to table rows labeled Myasthenia Gravis Composite (MGC) and Quantitative Myasthenia Gravis (QMG) scores to indicate that the MGC and QMG may be omitted if performing a remote visit.	Added per COVID-19 guidelines to allow flexibility for remote visits.
Appendix I QMG Score	Updated the version of the QMG form from v2.0 to v2.1.	Minor version update to the QMG form, which includes a vertical border in the column header separating "Raw" and "Scale" scores.

Rationale for Amendment 2

The objective of Amendment 2 was to remove language regarding details of storage conditions outlined in the Rationale for Amendment 1. This was because the storage conditions may vary by region and do not require further specification in the study protocol.

Additionally, changes to inclusion and exclusion criteria were made to provide better definitions, clarification of intent and removal of vague language. Updates to the Takeda serious adverse event reporting process, which now includes an acknowledgment of receipt, have been made in Section 10.2.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Changes in Amendment 2

1. Updated Inclusion Criterion 7 to clarify the intent to exclude only pulse steroid therapy. Dosing of corticosteroids with oral therapy every other day is as acceptable as daily.
2. Updated Exclusion Criterion 8 to exclude only those receiving live vaccines and not inactive vaccines.
3. Updated Exclusion Criterion 12 to clarify the intent not to exclude a minor, benign, resolved, localized herpes simplex infection not requiring systemic therapy.
4. Updated Exclusion Criterion 13f to change "lower limit of normal" to "5 g/L." As a result of this edit, subjects are excluded if the IgG is less than 5 g/L (500 mg/dL) at screening.
5. Updated Exclusion Criterion 16 to clarify the intent to exclude subjects with active hepatitis C and not those who have been fully cured of the disease. Additionally, more stringent criteria are used to exclude subjects with hepatitis B infection.

6. Updated the serious adverse event reporting procedure in Section 10.2 to include an acknowledgement of receipt.
7. Added a global fax number to the SAE Reporting Contact Information.
8. Descriptors for circulating biomarker samples and quantitative IgA/IgM/IgG samples have been changed from blood to serum in the schedule of events.
9. Updated the version number of the QMG scoring assessment tool (to Version 2.0; previously Version 1.0) which fixes a typographical error in the definition of severe forced vital capacity (FVC) (in Version 2 FVC is <50; in Version 1 FVC was ≤50).
10. Serum samples for hepatitis B, hepatitis C, and HIV have been added to the Section 9.0 Primary Specimen Collection Table.
11. Added serum pregnancy test at Week 32.
12. Eligibility criteria regarding immunosuppressive drugs now requires a stable dose for at least 3 months before screening. Stable dosing of azathioprine will remain at 6 months prior to screening**.**

Rationale for Amendment 1

The objective of this amendment was to remove language specifying that the site pharmacist is to be unblinded. The reason for this change is because the storage conditions for the placebo formulation were changed to be the same as for the active drug (both now refrigerated at 5°C, whereas previously the placebo was to be stored frozen at -20°C). This avoids the need for an unblinded site pharmacist. Therefore, all site personnel, including the site pharmacist, are to be blinded as to treatment assignments.

Additionally, a protocol subsection is added to provide information regarding potential interference with serological testing.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Changes in Amendment 1

1. Removal of language specifying that the site pharmacist is to be unblinded, as was previously detailed in Section 8.7.2 and Section 8.7.4. As a result of this edit, all site staff will be blinded as to treatment assignment through study Week 16.
2. The addition of a protocol subsection 8.5.3 to provide clarification regarding potential interference with serological testing

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Approval	03-Feb-2021 16:12 UTC
[redacted]	Clinical Pharmacology Approval	03-Feb-2021 16:41 UTC
[redacted]	Biostatistics Approval	03-Feb-2021 21:23 UTC