RAISE

Randomized Trial of Zilucoplan in SubjEcts with Myasthenia Gravis

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Confirm the Safety, Tolerability, and Efficacy of Zilucoplan in Subjects with Generalized Myasthenia Gravis

Protocol Number:	RA101495-02.301 (RAISE) (UCB study MG0010)
Protocol Version/Date:	Version 2.0/18.Dec.2020
Indication Studied:	Generalized Myasthenia Gravis
Developmental Phase of Study:	3
EudraCT Number:	2019-001564-30
Sponsor Address:	Ra Pharmaceuticals, Inc. (now part of UCB) 87 Cambridge Park Drive Cambridge, MA, 02140 | USA

This study will be conducted by Ra Pharmaceuticals, Inc. and affiliates in compliance with the protocol, Good Clinical Practice, and all other applicable regulatory requirements, including the archiving of essential documents.

CONFIDENTIAL

CENTER INVESTIGATOR SIGNATURE PAGE

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated. This trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and International Council for Harmonisation guidelines.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study.

I will use only the informed consent form approved by the Sponsor or its representative and will fulfill all responsibilities for submitting pertinent information to the Institutional Review Board/Independent Ethics Committee (IRB/IEC) responsible for this study.

I agree that the Sponsor or its representatives shall have access to any source documents from which case report form information may have been generated. I agree that regulatory authorities [Food and Drug Administration (FDA), European Medicines Agency (EMA), and other local and country-related agencies] can audit and review source documents.

I further agree not to originate or use the name of Ra Pharmaceuticals, Inc. or any of its employees, in any publicity, news release, or other public announcement, written or oral, whether to the public, press, or otherwise, relating to his protocol, to any amendment hereto, or to the performance hereunder, without the prior written consent of Ra Pharmaceuticals, Inc.

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Signature of Investigator Date

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Name of Investigator (Typed or Printed)

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Protocol Version**	**Date**
Original Protocol (Canada, US)	1.0	08 Apr 2019
Protocol Amendment (United Kingdom)	GB.1.1	02 Oct 2019
Protocol Amendment (Japan)	JP.1.1	29 Oct 2019
Protocol Amendment (Germany)	DE.1.1	13 Nov 2019
Protocol Amendment (Norway)	NO.1.1	13 Nov 2019
Protocol Amendment (Italy)	IT.1.1	26 Nov 2019
Protocol Amendment (Japan)	JP.1.2	06 Dec 2019
Protocol Amendment (France)	FR.1.1	06 Feb 2020
Protocol Amendment (Germany)	DE.1.2	26 Jun2020
Protocol Amendment (global)	2.0	18 Dec 2020

PROTOCOL AMENDMENT (GLOBAL) VERSION 2.0 (18 DEC 2020)

The purpose of this protocol amendment is to make the following changes to the original protocol (Version 1.0 dated 08 Apr 2019):

- The total sample size has been increased from 130 subjects (65 subjects per treatment group) to 156 subjects (78 subjects per treatment group). This increase was made to account for higher variability in the primary endpoint than originally assumed, and to maintain the power of the study.
- An unblinded interim analysis has been added to be performed after the final subject has completed the Week 12 visit, or after the final subject has prematurely discontinued prior to reaching Week 12. The purpose of this interim analysis is to perform a comprehensive evaluation of all available double-blind data to prepare regulatory submissions for approval of the MG target indication.
- Changes made in earlier country-specific protocol amendments (France, Germany, Italy, Japan, Norway, United Kingdom) have been consolidated into a single global protocol.
- The objectives and endpoints were revised to reflect current UCB practices for the categorization and description of study objectives, estimands, and endpoints.
- The protocol was updated to include provisions for the COVID-19 pandemic.
- Additional administrative updates were made in the protocol.

Section # and Name	Description of Change	Brief Rationale
Title Page	Updated version number and date; added UCB study number	Updates
Section 1, Synopsis, Study Population	Provided specific age range of study population	Clarification
Section 1, Synopsis, Planned Number of Subjects	Revised sample size	Update
Section 1, Synopsis, Study Design	Revised sample size	Update
Section 1, Synopsis, Study Design	Added enrollment rate for Japanese sites	Consolidation of earlier country-specific protocol amendments into global protocol
Section 1, Synopsis, Study Design	Added overnight hospitalization following Day 1 dose for Japanese sites	Consolidation of earlier country-specific protocol amendments into global protocol
Section 1, Synopsis, Study Design	Added information on the use of eculizumab as rescue therapy for German sites	Consolidation of earlier country-specific protocol amendments into global protocol
Section 1, Synopsis, Inclusion/Exclusion Criteria	Updated inclusion criterion 12 (contraception)	Consolidation of earlier country-specific protocol amendments into global protocol
Section 1, Synopsis, Inclusion/Exclusion Criteria	Updated exclusion criterion 12 (treatment with rituximab)	Consolidation of earlier country-specific protocol amendments into global protocol
Section 1, Synopsis, Inclusion/Exclusion Criteria	Added exclusion criterion 18 (hypersensitivity to study drug)	Consolidation of earlier country-specific protocol amendments into global protocol
Section 1, Synopsis, Study Objectives and Endpoints	Revised objectives and endpoints	Updated to reflect UCB practices for categorization and description of study objectives, estimands, and endpoints

Section # and Name	Description of Change	Brief Rationale
Section 1, Synopsis, Statistical Considerations, Efficacy Analyses	Minor revisions to description of efficacy analyses	Update and clarification
Section 1, Synopsis, Statistical Considerations, Determination of Sample Size	Increased total sample size to 156 subjects (78 subjects per treatment group)	Update to account for higher variability in the primary endpoint than the original assumption, and to maintain the power of the study
Section 2, Time and Events Table	Added table row for "Hospitalization"	Consolidation of earlier country-specific protocol amendments into global protocol
Section 2, Time and Events Table, footnote h	Revised to indicate collection of information for concomitant medications taken during the 30 days prior to Screening	Clarification
Section 2, Time and Events Table, footnote u	Added footnote u (COVID-19 provisions)	Update to include provisions for the COVID-19 pandemic
Section 2, Time and Events Table, footnote v	Added footnote v (overnight hospitalization in Japan)	Consolidation of earlier country-specific protocol amendments into global protocol
Section 2, Time and Events Table, footnote w	Added to footnote w (analysis for neutralizing antibodies included in ADA analysis)	Clarification
Section 4, List of Abbreviations and Definitions	Added additional abbreviations	Update
Section 5, Introduction	Added reference to benefit/risk analysis	Consolidation of earlier country-specific protocol amendments into global protocol
Section 5.1, Overview of Generalized Myasthenia Gravis, paragraph 3	Update of treatments for gMG	Consolidation of earlier country-specific protocol amendments into global protocol

Section # and Name	Description of Change	Brief Rationale
Section 6, Study Objectives and Endpoints	Revised objectives and endpoints	Updated to reflect UCB practices for categorization and description of study objectives, estimands, and endpoints
Section 7.1, Overview of Study Design, paragraph 1	Increased total sample size to 156 subjects (78 subjects per treatment group)	Update to account for higher variability in the primary endpoint than the original assumption, and to maintain the power of the study
Section 7.1, Overview of Study Design, paragraph 3	Added enrollment rate for Japanese sites	Consolidation of earlier country-specific protocol amendments into global protocol
Section 7.1, Overview of Study Design, paragraph 6	Added overnight hospitalization following Day 1 dose for Japanese sites	Consolidation of earlier country-specific protocol amendments into global protocol
Section 7.1, Overview of Study Design, paragraph 7	Added information on the use of eculizumab as rescue therapy for German sites	Consolidation of earlier country-specific protocol amendments into global protocol
Section 7.2.1.1, Screening and Enrollment, bullet point regarding concomitant medications	Revised to indicate collection of information for concomitant medications taken during the 30 days prior to Screening	Clarification and consolidation of earlier country-specific protocol amendments into global protocol
Section 7.2.1.1, Screening and Enrollment, bullet point regarding ADA testing	Revised to indicate that ADA testing also includes neutralizing antibody testing	Clarification
Section 7.2.1.2, Randomization and Blinding, paragraph 3	Added information on database locks, including interim database lock after the final subject has completed Week 12	Update
Section 7.2.2, Treatment Period, paragraph 2	Added information on overnight hospitalization following Day 1 dose for Japanese sites	Consolidation of earlier country-specific protocol amendments into global protocol

Section # and Name	Description of Change	Brief Rationale
Section 7.3, Early Termination, paragraph 1	Added sentence addressing termination of study based on new or emerging safety information	Consolidation of earlier country-specific protocol amendments into global protocol
Section 7.4, Study Conduct During COVID-19	Added new section	Update to include provisions for the COVID-19 pandemic
Section 8.1, Inclusion Criteria, Inclusion Criterion 12	Updated inclusion criterion 12 (contraception)	Consolidation of earlier country-specific protocol amendments into global protocol
Section 8.2, Exclusion Criteria, Exclusion Criterion 12	Updated exclusion criterion 12 (treatment with rituximab)	Consolidation of earlier country-specific protocol amendments into global protocol
Section 8.2, Exclusion Criteria, Exclusion Criterion 18	Added exclusion criterion 18 (hypersensitivity to study drug)	Consolidation of earlier country-specific protocol amendments into global protocol
Section 8.3.2, Premature Discontinuation	Updated reasons for discontinuation	Consolidation of earlier country-specific protocol amendments into global protocol
Section 9.1.1, Investigational Medicinal Product and Placebo, paragraph 2	Added information for the BD Ultrasafe Plus device (compliance with European regulations)	Consolidation of earlier country-specific protocol amendments into global protocol
Section 9.1.2, Dosing Schedule, paragraph 1	Added text to clarify that study medication is self-administered	Consolidation of earlier country-specific protocol amendments into global protocol
Section 9.1.3, Dose Presentation, paragraph 2	Added information regarding composition of placebo	Consolidation of earlier country-specific protocol amendments into global protocol
Section 9.1.3, Dose Presentation, paragraph 3	Added text referring to subjects with lower body weight (<43 kg)	Consolidation of earlier country-specific protocol amendments into global protocol
Section 9.1.3.1, Missed Doses, paragraph 1	Added text regarding timing of administration of study drug (Japan)	Consolidation of earlier country-specific protocol amendments into global protocol

Section # and Name	Description of Change	Brief Rationale
Section 9.2.1.1, Alternative Study Treatment Supply due to COVID-19 Pandemic	Added new section	Update to include provisions for the COVID-19 pandemic
Section 9.2.3, Disposal, Return, or Retention of Unused Drugs, paragraph 1	Added clarification for return of unused study drug and containers	Consolidation of earlier country-specific protocol amendments into global protocol
Section 10.1.3, Prior and Concomitant Medications, paragraph 1	Revised to indicate collection of information for concomitant medications taken during the 30 days prior to Screening	Clarification and consolidation of earlier country-specific protocol amendments into global protocol
Section 10.1.3, Prior and Concomitant Medications, paragraph 3	Added reference to Appendix 2 (Prohibited Concomitant Medications)	Consolidation of earlier country-specific protocol amendments into global protocol
Section 10.1.3.1, Rescue Therapy, paragraph 2 and paragraph 3	Added information on the use of eculizumab as rescue therapy	Consolidation of earlier country-specific protocol amendments into global protocol
Section 10.2.4.1, Hematology, Chemistry, and Coagulation, Table 4	Added RBC to tabular list of clinical laboratory tests	Consolidation of earlier country-specific protocol amendments into global protocol
Section 10.2.4.3, Pregnancy Testing and Contraception	Revised information on contraception	Consolidation of earlier country-specific protocol amendments into global protocol
Section 10.2.6, Immunogenicity	Revised to indicate that ADA testing also includes neutralizing antibody testing	Clarification
Section 10.2.8, Overnight Observational Hospitalization in Japan	Added new section describing overnight hospitalization following Day 1 dose for Japanese sites	Consolidation of earlier country-specific protocol amendments into global protocol
Section 11.1.1.1, Occurrence of COVID-19	Added section regarding reporting cases of COVID-19	Update to include provisions for the COVID-19 pandemic

Section # and Name	Description of Change	Brief Rationale
Section 11.1.2, Serious Adverse Events, final paragraph	Added text regarding overnight hospitalization (Japan)	Consolidation of earlier country-specific protocol amendments into global protocol
Section 11.4.1.2, Serious Adverse Events, final paragraph	Added text regarding reporting of SUSARs	Consolidation of earlier country-specific protocol amendments into global protocol
Section 11.4.3, Emergency Unblinding, final paragraph	Added text regarding safety follow-up	Consolidation of earlier country-specific protocol amendments into global protocol
Section 12.2.1, General Methods	Added text regarding interim and final database locks, and analyses to explore impact of COVID-19	Update
Section 12.2.5.1, Primary Efficacy Endpoint Analysis, paragraph 1	Deleted interaction terms baseline QMG Score×visit and geographical region×visit	Update
Section 12.2.5.2, Secondary Endpoint Analyses, paragraph 1 and paragraph 2	Revised text regarding analyses of secondary efficacy endpoints	Update
Section 12.2.6, Handling of Missing and Censored Data	Added bullet point regarding the expected impact of the COVID-19 pandemic on MG-ADL	Update
Section 12.2.6, Handling of Missing and Censored Data	Added reference to eculizumab as potential rescue therapy	Consolidation of earlier country-specific protocol amendments into global protocol
Section 12.2.6, Handling of Missing and Censored Data, final sentence	Added sentence referring to protocol deviations related to COVID-19	Update
Section 12.2.8.1, Pharmacokinetic and Pharmacodynamic Analyses	Added text describing population PK, PD, and PK/PD analyses	Update

Section # and Name	Description of Change	Brief Rationale
Section 12.2.9, Interim Analysis	Revised with addition of description of interim analysis based on interim database lock after the final subject has completed Week 12	Update
Section 12.3, Sample Size Determination	Increased total sample size to 156 subjects (78 subjects per treatment group)	Update to account for higher variability in the primary endpoint than the original assumption, and to maintain the power of the study
Section 13.2, Informed Consent of Study Subjects, paragraph 5	Added text regarding age of adulthood in Japan	Consolidation of earlier country-specific protocol amendments into global protocol
Section 16, Appendices, Appendix 2	Added Appendix 2 (Prohibited Concomitant Medications)	Consolidation of earlier country-specific protocol amendments into global protocol
Sponsor Signature Page	Moved sponsor signature page to end of document	Alignment with UCB document practices, including the use of electronic sponsor signatures

1 SYNOPSIS

Protocol Title	A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Confirm the Efficacy, Safety, and Tolerability of Zilucoplan in Subjects with Generalized Myasthenia Gravis
Protocol Number	RA101495-02.301 (RAISE) (UCB study MG0010)
Phase of Clinical Development	Phase 3
Investigational Medicinal Product (IMP)	Zilucoplan (RA101495) administered by daily subcutaneous (SC) injection (0.3 mg/kg)
Study Population	Male or female ≥18 years and <75 years with generalized myasthenia gravis (gMG)
Investigative Sites	Approximately 100 centers are planned worldwide
Planned Number of Subjects	Approximately 156 subjects (78 per treatment arm)

Study Objectives

- To confirm the efficacy of zilucoplan in subjects with gMG
- To confirm the safety and tolerability of zilucoplan in subjects with gMG

Study Design

Study RA101495-02.301 is a multicenter, randomized, double-blind, placebo-controlled study to confirm the efficacy, safety, and tolerability of zilucoplan in subjects with gMG.

The planned enrollment is approximately 156 subjects. Subjects will be randomized in a 1:1 ratio to receive daily SC doses of 0.3 mg/kg zilucoplan or placebo. Randomization will be stratified based on the baseline MG-Activities of Daily Living (MG-ADL) Score (≤9 versus ≥10), Quantitative Myasthenia Gravis (QMG) Score (≤17 versus ≥18), and geographical region.

In order to ensure a gradual initiation of the study in Japan, each Japanese site will be capped to an enrollment rate of no more than one subject per site per week).

The study includes a Screening Period of up to 4 weeks and a 12-week Treatment Period. During the Treatment Period, subjects will return to the clinic at Week 1, Week 2, Week 4, Week 8, and Week 12 to evaluate efficacy, safety, and tolerability. Additional assessments will include questionnaires, biomarker samples, pharmacokinetics, pharmacodynamics, and optional pharmacogenomics. Safety assessments will include physical examinations, vital signs, electrocardiogram (ECG), clinical laboratory tests, adverse event (AE) monitoring, immunogenicity, and Columbia-Suicide Severity Rating Scale (C-SSRS).

Randomized subjects will receive 0.3 mg/kg zilucoplan or matching placebo administered SC at the Day 1 visit. Following in-clinic education and training, all subjects will self-inject daily SC doses of blinded study drug, according to randomized treatment allocation, for the subsequent 12 weeks. Single-use pre-filled syringes in injection devices will be provided for use during the study.

In Japan, following their Day 1 dose, subjects will be hospitalized overnight for observation to ensure safety of study drug administration. Prior to discharge, subjects will be asked to self-administer their Day 2 dose under supervision to ensure that their technique for self-injection is adequate and appropriate, and to answer any additional questions. These pre-scheduled overnight

observational hospitalizations will not be considered SAEs in this study (even if hospital stay is extended, provided that the sole purpose of the extension is improvement of the injection technique). Subjects will continue to self-inject daily SC doses of blinded study drug, according to randomized treatment allocation, for the subsequent 12 weeks.

Subjects are expected to remain on stable doses of all medications unless medically indicated changes become necessary. All standard of care (SOC) therapy medications for gMG should be kept at the same dose throughout the 12-week study, including corticosteroids and immunosuppressant therapy (IST) drugs. If escalation of gMG therapy (i.e., 'rescue therapy') becomes necessary due to major deterioration of a subject's clinical status, or risk of myasthenia gravis (MG) crisis as per the investigator's judgment, the subject may receive intravenous immunoglobulin G (IVIG) or plasma exchange (PLEX) treatment as 'rescue therapy'. In Germany, the choice of eculizumab as 'rescue therapy' will not be withheld, if the investigator considers this to be the best course of action.

To reduce the risk of meningococcal infection (Neisseria meningitidis), all subjects must be vaccinated against meningococcal infections (with a quadrivalent vaccine and, where available and in accordance with local SOC, serogroup B vaccine) within 3 years prior to, or at the time of, initiating study drug. Subjects who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics (e.g., Penicillin V 500mg twice daily, third generation cephalosporin, etc.) until at least 2 weeks after the initial dose of vaccine(s). The use of fluoroquinolone or macrolide antibiotics is not recommended due to the potential for exacerbation of MG. Booster vaccinations should be administered in accordance with SOC.

During the Treatment Period, to mitigate the risk of infection, subjects will be counseled and reminded of the early signs and symptoms of *Neisseria meningitidis* infection. A patient safety card detailing the signs and symptoms of infection, with instructions to seek immediate medical attention if any such symptoms occur, will be provided to each subject.

The safety of subjects will be monitored in a blinded manner on an ongoing basis. If an unblinded data review should become necessary to ensure subject safety, a Safety Monitoring Committee (SMC) will convene and evaluate study data as appropriate.

At the end of the Treatment Period, all subjects will have the option to receive zilucoplan in a separate Extension Study, provided they meet the Extension Study inclusion criteria.

If a subject discontinues study drug treatment prior to the Week 12 visit for any reason, he/she will not be eligible for the Extension Study. For subjects who permanently discontinue study drug, a Safety Follow-up Visit will be performed at 40 days after the last dose of study drug, to collect information on any ongoing AEs or new serious adverse events (SAE) since the last study visit.

Duration of Study Participation

The duration of study participation will include a Screening Period of up to 4 weeks and a 12-week Treatment Period for a total of approximately 16 weeks.

Inclusion/Exclusion Criteria

To be eligible for this study, subjects must meet **ALL** the following inclusion criteria:

1. Male or female ≥18 years and <75 years
2. Able to provide informed consent, including signing and dating the informed consent form (ICF)

3. Diagnosis of gMG [Myasthenia Gravis Foundation of America (MGFA) Class II-IV] at Screening
4. Positive serology for acetylcholine receptor (AChR) binding autoantibodies
5. MG-ADL Score of ≥6 at Screening and Baseline
6. QMG Score of ≥12 at Screening and Baseline (off acetylcholinesterase inhibitor therapy for at least 10 hours)
7. 4 or more of the QMG test items must be scored at ≥2 at Screening and Baseline
8. No change in corticosteroid dose for at least 30 days prior to Baseline or anticipated to occur during the 12-week treatment period
9. No change in immunosuppressive therapy, including dose, for at least 30 days prior to Baseline or anticipated to occur during the 12-week treatment period
10. Vaccination with a quadrivalent meningococcal vaccine and, where available, meningococcal serotype B vaccine at least 14 days prior to the first dose of study drug at the Day 1 visit. A booster vaccination should also be administered as clinically indicated, according to the local SOC, for subjects who have been previously vaccinated against *Neisseria meningitidis*
11. Female subjects of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test within 24 hours prior to the first dose of study drug
12. Sexually active female subjects of childbearing potential (i.e., women who are not postmenopausal or who have not had a hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) and all male subjects (who have not been surgically sterilized by vasectomy) must agree to use effective contraception during the study and during the safety follow-up period of 40 days after the last dose of study drug. Postmenopausal women are, for the purposes of this protocol, defined as women who have not had menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Subjects who meet **ANY** of the following exclusion criteria must be excluded from the study:

1. Thymectomy within 12 months prior to baseline or scheduled to occur during the 12-week study
2. Abnormal thyroid function as determined by local standard
3. Known positive serology for muscle-specific kinase (MuSK)
4. Minimal Manifestation Status of MG based on the clinical judgement of the investigator
5. Fixed weakness (‘burnt out’ MG) based on the clinical judgement of the investigator
6. History of meningococcal disease
7. Current or recent systemic infection within 2 weeks prior to Baseline or infection requiring intravenous (IV) antibiotics within 4 weeks prior to Baseline
8. Pregnant, planning to become pregnant, or nursing female subjects
9. Recent surgery requiring general anesthesia within 2 weeks prior to Screening or expected to have surgery requiring general anesthesia during the 12-week Treatment Period

10. Prior treatment with a complement inhibitor
11. Treatment with an experimental drug within 30 days or 5 half-lives of the experimental drug (whichever is longer) prior to Baseline
12. Treatment with rituximab within 12 months prior to Baseline or planned to occur during the 12-week study (this exclusion criterion is implemented out of an abundance of caution, in the absence of data showing that complement inhibition in the context of B-cell elimination by rituximab is safe)
13. Treatment with IVIG, SC immunoglobulin, or PLEX within 4 weeks prior to Baseline
14. Active malignancy (except curatively resected squamous or basal cell carcinoma of the skin) requiring surgery, chemotherapy, or radiation within the prior 12 months (subjects with a history of malignancy who have undergone curative resection or otherwise not requiring treatment for at least 12 months prior to Screening with no detectable recurrence are allowed)
15. History of or current significant medical disorder, psychiatric disorder, or laboratory abnormality that in the opinion of the investigator would make the subject unsuitable for participation in the study
16. Participation in another concurrent clinical trial involving an experimental therapeutic intervention (participation in observational studies and/or registry studies is permitted)
17. Unable or unwilling to comply with the requirements of the study
18. Hypersensitivity to zilucoplan or any of its excipients, or to placebo

Study Objectives and Endpoints

Objectives	Estimands/Endpoints
Primary Efficacy Objective: To confirm the efficacy of zilucoplan in subjects with gMG	**Primary Estimand:** **Treatment:** Zilucoplan administered by daily subcutaneous (SC) injection (0.3 mg/kg) vs Placebo **Target Population:** Adults with generalized myasthenia gravis (gMG) with inclusion/exclusion criteria provided in Section 8.1 and Section 8.2 of the protocol. **Endpoint:** Change from Baseline (CFB) in Week 12 in Myasthenia Gravis-Activities of Daily Living (MG-ADL) Score **Intercurrent event handling:** If a subject experiences any of the following intercurrent events, then data at and after the point of the intercurrent event will be treated as missing using a hypothetical strategy: A participant receiving rescue therapy: The study is interested in the treatment effect assuming that the treatment effect is null, and no rescue effect occurs after a subject receives rescue medication. A subject discontinuing the study: For subjects that discontinue due to AEs related to study drug, it is assumed that the treatment effect is null. For subjects that discontinue for other reasons (i.e., unrelated to study drug) it is assumed that the subject had remained on their treatment throughout the study (i.e., a "Hypothetical strategy" assuming subjects did not discontinue the study and remained on treatment).

	Population level summary: The difference between the zilucoplan and placebo treatment groups in the mean CFB in the Week 12 MG-ADL. As described in Section 10.3.1, the MG-ADL is a brief 8-item survey designed to evaluate MG symptom severity. Higher scores are associated with more severe symptoms of MG. Appendix 1: MG-Activities of Daily Living Scale presents the 8 items with corresponding response scale, each scored on a 0-3 point scale (i.e., 0=none, 1=mild, 2=moderate, and 3=severe). The total score is the sum of the 8 individual scores and range 0–24.
Secondary Efficacy Objective: To confirm the efficacy of zilucoplan in subjects with gMG	**Secondary Efficacy Endpoints:** • CFB to Week 12 in the Quantitative Myasthenia Gravis (QMG) Score • CFB to Week 12 in the Myasthenia Gravis Composite (MGC) Score • CFB to Week 12 in the Myasthenia Gravis – Quality of Life revised (MG-QOL15r) Score • Time to first receipt of rescue therapy over the 12-week Treatment Period • Achieving Minimal Symptom Expression (MSE), defined as an MG-ADL of 0 or 1 at Week 12 without rescue therapy • Achieving a ≥ 3-point reduction in MG-ADL Score at Week 12 without rescue therapy • Achieving a ≥5-point reduction in QMG Score without rescue therapy at Week 12
Secondary Safety Objective: To confirm the safety and tolerability of zilucoplan in subjects with gMG	**Secondary Safety Endpoint:** • Incidence of treatment-emergent AEs
Other Safety Objective: To confirm the safety and tolerability of zilucoplan in subjects with gMG	**Other Safety Endpoints:** • Physical Examination • Vital Signs • ECG • Clinical Laboratory Tests • Immunogenicity • C-SSRS
Exploratory Objectives	
To assess the PK of zilucoplan	• Plasma concentrations of zilucoplan and its major metabolites

To assess the PD of zilucoplan	• Sheep red blood cell (sRBC) lysis assay for evaluation of classical complement pathway activation • Complement component 5 (C5) levels
To explore the efficacy on additional efficacy endpoints	• Achievement of Minimal Manifestation Status per MGFA Post-Intervention Status (MGFA-PIS) at Week 12 without rescue therapy • CFB to Week 12 in Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) • CFB to Week 12 in EQ-5D-5L [5-item questionnaire and visual analog scale (VAS)] • CFB to Week 12 in QMG sub-scores: ocular, bulbar, respiratory, limb • CFB to Week 12 in Neuro-QOL Short Form Fatigue Scale • Responder analysis for changes in QMG, MG-ADL, MG-QOL15r, and MG Composite Scores from baseline without rescue therapy
To evaluate the emergence of antidrug antibodies (ADAs) of zilucoplan	• ADAs and neutralizing antibodies at each scheduled assessment
To assess the effect on biomarkers	• Mechanistic biomarkers pertinent to MG pathophysiology [e.g., complement fixation, complement function, complement pathway proteins, autoantibody characterization (titer and immunoglobulin class) and inflammatory markers]

Statistical Considerations

Study Populations: The following study populations are defined:

- Intention-to-Treat (ITT) Population: All randomized subjects
- Per Protocol Population: All subjects in the ITT Population who completed the 12-week Treatment Period and have no major protocol deviations
- Safety Population: All subjects who received at least 1 dose of study drug with subjects to be analyzed based on the actual study treatment received

General Considerations: A disposition of subjects will be provided and will include a breakdown of subjects who were randomized, were treated, discontinued treatment, were lost to follow-up, or withdrew consent.

Continuous variables will be summarized using the number of observations, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

Randomization: Subjects will be randomized in a 1:1 ratio to receive daily SC doses of 0.3 mg/kg zilucoplan or placebo. Randomization will be stratified on the baseline MG-ADL Score (≤9 versus ≥10), baseline QMG Score (≤17 versus ≥18), and geographical region.

Efficacy Analyses:

Primary Efficacy Analysis:

For the primary efficacy endpoint, CFB to Week 12 in MG-ADL Score, treatment group differences will be assessed using a mixed model with repeated measures (MMRM) analysis of covariance (ANCOVA) with treatment, baseline MG-ADL Score, baseline QMG Score, geographical region, treatment×visit (interaction term), and baseline MG-ADL Score×visit (interaction term) as fixed effects and subject as a random effect. The MMRM ANCOVA will include Weeks 1, 2, 4, 8, and 12.

The primary efficacy analysis will be the comparison of the 0.3 mg/kg zilucoplan dose group versus placebo in CFB to Week 12 in MG-ADL Score at a 2-sided 0.05 significance level based on the ITT population.

Secondary Efficacy Analyses:

The continuous secondary efficacy endpoints: Week 12 CFB in QMG, MGC, and MG-QOL15r Survey will be analyzed by an MMRM ANCOVA model similar to the primary endpoint analysis.

The dichotomous secondary efficacy endpoints: received rescue therapy over the 12-week Treatment Period, achieving MSE, defined as an MG-ADL of 0 or 1, at Week 12 without rescue therapy, a ≥3-point reduction in MG-ADL Score at Week 12 without rescue therapy, and a ≥5-point reduction in QMG Score at Week 12 without rescue therapy will be analyzed by a logistic regression with treatment as a factor and baseline MG-ADL Score, baseline QMG Score, and geographical region as covariates.

For each of the secondary endpoints, the analysis will be the Week 12 comparison of the 0.3 mg/kg zilucoplan dose group versus placebo at a 2-sided 0.05 significance level based on the ITT population.

Multiplicity:

The primary efficacy endpoint will be tested at the 2-sided 0.05 significance level. The secondary endpoints will be tested using a fixed-sequential testing procedure in the following order:

- CFB to Week 12 in the QMG Score
- CFB to Week 12 in the MGC
- CFB to Week 12 in the MG-QOL15r Survey
- Received rescue therapy over the 12-week Treatment Period
- Achieving MSE, defined as an MG-ADL of 0 or 1, at Week 12 without rescue therapy
- Achieving a ≥3-point reduction in MG-ADL Score at Week 12 without rescue therapy
- Achieving a ≥5-point reduction in QMG Score at Week 12 without rescue therapy

Each secondary endpoint will be tested at the 2-sided 0.05 significance level. A secondary endpoint analysis will be considered statistically significant if the 2-sided p-value is ≤0.05 for the endpoint analysis and the primary efficacy endpoint analysis and all the secondary endpoint analyses occurring earlier in the fixed-sequence are also statistically significant (i.e., have a 2-sided p-value ≤0.05).

Safety: AEs will be coded using the Medical Dictionary for Regulatory (MedDRA). Incidence rates for treatment-emergent AEs (TEAEs) will be summarized overall, by maximum severity,

and by relationship to study drug for each treatment group. SAEs will also be summarized by treatment group.

Quantitative laboratory endpoints will be summarized by treatment group at each scheduled assessment time point using descriptive statistics.

Descriptive statistics for ECG parameters [i.e., heart rate (HR), PR interval, RR interval, QRS interval, and QT interval] at each assessment time point will be presented by treatment group.

Descriptive statistics for vital signs (HR, body temperature, and blood pressure) will be presented by treatment group.

Clinically significant physical examination abnormalities will be reported as AEs, when appropriate.

Pharmacokinetics: Individual PK results will be presented in listings and summarized using descriptive statistics.

Pharmacodynamics: Pharmacodynamic endpoints will be summarized by treatment group.

Determination of Sample Size: For the primary efficacy endpoint, CFB to Week 12 in MG-ADL Score, assuming a difference in treatment group least squares means of 2.3, a SD of 3.7, and 78 subjects per group, the study has approximately 94% power to detect a difference between an active and placebo treatment group based on a 2-sided alpha of 0.05. This assumes rates of rescue and dropout of up to 10% and 5%, respectively.

2 TIME AND EVENTS TABLE

Table 1: Time and Events Table

Study Procedure	Screening Days -28 to -1	Day 1[u] ('Baseline')	*Week 1* Day 8 (± 2 days)	*Week 2* Day 15 (± 2 days)	*Week 4* Day 29 (± 2 days)	*Week 8* Day 57 (± 7 days)	*Week 12* Day 84[a] End of Study (± 2 days)	Safety Follow-up Visit[b] (40 days ± 7 days)	Rescue Therapy Visit[c] (if applicable)
Informed consent[d]	X								
Review eligibility[d]	X								
Randomization[e]		X							
Medical history and demographics[f]	X								
Height and weight[g]	X						X		
Prior and concomitant medications[h]	X	X	X	X	X	X	X	X	X
Safety									
Physical examination	X	X	X	X	X	X	X	X	X
Vital signs[i]	X	X	X	X	X	X	X	X	X
12-Lead ECG	X						X		
Neisseria meningitidis vaccination[j]	X	SOC	SOC	SOC	SOC	SOC	SOC		
Hematology/Chemistry[k]	X	X	X	X	X	X	X		X
Coagulation[l]	X	X	X	X	X	X	X		X
Urinalysis	X	X	X	X	X	X	X		X
Pregnancy test[m]	X	X	X	X	X	X	X	X	
Adverse events[n]		X	X	X	X	X	X	X	X
Anti-drug antibody[w]	X	X	X		X		X	X	X
C-SSRS[o]		X	X	X	X	X	X	X	X
Hospitalization[v]		X							
Efficacy[p]									
MG-ADL	X	X	X	X	X	X	X		X
QMG Score	X	X	X	X	X	X	X		X
MG-QOL15r	X	X	X	X	X	X	X		X
MGC	X	X	X	X	X	X	X		X
Pharmacokinetic/Pharmacodynamic[q]									
Zilucoplan plasma PK		X	X	X	X	X	X		X
Pharmacodynamic analysis		X	X	X	X	X	X		X
Additional[r]									
Biomarker samples		X	X	X	X	X	X		X
Auto-antibodies		X			X		X		X
IgG subclasses		X			X		X		X
Pharmacogenomic analysis *(optional)* [s]	X								
WPAI:SHP		X	X	X	X	X	X		X
EQ-5D-5L		X	X	X	X	X	X		X
Neuro-QOL		X	X	X	X	X	X		X
MGFA Post-Intervention Status			X	X	X	X	X		X
Study Drug									
Zilucoplan or placebo administration[t]		X	X	X	X	X	X		X

See footnotes on following page.

a. If a subject prematurely discontinues study drug prior to completion of the Week 12 Visit, the subject should return to clinic for an End of Study Visit.

b. Subjects who choose not to enter the Extension Study or who terminate the study prior to Week 12 will be required to return to the clinic 40 ±7 days after their last dose to gather information on ongoing AEs and report any new SAEs since the last study visit.

c. For subjects who require rescue therapy (see Section 10.1.3.1), a Rescue Therapy Visit should be conducted prior to the initiation of rescue therapy. If the Rescue Therapy Visit coincides with a regularly scheduled study visit, then overlapping study procedures do not need to be duplicated.

d. Procedures performed as SOC during the Screening Period may be used to determine eligibility. Informed consent must be obtained prior to performing any study-specific procedures that are not SOC.

e. Eligibility must be confirmed prior to randomization on Day 1.

f. Screening includes disease history with diagnosis of gMG by the MGFA criteria (Class II-IV) and serology for AChR autoantibodies.

g. Height will be measured only at Screening.

h. All prescriptions and over-the-counter medications taken during the 30 days prior to Screening through the last study visit will be documented.

NOTE: A complete history of medications taken for the treatment of gMG will be collected.

i. The vital signs assessment will include measurement of HR, body temperature, and blood pressure in the sitting position.

j. To reduce the risk of meningococcal infection (Neisseria meningitidis), all subjects must be vaccinated against meningococcal infections (with a quadrivalent vaccine and, where available and in accordance with local SOC, serogroup B vaccine) within 3 years prior to, or at the time of, initiating study drug. Subjects who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics (e.g., Penicillin V 500mg twice daily, third generation cephalosporin, etc.) until at least 2 weeks after the initial dose of vaccine(s). The use of fluoroquinolone or macrolide antibiotics is not recommended due to the potential for exacerbation of MG. Booster vaccinations should be administered in accordance with SOC.

k. All laboratory samples should be obtained prior to administration of study drug at applicable visits.

l. Coagulation tests should be performed only in subjects who are receiving anticoagulant therapy.

m. For all female subjects of childbearing potential, a negative serum pregnancy test must be documented at Screening. All other pregnancy tests will be performed via urine.

n. All AEs and SAEs should be monitored until resolution or stabilization. SAEs that occur within 40 days after the last dose of study drug should be reported using the procedures outlined in the protocol.

o. In accordance with the draft FDA Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials Guidance for Industry (FDA 2012) subjects will be asked to complete the C-SSRS at study visits as specified.

p. The MG-ADL, QMG, MG-QOL15r, and MGC should be performed at approximately the same time of day (preferably in the morning) and administered by the same well-trained evaluator (e.g., neurologist, physical therapist, or other study staff) in the same order at each visit throughout the study.

NOTE: If a subject is receiving a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the QMG test.

q. Blood samples for PK and PD analysis will be obtained prior to administration of study drug (within 1 hour of dosing). If Rescue Therapy is administered at a location separate from the clinical site, then there is no need to collect blood samples for PK/PD. For local Rescue Therapy visits, PK and PD samples will be collected at the following time points:

During Rescue Therapy
ONLY at sites where rescue therapy is administered locally
Within 1 hour before administration of each round of rescue therapy
For PLEX only: PK will be measured in the exchanged plasma
Within 1 hour after administration of each round of rescue therapy

r. Blood samples for the additional tests will be obtained prior to administration of study drug (within 1 hour of dosing).

s. The pharmacogenomic sample is noted at Screening, however it may be collected at any study visit.

t. Dosing on study visit days should be held until all assessments (e.g., MG-ADL, QMG, MG-QOL15r, MGC, questionnaires, sample collection, etc.) have been completed. On days when rescue therapy is concurrently administered, study drug dosing should be held until after administration of rescue therapy and PK/PD sampling.

u. In circumstances where COVID-19 disruptions lead to subject being unable to return for Day 1 within 28 days of screening, additional days may be included in the screening period. Contact with the medical monitor is requested in such situations.

v. In Japan, following their Day 1 dose, subjects will be hospitalized overnight for observation to ensure safety of study drug administration. Prior to discharge, subjects will be asked to self-administer their Day 2 dose under supervision to ensure that their technique for self-injection is adequate and appropriate, and to answer any additional questions. These pre-scheduled overnight observational hospitalizations will not be considered SAEs in this study (even if hospital stay is extended, provided that the sole purpose of the extension is improvement of the injection technique). Subjects will continue to self-inject daily SC doses of blinded study drug, according to randomized treatment allocation, for the subsequent 12 weeks.

w. Anti-drug antibody analysis also includes analysis for neutralizing antibodies.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS

AChR	acetylcholine receptor
ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BUN	blood urea nitrogen
C5	complement component 5
CFB	change from baseline
CFB	change from baseline
COVID-19	corona virus disease 2019
CPK	creatine phosphokinase
CRO	clinical research organization
CRP	c-reactive protein
CSR	complete stable remission
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DAP	Data Analysis Plan
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
gMG	generalized myasthenia gravis
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
IEC	Independent Ethics Committee
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
ISR	injection site reaction
IST	immunosuppressant therapy
ITT	Intention-to-Treat
IV	intravenous
IVIG	intravenous immunoglobulin G
LFT	liver function test
LOCF	last observation carried forward
LSLV	last subject last visit
MAC	membrane attack complex
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
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
MGFA-PIS	MGFA Post-Intervention Status
MI	multiple imputation
MMRM	mixed model with repeated measures
MG-QOL15r	Myasthenia Gravis-Quality of Life Revised
MNAR	missing not at random
MSE	minimal symptom expression
MuSK	muscle-specific kinase
NMJ	neuromuscular junction
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PLEX	plasma exchange
PNH	paroxysmal nocturnal hemoglobinuria
PR	pharmacologic remission
PT	prothrombin time
PTT	partial thromboplastin time
RBC	red blood cell
QMG	Quantitative Myasthenia Gravis
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SC	subcutaneous(ly)
SD	standard deviation
SMC	Safety Monitoring Committee
SOC	standard of care
SOP	standard operating procedure
sRBC	sheep red blood cell
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TMF	trial master file
TSH	thyroid stimulating hormone
VAS	visual analog scale
WBC	white blood cell
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

5 INTRODUCTION

Ra Pharmaceuticals, Inc. is developing zilucoplan, a SC self-administered 15-amino acid cyclic peptide that binds to, and inhibits, the cleavage of C5.

Please refer to the Investigator's Brochure (IB) for additional information on the chemistry, toxicology, pharmacology, safety, and benefit/risk analysis of zilucoplan.

5.1 Overview of Generalized Myasthenia Gravis

MG is a rare complement-mediated autoimmune disease characterized by the production of autoantibodies targeting proteins that are critical for the normal transmission of neurotransmitter signals from nerves to muscles. The prevalence of MG in the United States and European Union is estimated at approximately 60,000 and 191,000 cases, respectively. In 15% of patients with MG, symptoms remain confined to the ocular muscles. In approximately 85% of patients MG progresses beyond the ocular muscles to affect multiple muscle groups throughout the body, a condition that is typically referred to as generalized MG (Gilhus 2016).

Patients with gMG present with muscle weakness that characteristically becomes more severe with repeated use and recovers with rest. Symptoms are typically at their mildest in the morning, when overnight inactivity enables replenishment of acetylcholine levels in presynaptic motor nerve terminals and worsen during the course of the day. Muscle weakness can be localized to specific muscles, but often progresses to more diffuse muscle weakness (Chamanza et al. 2010; Gilhus & Verschuuren 2015; Gilhus 2016). gMG symptoms can become life-threatening when muscle weakness involves the diaphragm and intercostal muscles in the chest wall that are responsible for breathing. The most dangerous complication of gMG, known as myasthenic crisis, requires hospitalization, intubation, and mechanical ventilation. Approximately 15% to 20% of patients with gMG will experience a myasthenic crisis within two years of diagnosis (Ramizuddin 2014).

The most common target of autoantibodies in gMG is the nicotinic AChR, located at the neuromuscular junction (NMJ), the point at which a motor neuron transmits chemical signals to a skeletal muscle fiber. Most therapies for gMG focus on either augmenting the AChR signal or nonspecifically suppressing the autoimmune response. First-line therapy for symptomatic gMG is treatment with acetylcholinesterase inhibitors such as pyridostigmine. Although sometimes adequate for control of mild ocular symptoms, pyridostigmine monotherapy is usually insufficient for the treatment of generalized weakness, and dosing is often limited by cholinergic side effects. Therefore, in patients who remain symptomatic despite pyridostigmine therapy, corticosteroids with or without systemic ISTs are used off-label (Riedemann et al. 2002; Sanders et al. 2016). ISTs used frequently in gMG include azathioprine and mycophenolate mofetil. Cyclosporine, methotrexate, tacrolimus, cyclophosphamide, and rituximab are also used occasionally. Well-controlled, randomized, efficacy data for these agents are sparse and no steroidal or IST has been approved for the treatment of gMG, with the exception of Japan where tacrolimus and cyclosporine are approved for gMG (Farmakidis et al. 2018). Moreover, all of these agents are associated with well-documented short-term as well as long-term toxicities. Surgical removal of the thymus may be recommended in patients with non-

thymomatous gMG and moderate to severe symptoms, in an effort to reduce the production of AChR autoantibodies (Wachtman 2012; Wolfe et al. 2016). IVIG and PLEX are invasive therapies, typically used short-term to manage worsening MG symptoms and in patients with myasthenic crisis or life-threatening signs such as respiratory insufficiency or dysphagia (Riedemann et al. 2002; Sanders et al. 2016). However, some patients with severe disease and multiple exacerbations may eventually require chronic IVIG or PLEX.

5.2 Etiology of Generalized Myasthenia Gravis and the Role of Complement

MG is caused by the failure of signal transmission from nerve terminals to muscle fibers. The structures that mediate this neuromuscular signal transmission are NMJs, sometimes also called neuromuscular synapses. NMJs are specialized regions of contact between nerve cells and muscle fibers that consist of the nerve terminal, the synaptic cleft and the post-synaptic membrane with the latter being a highly specialized region of the muscle fiber membrane itself. The postsynaptic membrane of the NMJ is characterized by deep folds and densely packed AChR at the top of the folds.

When an action potential originating from a motor neuron arrives at the nerve terminal of the NMJ, it triggers release of the acetylcholine. Only once a sufficiently high concentration of acetylcholine is reached in the synaptic cleft, are enough AChRs bound and activated to surpass the excitability threshold required for successful propagation of a muscle action potential and ensuing contraction of the muscle fiber.

In patients with MG, the process of signal transmission at the NMJ is inhibited by antibodies directed against proteins of the postsynaptic membrane. Most frequently (in approximately 80% of MG patients) such antibodies are specific for AChR.

There is substantial pre-clinical and clinical evidence supporting a role for the terminal complement cascade in the pathogenesis of gMG (Howard 2017; Kusner et al. 2018). The most common target of autoantibodies in gMG is the AChR. Among AChR autoantibodies, there is a predominance of IgG1 and IgG3 immunoglobulin subclasses which efficiently activate the classical pathway of complement. Therefore, binding of anti-AChR autoantibodies to AChR results in uncontrolled and inappropriate activation of the classical complement cascade at the NMJ. The immune complex formed by the autoantibody-antigen interaction is recognized by the initiating component of the classical complement pathway, the C1 complex. Binding of the C1 complex leads to a series of enzymatic cleavage steps culminating in the cleavage of C5 into C5a and C5b and deposition of membrane attack complex (MAC) onto the post-synaptic membrane of the NMJ with subsequent injury and electrochemical disruption of the neuromuscular endplate. As a result, NMJs in MG patients show complement-mediated tissue damage characterized by a marked disruption of cytoarchitecture and loss of membrane folds (i.e., decrease in overall area of the postsynaptic membrane) and a decrease in AChR density. The net effect of this complement-mediated attack is to make it less likely that a sufficient number of AChRs can be simultaneously activated to trigger a muscle action potential. Deposition of the terminal complement complex in the NMJ is a universal finding in gMG patients (Nakan & Engel 1993; Engel et al. 1977) and in rodent models of disease (Solyts et al. 2009).

5.3 Rationale for Complement Inhibition in Myasthenia Gravis

Terminal complement pathway inhibition is expected to rapidly restore the membrane potential at NMJs by eliminating the large hydrophilic pores that are formed when MAC is deposited in excitable membranes (Jackson et al. 1981). The reduced electrical leakage is expected to rapidly improve the safety factor of NMJs (Conti-Fine et al. 2006) and improve neuromuscular signal transmission. Sustained complement inhibition is expected to lead to restoration of the microanatomy of NMJs including normalization of the cytoarchitecture and restoration of the postsynaptic membrane folds, as has been observed in animal models of experimental autoimmune MG that were depleted of complement C5 with cobra venom (Lennon et al. 1978). From a clinical perspective, the persistent clinical benefit over several weeks after treatment discontinuation seen with the complement C5 inhibitor eculizumab in a Phase 2 crossover study (Howard et al. 2013) is consistent with, although not conclusive of, structural improvement in the NMJ rather than a rapidly reversible symptomatic treatment effect as is seen with acetylcholinesterase inhibitors (e.g., pyridostigmine).

Inhibition of C5 for the treatment of gMG has already been shown to be effective in two clinical studies with the C5-blocking antibody, eculizumab (Howard et al. 2013; Howard 2017), which established that inhibition of the terminal complement cascade by blocking cleavage of C5 is a clinically validated approach for treating gMG. These data are consistent with the beneficial clinical effect observed with zilucoplan in patients with gMG in Phase 2 (see Section 5.5.2.1).

5.4 Mechanism of Action of Zilucoplan

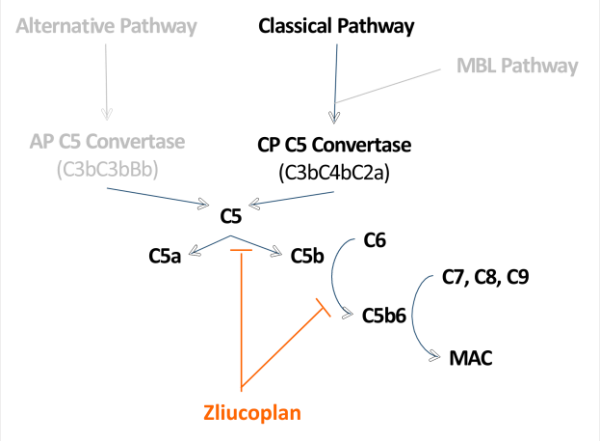
Zilucoplan targets C5, a component of the terminal complement activation pathway. Zilucoplan binds to C5 with high affinity and prevents its cleavage by C5 convertases into the cleavage products C5a and C5b. Inhibition of C5 cleavage prevents the downstream assembly and cytolytic activity of the MAC.

Using surface plasmon resonance and analysis of a high-resolution co-crystal structure, zilucoplan has been shown to bind to a specific site on C5 and to exhibit a strong and rapid association with C5, coupled with a slow dissociation rate. Zilucoplan binds to the portion of C5 which corresponds to C5b. In binding to this region of C5, should any C5b be formed, it will be blocked from binding to C6 by zilucoplan, which further prevents the subsequent assembly of the MAC (C5b-9).

Thus, zilucoplan inhibits MAC formation by a dual mechanism (Figure 1):

1. Prevention of downstream complement activation by allosterically inhibiting C5 cleavage.
2. Direct inhibition of the first step in MAC assembly: C5b-C6-binding.

Figure 1: Mechanism of Action of Zilucoplan in the Complement System



Abbreviations: AP: Alternative Pathway of the Complement Cascade; CP: Classical Pathway of the Complement Cascade; MBL: Mannose binding Lectin pathway of the complement cascade; MAC: membrane attack complex; Complement components are shown using their standard abbreviations.

The binding site of zilucoplan on the C5 protein is distinct from that of the complement C5 inhibitory monoclonal antibody eculizumab. Nishimura and colleagues have described 11 patients in Japan (≈3.2% of the PNH population) who carry mutations in the C5 gene that prevent the binding of eculizumab to C5 and who are resistant to treatment with the antibody (Nishimura et al. 2014). Zilucoplan has been shown to effectively bind to C5 from blood samples from patients with this mutation, and to inhibit complement activation in vitro.

Pharmacologically, zilucoplan has demonstrated dose-dependent inhibition of C5a and C5b formation following activation of classical or alternative complement pathways, as well as inhibition of red blood cell (RBC) lysis in the serum/plasma from various species. Zilucoplan is a potent complement inhibitor in humans and primates and a poor inhibitor in most other laboratory animal species.

5.5 Clinical Trial Experience with Zilucoplan

Zilucoplan is currently under clinical development by Ra Pharmacueticals, Inc. for the treatment of patients with gMG and paroxysmal nocturnal hemoglobinuria (PNH).

5.5.1 Zilucoplan Phase 1 Experience

RA101495-1001 was a randomized, double-blind, placebo-controlled, single-ascending dose (SAD) and multiple-dose (MD) study in healthy volunteers. The study was conducted to evaluate the safety, tolerability, PK, and PD of single-ascending doses of zilucoplan at dose levels of [redacted] administered by SC injection, and multiple-doses of [redacted] administered SC once daily for 7 days. Zilucoplan displayed a dose-proportional and predictable pharmacokinetic profile that was tightly correlated with the intended pharmacodynamic effect, suppression of the terminal complement pathway.

Study RA101495-03.101 was an open-label, single dose Phase 1 pharmacokinetic study of zilucoplan in subjects with severe renal impairment (as defined by a creatinine clearance < 30 ml/min) and healthy controls who received a single dose of 0.3 mg/kg

zilucoplan SC. A total of 16 subjects were enrolled into this study: 8 subjects with severe renal impairment and 8 healthy controls. Based on the data from this study, there is no significant impact of reduced creatinine clearance on the elimination of zilucoplan, and therefore no dose adjustment is needed for the use of zilucoplan in patients with renal impairment.

Study RA101495-01.102 was a double-blind, single- and multiple-dose Phase 1 study evaluating safety and tolerability of zilucoplan in healthy Japanese subjects in comparison to healthy Caucasian subjects. A total of 36 subjects were enrolled in this study: 18 Japanese subjects and 18 Caucasian subjects. There were two single dose cohorts (0.1 mg/kg and 0.3 mg/kg zilucoplan SC) and one multiple dose cohort (0.3 mg/kg zilucoplan SC for 14 days). Dose proportionality and metabolite profile were similar between the Caucasian and Japanese subjects. Based on the data from this study, there is no significant difference between Caucasian and Japanese subjects with respect to the pharmacokinetic, pharmacodynamic and safety profiles of zilucoplan.

A complete overview of results from these Phase 1 studies, including details of PK and PD measurements, is provided in the zilucoplan IB.

5.5.2 Zilucoplan Experience in gMG

5.5.2.1 Completed Phase 2 Study in gMG

The safety and efficacy of zilucoplan was evaluated in gMG subjects in the Phase 2 study RA101495-02.201. A total of 44 subjects were enrolled in Study RA101495-02.201 and randomized to receive placebo, 0.1 mg/kg or 0.3 mg/kg zilucoplan SC daily for 12 weeks. Thereafter, subjects randomized to active zilucoplan continue receiving their assigned dose, while subjects randomized to placebo were re-randomized to receive active zilucoplan at either the 0.1 mg/kg or 0.3 mg/kg dose level.

The following clinical assessments were performed in Study RA101495-02.201 to evaluate efficacy: The QMG scale was the primary outcome measure, and the secondary outcome measures included the MG-ADL, the MGC, and the MG-QOL15r. The study met its primary endpoint, showing a statistically significant and clinically meaningful difference on the QMG between the 0.3 mg/kg zilucoplan and placebo groups, favoring zilucoplan. Additional analyses supported the primary analysis and showed a consistent clinical benefit of zilucoplan over placebo. The results for the primary and secondary analyses are presented in Table 2.

Table 2: Clinical Efficacy Outcomes in Study RA101495-02.201 at Week 12 (ANCOVA)

	QMG	MG-ADL	MG-QOL15r	MGC
0.3 mg/kg zilucoplan CFB LS mean(se)	-6.0 (1.2)	-3.4 (0.9)	-5.9 (1.7)	-7.4 (1.6)
0.1 mg/kg zilucoplan CFB LS mean (se)	-5.5 (1.2)	-3.3 (0.9)	-7.4 (1.7)	-5.3 (1.5)
Placebo LS mean CFB (se)	-3.2 (1.2)	-1.1 (0.9)	-2.1 (1.7)	-3.3 (1.6)
0.3 mg/kg zilucoplan CFB LS mean difference vs. placebo	**-2.8 (1.7)**	**-2.3 (1.3)**	**-3.7 (2.4)**	**-4.1 (2.2)**
p- value*	**0.05**	**0.04**	**0.06**	**0.04**
0.1 mg/kg zilucoplan CFB LS mean difference vs. placebo (se)	-2.3 (1.7)	-2.2 (1.3)	-5.3 (2.4)	-2.0 (2.2)
p- value*	0.09	0.05	0.02	0.19

* p-values are one-sided based on an ANCOVA model with baseline values as a covariate and using LOCF for subjects who received rescue therapy
LS = least squares; CFB = Change from Baseline, se=standard error

Please refer to the zilucoplan IB for additional information regarding the results from studies RA101495-02.201.

5.6 Rationale for the Current Study

Zilucoplan is being developed to treat patients with gMG. Based on the data in Study RA101495-02.201, zilucoplan has the potential to provide several advantages over the currently approved therapy for gMG, eculizumab.

As detailed in Section 5.5.2.1 in Study RA101495-02.201, 0.3 mg/kg zilucoplan showed a statistically significant and clinically meaningful benefit as measured by improvement on the primary endpoint, the QMG, compared to placebo over 12 weeks as well as on the MG-ADL, MG-QOL15r, and MGC.

The clinical benefit of zilucoplan seen in the Phase 2 study compares favorably with published data on unapproved SOC therapies such as corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, cyclophosphamide, rituximab, PLEX, and IVIG for which only small investigator-initiated trials with positive data (cyclosporine, cyclophosphamide, IVIG), circumstantial evidence (azathioprine, PLEX), or negative clinical trial data (mycophenolate mofetil, methotrexate, rituximab) are available to support efficacy (Farmakidis et al. 2018).

Moreover, the placebo-corrected clinical efficacy of 0.3 mg/kg zilucoplan daily SC as measured by the QMG and MG-ADL at Week 12 is similar to the efficacy observed in Phase 3 (Howard et al. 2017) with the approved complement C5 inhibitor eculizumab at Week 26 after treatment initiation. Unlike eculizumab, zilucoplan provides patients with the advantages of SC self-administration at home and is being evaluated in a broad gMG population rather than being restricted to patients who are refractory to all other therapies.

Given the positive results of the Phase 2 gMG study with zilucoplan, confirmation of these findings in a pivotal Phase 3 trial is warranted.

5.6.1 Rationale for Blinding and Placebo Control

The primary objective of Study RA101495-02.301 is the evaluation of efficacy based on functional assessment of weakness measured by the MG-ADL Score, as well as additional clinical endpoints. Such clinical assessments are prone to placebo effects and may be influenced by knowledge of treatment assignment by the clinical evaluator and/or subject. Moreover, the evaluation of potential adverse effects may also be influenced by knowledge of treatment assignment. To enable rigorous efficacy and safety evaluation without the potential bias caused by knowledge of treatment assignment, this study was designed as a double-blind placebo-controlled study.

Subjects entering the study will be allowed to continue their SOC therapy, including escalation of treatment as medically necessary (see Section 10.1.3.1). Therefore, subjects receiving placebo will not be subject to increased risk due to withholding of medically necessary interventions. In addition, the placebo study drug contains substances that are known to be well-tolerated (phosphate buffered saline) and are delivered in a small volume < 1 mL; therefore, placebo administration by daily SC injection over the 12-week study period is expected to be well-tolerated. Consequently, administration of a placebo in Study RA101495-02.301 is not anticipated to cause undue burden or risk for study subjects.

Following the completion of the 12-week Treatment Period, all subjects will have the option to receive zilucoplan in a separate Extension Study, provided they meet the Extension Study inclusion criteria. Therefore, subjects originally randomized to placebo will eventually have the opportunity to receive active study drug.

5.6.2 Dose Selection and Presentation

[redacted]

6 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Estimands/Endpoints
Primary Efficacy Objective: To confirm the efficacy of zilucoplan in subjects with gMG	**Primary Estimand:** **Treatment:** Zilucoplan administered by daily subcutaneous (SC) injection (0.3 mg/kg) vs Placebo **Target Population:** Adults with generalized myasthenia gravis (gMG) with inclusion/exclusion criteria provided in Section 8.1 and Section 8.2 of the protocol. **Endpoint:** Change from Baseline (CFB) in Week 12 in Myasthenia Gravis-Activities of Daily Living (MG-ADL) Score **Intercurrent event handling:** If a subject experiences any of the following intercurrent events, then data at and after the point of the intercurrent event will be treated as missing using a hypothetical strategy: A participant receiving rescue therapy: The study is interested in the treatment effect assuming that the treatment effect is null, and no rescue effect occurs after a subject receives rescue medication. A subject discontinuing the study: For subjects that discontinue due to AEs related to study drug, it is assumed that the treatment effect is null. For subjects that discontinue for other reasons (i.e., unrelated to study drug) it is assumed that the subject had remained on their treatment throughout the study (i.e., a "Hypothetical strategy" assuming subjects did not discontinue the study and remained on treatment). **Population level summary:** The difference between the zilucoplan and placebo treatment groups in the mean CFB in the Week 12 MG-ADL. As described in Section 10.3.1, the MG-ADL is a brief 8-item survey designed to evaluate MG symptom severity.

Objectives	Estimands/Endpoints
	Higher scores are associated with more severe symptoms of MG. Appendix 1: MG-Activities of Daily Living Scale presents the 8 items with corresponding response scale, each scored on a 0-3 point scale (i.e., 0=none, 1=mild, 2=moderate, and 3=severe). The total score is the sum of the 8 individual scores and range 0–24.
Secondary Efficacy Objective: To confirm the efficacy of zilucoplan in subjects with gMG	**Secondary Efficacy Endpoints:** • CFB to Week 12 in the Quantitative Myasthenia Gravis (QMG) Score • CFB to Week 12 in the Myasthenia Gravis Composite (MGC) Score • CFB to Week 12 in the Myasthenia Gravis – Quality of Life revised (MG-QOL15r) Score • Time to first receipt of rescue therapy over the 12-week Treatment Period • Achieving Minimal Symptom Expression (MSE), defined as an MG-ADL of 0 or 1 at Week 12 without rescue therapy • Achieving a ≥ 3-point reduction in MG-ADL Score at Week 12 without rescue therapy • Achieving a ≥5-point reduction in QMG Score without rescue therapy at Week 12
Secondary Safety Objective: To confirm the safety and tolerability of zilucoplan in subjects with gMG	**Secondary Safety Endpoint:** • Incidence of treatment-emergent AEs
Other Safety Objective: To confirm the safety and tolerability of zilucoplan in subjects with gMG	**Other Safety Endpoints:** • Physical Examination • Vital Signs • ECG • Clinical Laboratory Tests • Immunogenicity • C-SSRS
Exploratory Objectives	
To assess the PK of zilucoplan	• Plasma concentrations of zilucoplan and its major metabolites
To assess the PD of zilucoplan	• Sheep red blood cell (sRBC) lysis assay for evaluation of classical complement pathway activation • Complement component 5 (C5) levels

Objectives	Estimands/Endpoints
To explore the efficacy on additional efficacy endpoints	• Achievement of Minimal Manifestation Status per MGFA Post-Intervention Status (MGFA-PIS) at Week 12 without rescue therapy • CFB to Week 12 in Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) • CFB to Week 12 in EQ-5D-5L [5-item questionnaire and visual analog scale (VAS)] • CFB to Week 12 in QMG sub-scores: ocular, bulbar, respiratory, limb • CFB to Week 12 in Neuro-QOL Short Form Fatigue Scale • Responder analysis for changes in QMG, MG-ADL, MG-QOL15r, and MG Composite Scores from baseline without rescue therapy
To evaluate the emergence of antidrug antibodies (ADAs) of zilucoplan	• ADAs and neutralizing antibodies at each scheduled assessment
To assess the effect on biomarkers	• Mechanistic biomarkers pertinent to MG pathophysiology [e.g., complement fixation, complement function, complement pathway proteins, autoantibody characterization (titer and immunoglobulin class) and inflammatory markers]

7 STUDY DESIGN

7.1 Overview of Study Design

Study RA101495-02.301 is a multicenter, randomized, double-blind, placebo-controlled study to confirm the efficacy, safety, and tolerability of zilucoplan in subjects with gMG. The planned enrollment is approximately 156 subjects.

Subjects will be randomized in a 1:1 ratio to receive daily SC doses of 0.3 mg/kg zilucoplan or placebo. Randomization will be stratified based on the baseline MG-ADL Score (≤9 versus ≥10), QMG Score (≤17 versus ≥18), and geographical region.

In order to ensure a gradual initiation of the study in Japan, each Japanese site will be capped to an enrollment rate of no more than one subject per site per week).

The study includes a Screening Period of up to 4 weeks and a 12-week Treatment Period. During the Treatment Period, subjects will return to the clinic at Week 1, Week 2, and monthly visits at Week 4, Week 8, and Week 12 to evaluate efficacy, safety, and tolerability. Additional assessments will include questionnaires, biomarker samples, pharmacokinetics, pharmacodynamics, and optional pharmacogenomics. Safety

assessments will include physical examinations, vital signs, ECG, clinical laboratory tests, AE monitoring, immunogenicity, and C-SSRS.

Randomized subjects will receive 0.3 mg/kg zilucoplan or placebo administered SC at the Day 1 visit. Following in-clinic education and training, all subjects will self-inject daily SC doses of blinded study drug, according to randomized treatment allocation, for the subsequent 12 weeks. Single use pre-filled syringes in injection devices will be provided for use during the study.

In Japan, following their Day 1 dose, subjects will be hospitalized overnight for observation to ensure safety of study drug administration. Prior to discharge, subjects will be asked to self-administer their Day 2 dose under supervision to ensure that their technique for self-injection is adequate and appropriate, and to answer any additional questions. These pre-scheduled overnight observational hospitalizations will not be considered SAEs in this study (even if hospital stay is extended, provided that the sole purpose of the extension is improvement of the injection technique). Subjects will continue to self-inject daily SC doses of blinded study drug, according to randomized treatment allocation, for the subsequent 12 weeks.

Subjects are expected to remain on stable doses of all medications unless medically indicated changes become necessary. All SOC therapy medications for gMG should be kept at the same dose throughout the study, including corticosteroids and IST drugs. If escalation of gMG therapy (i.e., 'rescue therapy') becomes necessary due to major deterioration of a subject's clinical status, or risk of MG crisis as per the investigator's judgment, the subject may receive IVIG or PLEX treatment as 'rescue therapy'. In Germany, the choice of eculizumab as 'rescue therapy' will not be withheld, if the investigator considers this to be the best course of action.

The safety of subjects will be monitored in a blinded manner on an ongoing basis. If an unblinded data review should become necessary to ensure subject safety, a SMC will convene and evaluate study data as appropriate (see Section 11.4.2.1).

To reduce the risk of meningococcal infection (Neisseria meningitidis), all subjects must be vaccinated against meningococcal infections (with a quadrivalent vaccine and, where available and in accordance with local SOC, serogroup B vaccine) within 3 years prior to, or at the time of, initiating study drug. Subjects who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics (e.g., Penicillin V 500mg twice daily, third generation cephalosporin, etc.) until at least 2 weeks after the initial dose of vaccine(s). The use of fluoroquinolone or macrolide antibiotics is not recommended due to the potential for exacerbation of MG. Booster vaccinations should be administered in accordance with SOC.

During the Treatment Period, to mitigate the risk of infection, subjects will be counseled and reminded of the early signs and symptoms of *Neisseria meningitidis* infection. A patient safety card detailing the signs and symptoms of infection, with instructions to seek immediate medical attention if any such symptoms occur, will be provided to each subject.

At the conclusion of the Treatment Period, all subjects will have the option to receive zilucoplan in a separate Extension Study, provided they meet the Extension Study inclusion criteria.

If a subject discontinues study drug treatment prior to the Week 12 visit for any reason, he/she will not be eligible for the Extension Study. For subjects who permanently discontinue study drug, a Safety Follow-up Visit will be performed at 40 days after the last dose of study drug, to collect information on any ongoing AEs or new SAEs since the last study visit.

7.2 Study Periods

The total duration of study participation for all subjects will be up to approximately 16 weeks, including a Screening Period of up to 4 weeks and a 12-week Treatment Period. For subjects who permanently discontinue study drug at any time, a Safety Follow-up Visit will be performed at 40 days after the last dose of study drug, to collect information on any ongoing AEs or new SAEs since the last study visit.

At the conclusion of the Treatment Period of the study, all subjects will have the option to receive zilucoplan in a separate Extension Study, provided they meet the Extension Study inclusion criteria. In the Extension Study, zilucoplan will be provided by the Sponsor until zilucoplan is approved and available in the territory, or the Sponsor terminates development of zilucoplan for gMG. In countries where zilucoplan is not approved or marketed, but in which sponsored clinical studies have been conducted, subjects may continue to receive zilucoplan through a compassionate use pathway.

7.2.1 Screening Period

The Screening visit(s) will occur no more than 28 days prior to the first dose of study drug on Day 1.

Subjects that do not meet the entry criteria for the study may rescreen after 8 weeks. Subjects may be rescreened no more than 2 times.

7.2.1.1 Screening and Enrollment

Procedures performed as SOC during the Screening Period may be used to determine eligibility. Informed consent must be obtained prior to performing any study-specific procedures that are not SOC.

At the Screening visit, subjects will be assigned a unique subject number. The following assessments will be performed during Screening:

- Informed consent
- Completion of the following efficacy assessments:
  - MG-ADL
  - QMG
  - MG-QOL15r
  - MGC

- Review of eligibility criteria
- Review of medical history and demographics, including collection of disease history with diagnosis of gMG according to MGFA criteria (Class II-IV), and confirmation of serology for AChR autoantibodies
- Measurement of height and weight
- Review and documentation of prior and concomitant medications
  NOTE: A complete history of medications taken for the treatment of gMG will be collected. All medications taken during 30 days prior to Screening will be recorded.
- Full physical examination
- Vital signs (HR, body temperature, blood pressure in the sitting position)
- 12-lead ECG
- *Neisseria meningitidis* vaccination: To reduce the risk of meningococcal infection (Neisseria meningitidis), all subjects must be vaccinated against meningococcal infections (with a quadrivalent vaccine and, where available and in accordance with local SOC, serogroup B vaccine) within 3 years prior to, or at the time of, initiating study drug. Subjects who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics (e.g., Penicillin V 500mg twice daily, third generation cephalosporin, etc.) until at least 2 weeks after the initial dose of vaccine(s). The use of fluoroquinolone or macrolide antibiotics is not recommended due to the potential for exacerbation of MG. Booster vaccinations should be administered in accordance with SOC.
- Collection of blood samples for laboratory testing: hematology, chemistry, and coagulation (if applicable)
- Collection of urine sample for urinalysis
- Serum pregnancy testing for females of childbearing potential only
- Collection of blood sample for anti-drug antibody (ADA) testing (including neutralizing antibody testing)
- Collection of blood sample for pharmacogenomic analysis (optional)
  NOTE: If the pharmacogenomic analysis sample is not collected at the Screening visit, it may also be collected on any other visit during the study

7.2.1.2 Randomization and Blinding

Subjects who meet all entry criteria will be randomized in a 1:1 ratio to receive daily SC doses of 0.3 mg/kg zilucoplan or placebo. Subjects will be assigned to study arms in a blinded fashion using a computerized randomization algorithm. Randomization will be stratified based on the baseline MG-ADL Score (≤9 versus ≥10), and QMG Score (≤17 versus ≥18), and geographical region.

This is a double-blind study. Subjects and study staff will remain blinded to treatment assignments until after the data have been cleaned, locked, and unblinded.

To facilitate a comprehensive evaluation of all available double-blind data to prepare regulatory submissions for approval of the MG target indication, two database locks are planned for this study. The first interim lock will occur once the last subject has completed Week 12, or after the last subject has prematurely discontinued prior to

reaching Week 12. A copy of the randomization list will then be sent to the responsible statistician after the first database lock. Only study staff involved in data analysis and review will have access to unblinded results. Investigators and site personnel will not be unblinded to treatment assignments after the first database lock. A final database lock will occur after all data (through to the SFU visit) have been collected. If all the subjects have completed the study at the interim look (the last participants entered the extension study), then the interim database lock will be the final lock.

Instructions for emergency unblinding, if warranted, for safety reasons are provided in Section 11.4.3.

7.2.2 Treatment Period

Subjects will receive treatment with 0.3 mg/kg zilucoplan or placebo, according to randomization, from Day 1 to Week 12 during the Treatment Period.

In Japan, following their Day 1 dose, subjects will be hospitalized overnight for observation to ensure safety of study drug administration. Prior to discharge, subjects will be asked to self-administer their Day 2 dose under supervision to ensure that their technique for self-injection is adequate and appropriate, and to answer any additional questions. These pre-scheduled overnight observational hospitalizations will not be considered SAEs in this study (even if hospital stay is extended, provided that the sole purpose of the extension is improvement of the injection technique). Subjects will continue to self-inject daily SC doses of blinded study drug, according to randomized treatment allocation, for the subsequent 12 weeks.

In consultation with the treating physician, subjects who complete the Week 12 Visit (including those randomized to the placebo arm) will have the option to continue treatment with zilucoplan in a separate Extension Study.

If a subject chooses not to participate in the Extension Study, the subject will complete an End of Study Visit (see Section 7.2.2.1) and receive standard-of-care treatment off-study, as recommended by the treating physician. For subjects who permanently discontinue study drug at any time, a Safety Follow-up Visit will be performed at 40 days after the last dose of study drug, to collect information on any ongoing AEs or new SAEs since the last study visit.

Please refer to Table 1 for details regarding assessments that must be completed at visits during the Treatment Period.

7.2.2.1 Discontinuation of Investigational Medicinal Product

If a subject discontinues study drug after the Treatment Period and does not enter the Extension Study, the Week 12 Visit and the End of Study Visit are one and the same.

If a subject prematurely discontinues study drug at any time prior to Week 12 (see Section 8.3.2), the subject should return to clinic for a stand-alone End of Study Visit.

For subjects who permanently discontinue study drug at any time, a Safety Follow-up Visit will be performed at 40 days after the last dose of study drug, to collect information on any ongoing AEs or new SAEs since the last study visit.

The following procedures will be completed at the End of Study/Week 12 visit:

- Completion of the following efficacy assessments:
  - MG-ADL
  - MG-QOL15r
  - QMG
  - MGC
- Completion of the following additional assessments:
  - MGFA-PIS
  - EQ-5D-5L
  - WPAI:SHP
  - Neuro-QOL
- Measurement of weight
- Review and documentation of concomitant medications
- Full physical examination
- Vital signs (HR, body temperature, blood pressure in the sitting position)
- 12-lead ECG
- Collection of blood samples for laboratory testing: hematology, chemistry, and coagulation (if applicable)
- Collection of urine sample for urinalysis
- Urine pregnancy testing for females of childbearing potential only
- Record AEs
- C-SSRS
- Collection of blood samples for the following assessments:
  - ADA sampling
  - Biomarker analysis
  - PK analysis
  - Auto-antibodies
  - PD analysis
  - IgG Subclasses
- Return of all used and unused study drug syringes to site

7.3 Early Study Termination

The Sponsor may terminate this study early (in its entirety, in part, or at 1 or more study sites) for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at the site for reasonable cause, after providing written notice to the Sponsor in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. The Sponsor may terminate the study for new or emerging safety information that affects the benefit/risk assessment of the product or the clinical trial negatively. If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the investigator and subsequently provide written instructions for

If the Sponsor terminates or suspends the study, all applicable Competent Regulatory Authorities will be informed as per applicable legislation.

The end of study, or study termination, is defined as the time at which the last subject has performed their last visit (LSLV). Following LSLV, all remaining data will be collected in the appropriate case report forms (see Section 14.3.1) and the study results will be summarized in the clinical study report (see Section 14.5).

7.4 Study Conduct During COVID-19

The protocol-mandated visit schedule should be followed to the extent possible, based on the judgment of the investigator. However, during the COVID-19 outbreak or under other exceptional circumstances, remote follow-up will be conducted and the subjects will be contacted by telephone/video contact to assess as many details as possible, according to the protocol scheduling, to verify that the subject is suitable for continuing study treatment. Some procedures may be collected by other remote means if feasible. Study sites should make efforts to inform the sponsor or the CRO in the event that procotol procedures cannot be completed due to COVID-19.

In those situations when the subject cannot return to the study site, the investigators will assess the subject's safety by telephone/video contact. Based on information gathered from the telephone/video contact, investigators will confirm whether the subject could continue the current IMP treatment after the assessment. If the subject is suitable for study treatment continuation, the investigator or designee will assess if the subject agrees to provide name, address, telephone number and email to the appointed courier. The subject will confirm his/her consent by email or verbally in order to receive IMP via courier. If the email option is not possible, the site must obtain consent via phone and document it in the medical record.

If the shipment is agreed, the investigator or designee will clearly explain to the subject everything needed regarding the handling (in case of inconsistencies at delivery) and administration of the study drug and how to return all unused IMP to the study site at the next on-site visit. Only after approval by the study staff for the correct shipment, the subject will start taking the treatment. The whole process and communication with subject will be documented in the subject's medical source record. Changes in the study treatment supply in this situation are described in Section 9.2.1.1.

Ad hoc subject contact may be warranted to understand the current health status of the subjects, to follow up on AEs, and inform them of any protective measures taken by the clinical site as a result of the COVID-19 pandemic (eg, any measures that may limit access to the site or may require additional actions by the subject prior to entry to the site).

If a subject needs to be discontinued and cannot come into the clinic, a visit will be scheduled to perform final safety assessments as soon as possible.

If a subject visits another facility for a medical issue, the investigator should request contact with the physician providing care to provide a detailed explanation of the

subject's condition and his/her participation in the clinical study. Subjects or caregivers shall be reminded to completely collect and keep records of this visit.

Deviations to data collection including inability to perform some assessments, or alternative methods of assessment, such as phone calls, should be recorded in the source documentation and notated as "not done" in the eCRF.

8 SELECTION OF STUDY POPULATION

8.1 Inclusion Criteria

To be eligible for this study, subjects must meet **ALL** of the following inclusion criteria:

1. Male or female ≥18 years and <75 years
2. Able to provide informed consent, including signing and dating the informed consent form (ICF)
3. Diagnosis of gMG [Myasthenia Gravis Foundation of America (MGFA) Class II-IV] at Screening
4. Positive serology for acetylcholine receptor (AChR) binding autoantibodies
5. MG-ADL Score of ≥6 at Screening and Baseline
6. QMG Score of ≥12 at Screening and Baseline (off acetylcholinesterase inhibitor therapy for at least 10 hours)
7. 4 or more of the QMG test items must be scored at ≥2 at Screening and Baseline
8. No change in corticosteroid dose for at least 30 days prior to Baseline or anticipated to occur during the 12-week treatment period
9. No change in immunosuppressive therapy, including dose, for at least 30 days prior to Baseline or anticipated to occur during the 12-week treatment period
10. Vaccination with a quadrivalent meningococcal vaccine and, where available, meningococcal serotype B vaccine at least 14 days prior to the first dose of study drug at the Day 1 visit. A booster vaccination should also be administered as clinically indicated, according to the local SOC, for subjects who have been previously vaccinated against *Neisseria meningitidis*
11. Female subjects of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test within 24 hours prior to the first dose of study drug
12. Sexually active female subjects of childbearing potential (i.e., women who are not postmenopausal or who have not had a hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) and all male subjects (who have not been surgically sterilized by vasectomy) must agree to use effective contraception during the study and during the safety follow-up period of 40 days after the last dose of study drug. Postmenopausal women are, for the purposes of this protocol, defined as women who have not had menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

8.2 Exclusion Criteria

Subjects who meet **ANY** of the following exclusion criteria must be excluded from the study:

1. Thymectomy within 12 months prior to baseline or scheduled to occur during the 12-week study
2. Abnormal thyroid function as determined by local standard
3. Known positive serology for muscle-specific kinase (MuSK)
4. Minimal Manifestation Status of MG based on the clinical judgement of the investigator
5. Fixed weakness ('burnt out' MG) based on the clinical judgement of the investigator
6. History of meningococcal disease
7. Current or recent systemic infection within 2 weeks prior to Baseline or infection requiring intravenous (IV) antibiotics within 4 weeks prior to Baseline
8. Pregnant, planning to become pregnant, or nursing female subjects
9. Recent surgery requiring general anesthesia within 2 weeks prior to Screening or expected to have surgery requiring general anesthesia during the 12-week Treatment Period
10. Prior treatment with a complement inhibitor
11. Treatment with an experimental drug within 30 days or 5 half-lives of the experimental drug (whichever is longer) prior to Baseline
12. Treatment with rituximab within 12 months prior to Baseline or planned to occur during the 12-week study (this exclusion criterion is implemented out of an abundance of caution, in the absence of data showing that complement inhibition in the context of B-cell elimination by rituximab is safe)
13. Treatment with IVIG, SC immunoglobulin, or PLEX 4 weeks prior to Baseline
14. Active malignancy (except curatively resected squamous or basal cell carcinoma of the skin) requiring surgery, chemotherapy, or radiation within the prior 12 months (subjects with a history of malignancy who have undergone curative resection or otherwise not requiring treatment for at least 12 months prior to Screening with no detectable recurrence are allowed)
15. History of or current significant medical disorder, psychiatric disorder, or laboratory abnormality that in the opinion of the investigator would make the subject unsuitable for participation in the study
16. Participation in another concurrent clinical trial involving an experimental therapeutic intervention (participation in observational studies and/or registry studies is permitted)
17. Unable or unwilling to comply with the requirements of the study
18. Hypersensitivity to zilucoplan, any of its excipients, or to placebo

8.3 Removal of Subjects in the Study

8.3.1 Withdrawal of Consent

A subject may withdraw consent to participate in this study at any time without penalty or loss of benefits to which the subject is otherwise entitled to. When a subject wishes to withdraw consent, it is important to distinguish between withdrawing his/her consent for a particular study procedure or visit versus withdrawing his/her consent from the study entirely (i.e., premature discontinuation).

When a subject withdraws consent from the study (or study procedure), the reason(s) for withdrawal will be recorded by the investigator or designee on the relevant page of the electronic case report form (eCRF).

8.3.2 Premature Discontinuation

Every reasonable effort should be made to encourage retention of subjects in the study, maximize compliance with study drug, and facilitate attendance at all scheduled study visits/assessments.

All subjects have the right to refuse further participation in the study at any time and for any reason. A subject's participation must, therefore, be terminated immediately upon his/her request.

The investigator will make every attempt to ascertain the reason(s) for discontinuation and to document this in detail in the source documentation and the appropriate sections of the eCRF. A subject must be withdrawn from the study for any of the following reasons:

- Withdrawal by subject
- Protocol Violation/Noncompliance (defined as refusal or inability to adhere to the study procedures)
- Pregnancy while receiving study drug
- At the request of the Sponsor, regulatory agencies, or IRB/IEC
- Physician decision
- Loss to follow-up
- Death
- Safety/best interest of the subject as determined by the investigator or Sponsor
- Intolerability of study medication

Dosing of a subjects may be interrupted or permanently discontinued if, in the opinion of the investigator and / or Sponsor, it is unsafe for the subject to continue dosing with study medication. Subjects diagnosed with meningococcal disease will be discontinued immediately and permanently.

All subjects who prematurely discontinue study treatment (i.e., prior to Week 12 visit) for any reason will not be eligible to participate in the Extension Study.

8.3.3 Replacement of Subjects

Subjects who prematurely discontinue participation prior to the Day 84 visit may be replaced to obtain an adequate number of subjects that complete the study (see Section 12.3), additional subjects may be enrolled into the study, at the discretion of the Sponsor.

9 INVESTIGATIONAL MEDICINAL PRODUCTS AND TREATMENTS

9.1 Study Treatment Administration

9.1.1 Investigational Medicinal Product and Placebo

[redacted] Table 3.

The BD Ultrasafe Plus device complies with applicable European requirements for a Class I medical device under Rule 1 of Annex IX of the Directive; a Declaration of Conformity per Annex VII of the EU Medical Device Directive (Council Directive 93/42/EEC concerning medical devices) is available for this device.

9.1.2 Dosing Schedule

All eligible subjects will be randomized 1:1 to receive 0.3 mg/kg zilucoplan or placebo administered SC at the Day 1 visit, which will be performed by the subject while observed by the site staff at the study visit. Following in-clinic education and training, all subjects will self-inject daily SC doses of study drug at approximately the same time each day for the remainder of the Treatment Period.

Dosing on study visit days should be held until all assessments (e.g., MG-ADL, QMG, MG-QOL15r, MGC, questionnaires, sample collection, etc.) have been completed. On days when rescue therapy is concurrently administered, study drug dosing should be held until after administration of rescue therapy and PK/PD sampling.

At each study visit, dosing should be supervised to ensure correct injection technique.

9.1.3 Dose Presentation

[redacted]

[redacted]

Subjects who present with a higher body weight (≥150 kg) or a lower body weight (<43 kg) will be accommodated on a case-by-case basis, in consultation with the medical monitor.

9.1.3.1 Missed Doses

In Japan, subjects will be instructed to self-inject SC doses daily at approximately the same time each day. A missed dose will be defined as a dose missed 36 hours from the previous dose.

Study personnel will assess study drug compliance at every visit to record whether any doses were missed. If a subject misses 1 dose (i.e., 1 day) of study drug, he/she should take the next planned dose as scheduled and the investigator should be contacted as soon as possible. If a subject misses 2 or more doses, he/she must notify the investigator immediately and the medical monitor should be consulted.

If a subject misses 10 or more consecutive doses, he/she must notify the investigator immediately, the medical monitor should be consulted, and this will be considered a major protocol deviation.

9.2 Study Treatment Management

9.2.1 Preparation and Dispensing

Prefilled syringes will be dispensed to each subject at each study visit, beginning on Day 1 of the Treatment Period.

Subjects will be provided with training and detailed instructions on the administration of study drug using the single use pre-filled syringes in injection devices.

9.2.1.1 Alternative Study Treatment Supply Due to COVID-19 Pandemic

In circumstances where the subject is not allowed to visit the site, the IMP may be delivered directly to the subject via qualified courier that will act as a liaison between sites and subjects to deliver the drug during the outbreak.

If the shipment of the drug directly to the subject is agreed, the investigator or designee will clearly explain proper handling and administration of the study drug. Subjects will be instructed to return all unused IMP at the next on-site visit.

9.2.2 Study Drug Supply, Storage, and Handling

Zilucoplan and placebo should be stored at 2°C to 8°C at the study site. Once dispensed to subjects, zilucoplan and placebo may be stored at room temperature [20°C to 25°C (68°F to 77°F)] for up to 45 days protected from sources of heat, light, and damage. Storage of zilucoplan and placebo outside of room temperatures should be avoided. Please refer to the study Pharmacy Manual for additional details.

Subjects will be instructed to self-inject SC doses daily at approximately the same time each day. The subject may inject study drug into the abdomen (preferred site), thigh, or upper arm.

All subjects will receive study drug kits, each of which will include 7 single-dose, prefilled syringes (pre-loaded into self-injection devices) containing study drug, alcohol wipes, and adhesive dressings, as well as a syringe disposal container.

9.2.3 Disposal, Return, or Retention of Unused Drug

Subjects will receive secure containers to dispose of used syringes while at home. At each visit, the subject should return the container containing all used syringes to the site. The unused study drug (i.e., unused syringes) and containers should be returned by the subject at each study visit.

All unused study drug syringes and disposal containers containing used syringes must be returned to the site at the last study visit (i.e., End of Study Visit).

9.2.4 Drug Accountability

It is the responsibility of the pharmacist to ensure that a current record of inventory/drug accountability is maintained. Inventory records must be readily available for inspection by the study monitor and are open to inspection by regulatory authorities at any time. For further details, please consult the Pharmacy Manual.

10 STUDY ASSESSMENTS

Please refer to Table 1 for the timing of study assessments. All assessments are to be completed in the same order and approximately at the same time at each visit, starting with efficacy assessments, additional clinical and safety assessments, laboratory evaluations and study drug administration.

10.1 Subject and Baseline Disease Characteristics

10.1.1 Medical History and Demographics

Relevant medical history (including surgical history) will be documented at the Screening visit to assess subject eligibility. The following demographic data will be collected: date of birth, gender, ethnicity, and race.

The Screening assessment will also include disease history with documentation of the diagnosis of gMG by MGFA criteria (Class II-IV), serology for AChR autoantibodies,

and efficacy assessments (i.e., MG-ADL, QMG, MG-QOL15r, and MGC) (see Section 10.3.1 for additional instructions).

10.1.2 Height and Weight

Height (cm) will be collected at the Screening visit only. Weight (kg) will be measured at the study visits indicated in Table 1.

10.1.3 Prior and Concomitant Medications

All prescriptions and over-the-counter medications taken during the 30 days prior to Screening through the last study visit will be documented. NOTE: A complete history of medications taken for the treatment of gMG will be collected.

Concomitant medications include any prescription or over-the-counter medication that is ongoing on Day 1 or that is initiated following the first dose of study drug on Day 1.

Medications, including over the counter therapeutics, natural products, and vitamins, should not be changed during the Screening or Treatment Periods, unless medically necessary. Please refer to Appendix 2: Prohibited Concomitant Medications for a list of prohibited concomitant medications.

Subjects are expected to remain on stable doses of SOC therapy for gMG throughout the study, including corticosteroids and IST drugs. The pyridostigmine dose may be reduced if the investigator identifies intolerable side effects clearly related to pyridostigmine. Prior to altering the dose of pyridostigmine, the investigator should contact the medical monitor. Any pyridostigmine, regardless of the dosing regimen, is to be withheld for a minimum of 10 hours prior to clinical evaluation.

Dose of SOC treatment should not be increased during the study. Instead, rescue therapy as described in Section 10.1.3.1 should be administered.

Medications will be recorded on the subject's source documents and entered on the appropriate eCRF. Any changes to concomitant medications will be recorded in the eCRF. Physical therapy interventions and medical devices are considered concomitant interventions and will be captured in the procedures eCRF.

10.1.3.1 Rescue Therapy

Subjects are expected to remain on stable doses of all medications unless medically indicated changes become necessary. All SOC therapy medications for gMG should be kept at the same dose throughout the study, including corticosteroids and IST drugs. If escalation of gMG therapy (i.e., 'rescue therapy') becomes necessary due to major deterioration of a subject's clinical status, or risk of MG crisis as per the investigator's judgment, the subject may receive IVIG or PLEX treatment as 'rescue therapy'.

In Germany, the choice of eculizumab as 'rescue therapy' will not be withheld, if the investigator considers this to be the best course of action. In subjects with refractory gMG, the use of eculizumab (according to its marketing authorization) may only be

waived if the use of eculizumab is contraindicated, ineffective, or not tolerated. Upon initiation of eculizumab, subjects will discontinue study drug, but will otherwise complete the study as planned. Initiation of eculizumab is considered 'rescue therapy' as per protocol.

If such rescue therapy becomes necessary, the choice of IVIG vs. PLEX vs eculizumab, as well as the frequency and duration of such therapy, will be determined by the investigator. Escalation of doses of corticosteroids or IST drugs (other than initiation of eculizumab) for rescue is not permitted. The Sponsor should be notified immediately upon determination that rescue therapy is necessary in any given subject.

A Rescue Therapy Visit should be performed prior to initiation of rescue therapy (see Table 1 for a list of applicable study procedures).

Unblinding of treatment assignment prior to initiation of rescue therapy will not be allowed, unless critical for reasons of subject safety. The subject will continue their blinded treatment and complete all study-specified assessments while undergoing rescue therapy and through the end of the study if the investigator, in consultation with the medical monitor, considers this course of action in the best interest of the subject. Details on the rescue therapy, as well as reasons for initiation of rescue therapy, will be collected.

10.2 Safety Assessments

10.2.1 Physical Examination

A physical examination will be performed on all subjects at the visits listed in Table 1 and will include the following assessments:

- Abdomen
- Cardiac
- Eyes, Ears, Nose & Throat
- General appearance
- Head & Neck
- Musculoskeletal
- Neurological
- Respiratory
- Skin/Mucosal

Clinically significant physical examination abnormalities will be reported as AEs, when appropriate.

Physical examinations should also include an examination of the injection site(s). If an injection site reaction (ISR) is observed or reported by the subject, it should be recorded as an AE in the eCRF.

10.2.2 Vital Signs

Vital signs (HR, body temperature, and blood pressure) will be measured in the sitting position. If blood samples are scheduled at the same time, vital signs should be measured before the blood draw. Blood pressure may be measured manually or by automated device, preferably using the non-dominant arm. The same measurement technique should be used throughout the study for the same subjects.

10.2.3 Electrocardiogram

12-lead ECGs will be assessed as normal or abnormal by the investigator or delegate; any abnormal findings will be described in the eCRF and the investigator will assess clinical significance. The ECG recording strip will be signed and dated by the investigator and stored in the medical records.

Subjects should be in the supine position for at least 5 minutes prior to and during the ECG measurement. ECGs should be performed prior to blood draws when both assessments are required at the same visit.

10.2.4 Laboratory Safety Assessments

Safety laboratory tests for this study [chemistry, hematology, coagulation (for applicable subjects), and urinalysis] are to be performed by a central laboratory, and only values from the central laboratory are to be entered into the laboratory section of the study database. Values from local laboratories may be used to determine eligibility for study enrollment and as the basis for clinical decisions.

10.2.4.1 Hematology, Chemistry, and Coagulation

Hematology, chemistry, and coagulation analytes that will be assessed during the study are identified in Table 4 and should be performed as specified in Table 1.

All laboratory samples should be collected prior to the administration of study drug at applicable visits.

Coagulation tests should only be performed in subjects receiving anticoagulant therapy.

Table 4: Chemistry, Hematology, and Coagulation Analytes

Chemistry	Hematology
Alanine aminotransferase (ALT)	Hematocrit
Albumin	Hemoglobin
Alkaline phosphatase (ALP)	Mean corpuscular hemoglobin (MCH)
Amylase	Mean corpuscular hemoglobin concentration (MCHC)
Aspartate aminotransferase (AST)	Mean corpuscular volume (MCV)
Bilirubin (total)	Platelet count
Blood urea nitrogen (BUN)	Red blood cell (RBC) count
Calcium	White blood cell (WBC) count and differential (%)
Chloride	Basophils (% and absolute)
Creatinine	Eosinophils (% and absolute)
Gamma-glutamyl transferase (GGT)	Lymphocytes (% and absolute)
Glucose	Monocytes (% and absolute)
Lipase	Neutrophils (% and absolute)
Potassium	**Coagulation**
Sodium	International normalized ratio (INR)/prothrombin time (PT)
Total protein	Partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT)
	Other
	C-reactive protein (CRP)
	Thyroid Stimulating Hormone (TSH) – screening only

10.2.4.2 Urinalysis

A urinalysis will be performed to measure pH, specific gravity, protein (qualitative), glucose (qualitative), ketones (qualitative), bilirubin (qualitative), urobilinogen, occult blood, hemoglobin, and cells. A microscopic examination will be performed, if necessary.

10.2.4.3 Pregnancy Testing and Contraception

A serum pregnancy test for human chorionic gonadotropin will be performed on female subjects of childbearing potential at Screening.

A urine dipstick pregnancy test (human chorionic gonadotropin) will be performed on female subjects of childbearing potential at all other study visits as specified in Table 1.

Negative pregnancy tests must be documented for all female subjects of childbearing potential prior to dosing at applicable study visits.

Sexually active female subjects of childbearing potential (i.e., women who are not postmenopausal or who have not had a hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) and all male subjects (who have not been surgically sterilized by vasectomy) must agree to use effective contraception during the study and during the safety follow-up period of 40 days after the last dose of study drug. Postmenopausal women are, for the purposes of this protocol, defined as women who have not had menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Effective contraception is defined as:

- Hormonal contraception (e.g., oral contraceptive, transdermal contraceptive, contraceptive implant, or injectable hormonal contraceptive) for at least 3 months prior to study drug administration, throughout the study, and for 40 days after the last dose of study drug.
- In countries other than Germany and Norway, double-barrier birth control (e.g., a combination of male condom with either cap, diaphragm, or sponge together with spermicide) starting at the Screening visit, throughout the study, and for at least 40 days after the last dose of study drug.
  NOTE: Use of a male and female condom simultaneously is NOT an acceptable method of double-barrier birth control.
- Intrauterine contraception/device starting at the Screening visit, throughout the study, and for 40 days after the last dose of study drug.
- Total abstinence from sexual intercourse (only acceptable if it is the preferred and usual lifestyle of the subject) for at least 1 complete menstrual cycle prior to the Screening visit, throughout the study, and for 40 days after the last dose of study drug.
- Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy.

NOTE: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception.

10.2.5 Adverse Event Recording

Guidance on the identification, monitoring, and reporting of AEs is provided in Section 11.

10.2.6 Immunogenicity

Blood samples for ADA and neutralizing antibody assessment will be collected as specified in Table 1 in all enrolled subjects. These samples will be banked and used to investigate and characterize any ADA and neutralizing antibody response over time in the general study population.

Detailed instructions regarding sample collection, processing, and shipping will be provided to sites.

10.2.7 Columbia-Suicide Severity Rating Scale

In accordance with the draft FDA *Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials Guidance for Industry* (FDA 2012) subjects will be asked to complete the C-SSRS at study visits as specified in Table 1.

10.2.8 Overnight Observational Hospitalization in Japan

In Japan, following their Day 1 dose, subjects will be hospitalized overnight for observation to ensure safety of study drug administration. Prior to discharge, subjects will be asked to self-administer their Day 2 dose under supervision to ensure that their technique for self-injection is adequate and appropriate, and to answer any additional questions. These pre-scheduled overnight observational hospitalizations will not be considered SAEs in this study (even if hospital stay is extended, provided that the sole purpose of the extension is improvement of the injection technique). Subjects will continue to self-inject daily SC doses of blinded study drug, according to randomized treatment allocation, for the subsequent 12 weeks.

10.3 Efficacy Assessments

10.3.1 Primary Efficacy Assessments

The primary efficacy endpoint is the CFB to Week 12 in MG-ADL Score.

The MG-ADL is a brief 8-item survey designed to evaluate MG symptom severity. Higher scores are associated with more severe symptoms of MG. A 2-point change in MG-ADL Score is considered clinically meaningful (Wolfe et al. 1999; Muppidi et al. 2011).

Clinical Evaluators must be adequately trained prior to conducting any efficacy assessments. The MG-ADL assessment will be performed at Screening to assess subject

eligibility and at each study visit according to Table 1. The MG-ADL assessment must be performed at approximately the same time of day (preferably in the morning) and administered by the same well-trained evaluator (e.g., neurologist, physical therapist, or other study staff experienced in clinical assessments) at each visit throughout the study. If a subject is receiving a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the assessment. Detailed instructions regarding the administration of the MG-ADL test will be provided to sites.

10.3.2 Secondary Efficacy Assessments

Detailed instructions regarding the administration of the secondary efficacy assessments will be provided to sites.

10.3.2.1 Quantitative Myasthenia Gravis

The QMG is a standardized and validated quantitative strength scoring system that was developed specifically for MG. If a subject is receiving a cholinesterase inhibitor, the dose must be withheld for at least 10 hours prior to the assessment. Higher scores are representative of more severe impairment. A change in the QMG Score of 3 points or more may be considered clinically meaningful, in a typical clinical trial population of MG patients (Barohn et al. 1998; Katzberg et al. 2014).

10.3.2.2 MG Composite

The MGC is a 10-item scale that has been used to measure the clinical status of patients with MG, both in the practice setting and in clinical trials, in order to evaluate treatment response. Higher scores in the MGC indicate more severe impairment due to the disease. A 3-point change in this assessment is considered clinically meaningful (Benatar et al. 2012; Sadjadi 2012).

10.3.2.3 MG-QOL15r

The MG-QOL15r is a 15-item survey that was designed to assess quality of life in patients with MG. Higher scores indicate more severe impact of the disease on aspects of the patient's life (Burns et al. 2010; Burns et al. 2016).

10.3.2.4 Minimal Symptom Expression

MSE is designed to assess how many subjects become free or virtually free of MG symptoms as measured by achieving an MG-ADL total score of 0 or 1 on therapy (Vissing et al. 2018).

10.4 Pharmacokinetic Assessments/Pharmacodynamic Assessments

Blood samples for PK/PD assessments will be collected from all subjects and include measurements of:

- Plasma concentration of zilucoplan and its major metabolites
- sRBC lysis assay for evaluation of classical complement pathway activation
- C5 levels

Blood samples for PK and PD analysis will be obtained prior to administration of study drug (within 1 hour of dosing). If Rescue Therapy is administered at a location separate from the clinical site, then there is no need to collect blood samples for PK/PD. For local Rescue Therapy visits, PK and PD samples will be collected at the following time points:

During Rescue Therapy
ONLY at sites where rescue therapy is administered locally
Within 1 hour before administration of each round of rescue therapy
For PLEX only: PK will be measured in the exchanged plasma
Within 1 hour after administration of each round of rescue therapy

All samples will be sent to an accredited laboratory for analysis, and results will remain blinded until after database lock. Detailed instructions regarding PK/PD sample collection, processing, and shipping will be provided to sites.

10.5 Additional Assessments

10.5.1 MGFA Post-Intervention Status

The MGFA-PIS is a physician-determined assessment of a clinical symptoms of MG after initiation of MG specific therapy. Minimal Manifestation is defined as follows:

'The patient has no symptoms of functional limitations from MG but has some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of Complete Stable Remission (CSR) or Pharmacologic Remission (PR) do have weakness that is only detectable by careful examination.'

For the purpose of the current study, Minimal Manifestation will be determined at each timepoint after treatment initiation (rather than after 1 year). Change in status (improved, unchanged, worse, exacerbation, or died of MG) will also be determined.

10.5.2 Work Productivity and Activity Impairment Questionnaire

The WPAI:SHP is a standardized 6-item questionnaire for assessing the amount of both absenteeism (work time missed) and presenteeism (reduced on-the-job effectiveness) due to health problems (Reilly et al. 1993). All subjects will be asked to complete the WPAI:SHP questionnaire in accordance with Table 1.

10.5.3 EQ-5D-5L

The EQ-5D-5L is a standardized instrument for measuring generic health status. The EQ-5D which consists of the EQ-5D descriptive system and the EQ VAS. The EQ-5D descriptive system is comprised of the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression; each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, extreme problems (EuroQOL Group 1990). Subjects answer questions based on symptoms and health status on the day the questionnaire is completed. All subjects will be asked to complete the EQ-5D-5L in accordance with Table 1.

10.5.4 Neuro-QOL Fatigue Short Form

The Neuro-QOL Fatigue Short Form is part of the Neuro-QOL battery of measures that quantify the physical, mental, and social effects experienced by patients with neurological conditions. The Neuro-QOL Scales were developed with National Institutes of Health (NIH) funding to standardize assessments of these evaluations across patients with neurological diseases. Fatigue is a frequent complaint in subjects with MG but has rarely been formally assessed to date. The Neuro-QOL Short Form will be used to explore any potential effect of treatment of zilucoplan on fatigue. All subjects will be asked to complete the Neuro-QOL Fatigue Short Form in accordance with Table 1.

10.5.5 Biomarkers

Blood samples for mechanistic biomarker testing [e.g., complement fixation, complement function, complement pathway proteins, autoantibody characterization (titer and immunoglobulin class), and inflammatory markers] will be obtained prior to administration of study drug (within 1 hour of dosing) in accordance with Table 1.

Detailed instructions regarding sample collection, processing, and shipping will be provided to sites.

The analysis of biomarkers pertaining to the pathophysiology of MG [e.g., complement fixation, complement function, complement pathway proteins, autoantibody characterization (titer and immunoglobulin class), and inflammatory markers] may provide further insight into the clinical efficacy and safety of zilucoplan in subjects with gMG. Complement protein levels and complement activity will be tested to evaluate response to zilucoplan and to understand subject characteristics related to variations in response to drug. Markers of inflammation may be tested to assess correlation with complement function and clinical response to zilucoplan. A list of analytes will be created through review of the literature, ongoing clinical studies, and ongoing exploratory work and may be finalized after completion of the study.

The completion of these investigations may be conditional based on the results of this or other clinical studies, and samples may be selected for analysis on the basis of clinical outcome. The results of the biomarker analysis may be reported separately from the main clinical study report.

10.5.6 Pharmacogenomic Assessments

Participation in the pharmacogenomic assessment is optional, and subjects must provide additional consent for the pharmacogenomic analysis.

For subjects who choose to participate in pharmacogenomic studies, a blood sample will be obtained. All genomic analyses will be performed at an accredited laboratory. Detailed instructions regarding sample collection, processing, and shipping will be provided to sites.

Genomic studies (e.g., deoxyribonucleic acid (DNA) sequencing) including exploration of whether specific genomic features correlate with response or resistance to study drug, may be performed.

The completion of these investigations may be conditional based on the results of this or other clinical studies, and samples may be selected for analysis on the basis of clinical outcome. The results of the genomic investigations may be reported separately from the main clinical study report.

11 SAFETY REPORTING

11.1 Definitions

11.1.1 Adverse Events

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with study treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following are not considered to be AEs despite requiring hospitalization:

- Pre-existing conditions that, in the opinion of the investigator, did not worsen or progress during study participation
- Routinely scheduled procedures or treatment
- Elective procedures that were scheduled prior to study participation (i.e., signing of the ICF)

All AEs should be appropriately recorded according to the instructions in Section 11.4.

11.1.1.1 Occurrence of COVID-19

Occurrence of COVID-19 in subjects should be reported as either “suspected COVID-19” or “confirmed COVID-19” along with all available relevant data, including diagnostic and laboratory data. For subjects where COVID-19 is still suspected despite a negative viral test, please report as “suspected COVID-19” and provide relevant data to support the diagnosis as well as the test results.

11.1.2 Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is life-threatening (note that this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

An SAE may also be any other important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or

require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events include intensive treatment in an emergency room or at home for bronchospasm, hyperkalemia, or convulsions that do not result in a formal hospitalization.

Elective hospitalizations that were scheduled prior to study participation (i.e., signing of the ICF) are not considered to be SAEs and should not be reported.

Also, in Japan, overnight observational hospitalizations to ensure to ensure safety of study drug administration will not be considered SAEs in this study (even if extended, provided that the sole purpose of the extension is improvement of the injection technique).

11.2 Monitoring of Infection

All subjects will be monitored at every study visit for signs and symptoms of *Neisseria meningitidis* infection.

To reduce the risk of meningococcal infection (Neisseria meningitidis), all subjects must be vaccinated against meningococcal infections (with a quadrivalent vaccine and, where available and in accordance with local SOC, serogroup B vaccine) within 3 years prior to, or at the time of, initiating study drug. Subjects who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics (e.g., Penicillin V 500mg twice daily, third generation cephalosporin, etc.) until at least 2 weeks after the initial dose of vaccine(s). The use of fluoroquinolone or macrolide antibiotics is not recommended due to the potential for exacerbation of MG. Booster vaccinations should be administered in accordance with SOC.

To mitigate the risk of infection, subjects will be counseled and reminded of the early signs and symptoms of *Neisseria meningitidis* infection. A patient safety card detailing the signs and symptoms of infection, with instructions to seek immediate medical attention if any such symptoms occur, will be provided to each subject.

11.3 Evaluation and Classifications

11.3.1 Severity

The investigator should determine the severity of the reported AE by using the Common Terminology Criteria for Adverse Events (CTCAE).

For any reported AE not described in the CTCAE, the following guidelines must be considered for severity evaluation:

Adverse Event Severity	
Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s).

Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

11.3.2 Causality

The causal relationship of the AE to study drug will be assessed by both the investigator and the Sponsor. The assessment of causal relationship to study drug should be evidence-based, and not based on the premise that all AEs are causally related to study drug until proven otherwise. Default categorization of 'related' without supportive evidence for a causal relationship to study drug is generally uninformative and does not contribute to understanding of the safety profile of the drug with respect to the intended population.

Examples of evidence that would suggest a causal relationship between the study drug and the AE include the occurrence of an AE that is known to be strongly associated with drug exposure (e.g., ISRs) or an AE that is otherwise uncommon in the study population. Lack of efficacy of study drug, in isolation, leading to unmasking of underlying symptoms and signs of disease, should **NOT** be considered evidence of relatedness.

The causal relationship of each AE is assessed using a binary system, with all AEs classified as either 'related' or 'not related'.

Related: There is 'reasonable possibility' that the study drug caused the AE. The AE follows a reasonable temporal association from the time of study drug administration. There is supportive evidence to suggest a possible causal relationship, irrespective of the degree of certainty, between the observed AE and the study drug. There is no alternative more likely explanation for the AE. Lack of study drug efficacy is not considered, by itself, to be evidence of relatedness.

Not Related: Lack of a reasonable temporal or causal association from the administration of the study drug and the occurrence of the AE. There is evidence of an alternative explanation that is more likely the cause of the AE.

11.4 Recording, Reporting, and Monitoring

11.4.1 Recording and Reporting

The investigator must make every effort to properly evaluate all information relevant to the reported AE in such a way that a diagnosis can be confidently made and reported. For example, it is preferable to report 'pneumonia' as the AE rather than its symptoms (e.g., 'rales' or 'fever') as separate AEs.

When recording and/or reporting AEs or SAEs, the following elements must be included:

- The fulfilled criteria for seriousness as presented in Section 11.1.2
- The severity of the event as defined in Section 11.3.1
- The relationship of the event to study treatment as defined in Section 11.3.2

Actions taken in relation to the AE will be recorded as drug discontinued, drug interrupted, concomitant medication, other action (e.g., diagnostic testing), or no action. Any medication given to treat the AE will be recorded separately in the concomitant medication list of the eCRF.

The outcome of the AE will be recorded as date ended, ongoing, or resulting in death with date of death.

11.4.1.1 Adverse Events

Pre-existing conditions that are detected prior to administration of the first dose of study drug will be recorded as part of the medical history. For all subjects, the AE reporting period will start with the first administration of study drug on Day 1 and will end with the last study visit (i.e., End of Study Visit, Week 12 Visit), after which no new non-serious AEs are to be reported. The subjects will be monitored throughout the study for any AEs, including clinically significant findings at vital signs measurements, spontaneous reports by study subjects, and observations by the study personnel.

When possible, ongoing AEs assessed as related to the study drug will be followed until resolved or stabilized. Sites will call subjects 40 days after their last dose to gather information on ongoing AEs and report any new SAEs since the last study visit (see Section 11.4.1.2 for SAE reporting instructions).

All AEs will be recorded in the eCRF. The investigator will assess and record any AE in detail including the date and time of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date or ongoing), relationship of the AE to study drug, and action(s) taken. All AEs should be reported separately (i.e., 1 record per event). Reporting of AEs is event-based (i.e., an ongoing event will not be closed until resolved or at the end of study). For the AE description, a diagnosis is preferred over symptoms. If no diagnosis can be made, each symptom will be reported as a separate AE. Abbreviations should be avoided. Descriptive words should be used for ongoing conditions as applicable (e.g., worsening of eczema).

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) after the eCRFs have been monitored and signed by the investigator.

11.4.1.2 Serious Adverse Events

Any SAE experienced by the subject from signing the ICF through to 40 days after the last dose of study drug, regardless of severity or causality, must be recorded on the eCRF and SAE forms. Sites will call subjects 40 days after their last dose to gather information on ongoing AEs and report any new SAEs since the last study visit.

The study site must formally notify the Sponsor (or delegate) of the SAE within 24 hours from the time the study site becomes aware of the SAE. A formal notification must be submitted to the Sponsor regardless of the following:

- Severity
- Causality
- Whether or not the subject received study treatment or underwent study related procedures

The IRB/IEC will be notified as required by local regulations. The investigator will be responsible for submitting the required safety information to the appropriate IRB/IEC, including any safety reports received from the Sponsor as well as any SAEs occurring at his/her site.

The Sponsor, or designee, will prepare any required safety reports for Competent Regulatory Authorities and all active investigators. These reports will be provided as addenda to the IB, and the investigator will place these with the IB. All Competent Regulatory Authorities will be informed as per applicable legislation. Reporting of suspected unexpected serious adverse reactions (SUSARs) will be in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

11.4.1.3 Death

Any event with an outcome of death should be appropriately recorded in the eCRF. All identified causes of death, including an assessment of the possible relationship of each to study treatment, must be reported as SAEs as outlined in Section 11.4.1.2. Any autopsy or other postmortem findings (including a coroner's report) should be provided if available.

11.4.1.4 Abnormal Laboratory Values

All central laboratory data generated during the study will be included in standard Statistical Analysis System (SAS) datasets. Throughout this study, subjects will have samples sent to local laboratories and to the central laboratory. Only the values from the central laboratory will be captured in the database and used for the safety analysis. Investigators may report AEs based upon local laboratory values, if clinically relevant. In this event, the actual value and the normal range for the local laboratory should be recorded on the AE eCRF.

11.4.2 Safety Monitoring

All AEs should be monitored by the investigator until resolution or stabilization.

11.4.2.1 Safety Monitoring Committee

The safety of study subjects will be monitored throughout the study on an ongoing basis. Given the double blind, placebo-controlled design of Study RA101495.02.301, this standard safety data review will be performed while blinded to treatment assignment.

If an unblinded data review should become necessary to ensure subject safety, a separate SMC will convene and evaluate study data as appropriate. To ensure the scientific integrity of the study, members of the SMC will not be directly involved in management of the study. The composition, duties, and purview of the SMC will be outlined in a separate SMC Charter.

11.4.2.2 Post-study Events

Any SAE that was continuing at the time of subject discontinuation or study completion should be monitored by the investigator until resolution or stabilization.

SAEs that occur within 40 days after the subject discontinues from or completes the study should be reported using the same procedures outlined in Section 11.4.1.2. These SAEs should be recorded in the eCRF. Subjects will visit the clinic 40 days after their last dose of study drug to gather information on ongoing AEs and report any new SAEs since the last study visit (see Section 11.4.1.2 for SAE reporting instructions). All SAEs will be followed to resolution or stabilization.

11.4.3 Emergency Unblinding

The study drug treatment assignment may be unblinded only in emergency situations when knowledge of the treatment assignment is considered absolutely necessary for medical management of the subject or for clinical decision-making (i.e., when knowledge of the treatment assignment would impact a treatment decision). The investigator will have unrestricted and immediate access to unblind the treatment code in the IXRS. The instructions for unblinding a subject in the IXRS can be found in the IXRS User Guide.

In the event unblinding is necessary, the investigator is strongly encouraged, but not required, to contact the appropriate medical monitor to discuss the situation and the subject's medical status prior to unblinding.

When a subject's treatment assignment is unblinded, a comprehensive source note must be completed by the unblinding investigator that includes the date and time and the reason(s) the subject's treatment code was unblinded. In the event the investigator chooses to discuss the unblinding with the medical monitor, the source note must also include a record of the discussion.

It is mandatory that all personnel who are involved in the unblinding and who have access to the unblinded treatment assignment information maintain the confidentiality of the information by not divulging the treatment assignment.

Following emergency unblinding, the subject's further participation in the study should be discussed with the medical monitor. Unblinded subjects will receive the same safety follow-up as required by non-unblinded study subjects.

11.5 Special Circumstances

11.5.1 Pregnancy

Subjects and their partners should avoid pregnancy throughout the course of the study. Pregnancy in a study subject or partner must be reported to the Sponsor within 24 hours of the study site becoming aware of the pregnancy. Subjects with a positive pregnancy test before study drug dosing must not be dosed.

Information regarding a pregnancy occurrence in a study subject or partner and the outcome of the pregnancy will be collected.

Pregnancy in a study subject or partner is not, in itself, considered an AE. However, the medical outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered an SAE and must be reported to the Sponsor within 24 hours of the site becoming aware of the event. The procedure of elective abortion should not be reported as an AE.

11.5.2 Other

Certain safety events, called 'Special Situations', that occur in association with study drug(s) may require reporting. These Special Situations include, but are not limited to, the following:

- Overdose of the medicinal product, where 'overdose' is defined as a subject receiving ≥ 2 times the intended dose for any given SC injection
- Suspected abuse/misuse of the medicinal product
- Inadvertent or accidental exposure to the medicinal product
- Medication error involving study drug (with or without subject exposure to the Sponsor's medicinal product, e.g., name confusion)

Special situations should be reported on the Special Situations form whether they result in an AE/SAE or not. Special Situations associated with an AE/SAE should also be reported on the corresponding AE/SAE forms.

12 STATISTICAL AND ANALYTICAL PLANS

12.1 Analysis Populations

12.1.1 Intention-to-Treat Population

The Intention-to-Treat (ITT) Population will include all randomized subjects.

12.1.2 Per Protocol Population

The Per Protocol Population will include all subjects in the ITT Population who have completed the 12-week Treatment Period and have no major protocol deviations.

12.1.3 Safety Population

The Safety Population will include all subjects who received at least 1 dose of study drug with subjects to be analyzed based on the actual study treatment received.

12.2 Analysis Methods

12.2.1 General Methods

Details of the statistical analysis methodology will be provided in a statistical analysis plan (SAP), which will be finalized prior to study unblinding.

Continuous variables will be summarized using the number of observations, mean, SD, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

Once all subjects have completed the Day 84 visit, the study database will be locked (interim database lock), unblinded, and the analyses for the study will be performed. If necessary, all TFLs will be produced again after final database lock once all the subjects have completed the study (after SFU visit).

Additional statistical summaries will be provided to explore the impact of COVID-19 on this study. More details will be provided in the SAP.

12.2.2 Subject Disposition

A disposition of subjects will be provided and will include a breakdown of subjects who were randomized, were treated, and discontinued treatment, were lost to follow up, or withdrew consent. Additionally, a summary of subjects included in each of the analysis populations defined in Section 12.1 will be provided.

12.2.3 Demography and Baseline Disease Characteristics

Demographic and baseline disease characteristics will be summarized by treatment group and overall.

12.2.4 Estimands

The estimand corresponding to the primary objective and efficacy endpoint analysis for this study is described below.

A. Population: The population is characterized by the inclusion/exclusion criteria provided in Section 8.1 and Section 8.2.
B. Endpoint: The endpoint is the CFB in the Week 12 MG-ADL Score.
C. Intercurrent Events: The intercurrent events considered in this trial are:
    1. A subject receiving rescue therapy: The study is interested in the treatment effect assuming that the treatment effect is null, and no rescue effect occurs after a subject receives rescue medication.
    2. A subject discontinuing the study: For subjects that discontinue due to AEs related to study drug, it is assumed that the treatment effect is null. For subjects that discontinue for other reasons (i.e., unrelated to study drug) it is assumed that the subject had remained on their treatment throughout the study (i.e., a "Hypothetical-strategy" assuming subjects did not discontinue the study and remained on treatment).
D. Population-level summary: The population summary is the difference between the zilucoplan and placebo treatment groups in the mean CFB in the Week 12 MG-ADL.

12.2.5 Efficacy Analysis

12.2.5.1 Primary Efficacy Endpoint Analysis

For the primary efficacy endpoint, CFB to Week 12 in MG-ADL Score, treatment group differences will be assessed using a MMRM ANCOVA with treatment, baseline MG-ADL Score, baseline QMG Score, geographical region, treatment×visit (interaction term), and baseline MG-ADL Score×visit (interaction term) as fixed effects and subject as a random effect. The MMRM ANCOVA will include Weeks 1, 2, 4, 8, and 12.

The visit, treatment, and geographical region terms in the MMRM model will be treated as categorical, and the baseline MG-ADL and QMG Scores will be treated as continuous.

The primary efficacy analysis will be the comparison of the 0.3 mg/kg zilucoplan dose group versus placebo in CFB to Week 12 in MG-ADL Score at a 2-sided 0.05 significance level based on the ITT population using least squares means.

Sensitivity analyses for the primary efficacy endpoint analysis will be provided in the SAP.

12.2.5.2 Secondary Endpoint Analyses

The continuous secondary efficacy endpoints: Week 12 CFB in QMG, MGC, and MG-QOL15r survey will be analyzed by an MMRM ANCOVA model similar to the primary endpoint analysis. More details will be provided in the SAP.

The dichotomous secondary efficacy endpoints: received rescue therapy over the 12-week Treatment Period, achieving MSE, defined as an MG-ADL of 0 or 1, at Week 12 without rescue therapy, a ≥3-point reduction in MG-ADL Score at Week 12 without rescue therapy, and a ≥5-point reduction in QMG Score at Week 12 without rescue therapy will be analyzed by a logistic regression with treatment as a factor and baseline MG-ADL Score, baseline QMG Score, and geographical region as covariates.

For each of the secondary endpoints, the analysis will be the Week 12 comparison of the 0.3 mg/kg zilucoplan dose group versus placebo at a 2-sided 0.05 significance level based on the ITT population.

12.2.6 Handling of Missing and Censored Data

It is anticipated that:

- Approximately 5% of subjects will be missing MG-ADL data during the 12-week treatment period.
  This is based on the results of the zilucoplan Phase 2 study (RA101495-02.201) where 2.3% of subjects (n=1 out of 44) were missing their Week 12 visit MG-ADL Score, and, from the eculizumab Phase 3 study, where 5.5% (7/126) of subjects did not complete the 26-week treatment period (Howard et al. 2017).
- Approximately 10% of subjects will receive rescue therapy during the 12-week treatment period.
  This is based on the results of the zilucoplan Phase 2 study (see Section 5.5.2.1) where 9.1% of subjects (n=4 out of 44, n=0 subjects on the 0.3 mg/kg dose) received rescue therapy during the 12-week treatment period and, from the eculizumab Phase 3 study where 14.3% (18/126) of subjects received rescue therapy during the 26-week treatment period (6 subjects in the eculizumab group and 12 subjects in the placebo group).
- The amount of non-monotonic missing data will be minimal
  This is based on the results of the zilucoplan Phase 2 study (RA101495-02.201) where, across the scheduled treatment visits during the 12-Week treatment period, there was no non-monotonic missing data for MG-ADL (i.e., the one subject who was missing MG-ADL at the Week 8 visit also had a missing value MG-ADL value at the Week 12 visit).
- The impact of the COVID-19 pandemic on MG-ADL will be minimal because this assessment can be conducted remotely.

Based on these estimates from the zilucoplan Phase 2 study (RA101495-02.201) and the eculizumab Phase 3 study, it is anticipated that the percentage of subjects with missing/censored data during the 12-week treatment period will be approximately 15%. The missing data pattern for the secondary endpoints is anticipated to be similar to the primary endpoint.

For the primary efficacy endpoint analysis, multiple imputation (MI) methods will be used to handle missing data and data after rescue therapy use (i.e., data collected after a subject has used rescue therapy will be censored and treated as missing data for the primary efficacy analysis). The following is a summary of the imputation method.

For the primary efficacy analysis, 100 imputed datasets will be created using monotone linear regression imputation methods which will impute the subjects' missing

post-baseline scores at each of the scheduled visits in the study (i.e., Weeks 1, 2, 4, 8, and 12). If the missing data does not follow a monotonic pattern, a sequential approach to imputing the data to produce a monotone missing data pattern will be applied, (i.e., then the monotone linear regression imputation methods will be applied.).

Imputation will be performed by treatment group, with the underlying imputation distribution based on the reason for the missing data.

Data will be imputed based on the placebo group distribution, irrespective of individual treatment assignment, under the following scenarios:

- Discontinuation from the study due to AE(s) related to study drug
- Received rescue therapy for MG worsening with IVIG or PLEX or eculizumab (i.e., treatment failure)

Missing data will be imputed based on the subject's assigned treatment group distribution under the following scenarios:

- Discontinuation from the study for reasons unrelated to study drug
- Any other reason for missing data

This MI method allows for a pattern-mixture model approach assuming the data are missing not at random (MNAR) under the scenarios where a subject's discontinuation from the study is related to study drug or the subject received rescue medications.

For each of the 100 imputed datasets, the endpoint will be analyzed using the specified MMRM ANCOVA model and the results combined across the imputed datasets to produce an overall p-value (e.g., using SAS Proc MIANALYZE).

Similar MI methods for handling missing data will be applied to the secondary efficacy analyses.

Sensitivity analyses for the primary efficacy endpoint analysis, considering other methods of handling missing and censored data will be provided in the SAP.

Protocol deviations (eg, missing assessments or visits) related to COVID-19 will be documented.

12.2.6.1 Multiplicity

The primary efficacy endpoint will be tested at the 2-sided 0.05 significance level. The secondary endpoints will be tested using a fixed-sequential testing procedure in the following order:

- CFB to Week 12 in the QMG Score
- CFB to Week 12 in the MGC
- CFB to Week 12 in the MG-QOL15r Survey
- Received rescue therapy over the 12-week Treatment Period
- Achieving MSE, defined as an MG-ADL of 0 or 1, at Week 12 without rescue therapy

- Achieving a ≥3-point reduction in MG-ADL Score at Week 12 without rescue therapy
- Achieving a ≥5-point reduction in QMG Score at Week 12 without rescue therapy

Each secondary endpoint will be tested at the 2-sided 0.05 significance level. A secondary endpoint analysis will be considered statistically significant if the 2-sided p-value is ≤ 0.05 for the endpoint analysis and the primary efficacy endpoint analysis and all the secondary endpoint analyses occurring earlier in the fixed-sequence are also statistically significant (i.e., have a 2-sided p-value ≤ 0.05).

This method provides strong control of the family-wise error rate at the two-sided 0.05 level.

12.2.7 Safety Analysis

Safety analyses will be performed on the Safety Population.

12.2.7.1 Adverse Events

AEs will be coded using the MedDRA. Incidence rates for TEAEs will be summarized overall, by maximum severity, and by relationship to study drug for each treatment group. SAEs will also be summarized by treatment group.

12.2.7.2 Infection

AEs related to infection with *Neisseria meningitidis* will be summarized by system organ class and preferred term.

12.2.7.3 Clinical Laboratory Evaluation

Quantitative laboratory endpoints will be summarized by treatment group at each scheduled assessment time point using descriptive statistics.

12.2.7.4 Electrocardiograms

Descriptive statistics for ECG parameters (i.e., HR, PR interval, RR interval, QRS interval, and QT intervals) at each assessment time point will be presented by treatment group.

12.2.7.5 Vital Signs

Descriptive statistics for vital signs (i.e., HR, body temperature, and blood pressure) will be presented by treatment group.

12.2.7.6 Physical Examination

Clinically significant physical examination abnormalities will be included and summarized as AEs, when appropriate.

12.2.8 Clinical Pharmacology Analysis

12.2.8.1 Pharmacokinetic and Pharmacodynamic Analyses

Pharmacokinetic and pharmacodynamic endpoints will be summarized using descriptive statistics by treatment and nominal time point.

Pharmacokinetic and pharmacodynamic assessments in subjects undergoing rescue therapy will be analyzed separately, as appropriate.

Plasma concentration data of zilucoplan may be subjected to population PK analysis to derive population estimates of PK parameters and test the effect of various covariates such as anti-drug antibodies, age, weight, gender. Details of the analysis will be described in a separate Data Analysis Plan (DAP). This analysis may be performed by combining the data from the current study with data from other zilucoplan studies if deemed appropriate. The results of the population PK analysis will not be reported in the clinical study report (CSR) but in a separate modelling report

Population PD or population PK/PD analyses may be conducted for the PD variables of interest. Details of such PD or PK/PD analyses will be described in a separate DAP. The results of the analyses will not be reported in the CSR but in a separate report.

12.2.9 Interim Analysis

After the last subject has completed the Week 12 visit, or after the last subject has prematurely discontinued prior to reaching Week 12, an unblinded interim analysis will be performed and a corresponding interim CSR may be written. The purpose of this interim analysis is to perform a comprehensive evaluation of all available double-blind data to prepare regulatory submissions for approval of the MG target indication. If necessary, a final analysis and updated final CSR will be prepared once all data (through to the SFU visit) have been collected. If all the subjects have completed the study at the interim database lock (the last participants entered the extension study), then the interim database lock will be the final lock.

12.3 Sample Size Determination

For the primary efficacy endpoint, CFB to Week 12 in MG-ADL Score, assuming a difference in treatment group least squares means of 2.3, a SD of 3.7, and 78 subjects per group (156 subjects in total), the study has approximately 94% power to detect a difference between an active and placebo treatment group based on a 2-sided alpha of 0.05. This assumes rates of rescue and dropout of up to 10% and 5%, respectively.

13 ETHICAL CONSIDERATIONS

This study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice (GCP) and applicable regulatory requirement(s).

13.1 Institutional Review Board/Independent Ethics Committee Communications

Prior to study initiation, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the study protocol, written ICF, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects. A current copy of the IB must be provided to the IRB/IEC as part of the written application. During the study, the investigator/institution should provide to the IRB/IEC all documents subject for review.

13.1.1 Progress Reports

The investigator should submit written summaries of the study status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

13.1.2 Final Investigator Report

Upon completion of the study, the investigator/institution should provide a summary of the study's outcome to the IRB/IEC and the regulatory authorities with any required reports.

13.2 Informed Consent of Study Subjects

In obtaining and documenting informed consent, the investigator must comply with the applicable regulatory requirement(s) and adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

The written ICF and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written ICF and written information should receive the IRB/IEC's approval/favorable opinion in advance of use. The subject or the subject's legally acceptable representative will be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

The investigator will fully inform the subject or the subject's legally acceptable representative of all pertinent aspects of the study, including the written information and the approval/favorable opinion by the IRB/IEC. Before informed consent may be obtained, the investigator should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

Prior to a subject's participation in the study, the written ICF must be signed and personally dated by the subject or by the subject's legally acceptable representative and by the person who conducted the informed consent discussion. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness will be present during the entire informed consent discussion.

In Japan, age of adulthood is defined as 20 years or older. If a subject is 18-19 years old, the subject and his/her legal representative must both sign the ICF.

Prior to participation in the study, the subject or the subject's legally acceptable representative will receive a copy of the signed and dated written ICF and any other written information provided to the subjects. During a subject's participation in the study, the subject or the subject's legally acceptable representative will receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

Subjects will provide additional consent to participate in optional pharmacogenomic testing.

13.3 Protocol Compliance

The investigator/institution will conduct the study in compliance with the protocol agreed to by the Sponsor and regulatory authorities (if required) and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the Sponsor should sign the protocol, or an alternative contract, to confirm agreement.

The investigator should not implement any deviation from, or changes to, the protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate immediate hazard(s) to study subjects or when the change involves only logistical or administrative aspects of the study (e.g., change in monitor, change of telephone number). When an important deviation from the protocol is deemed necessary for an individual subject, the investigator must contact the medical monitor for the study.

Such contact must be made as soon as possible to permit a review by the Sponsor to determine the impact of the deviation on the subject's participation and/or the assessment of safety or efficacy in the study. Any significant protocol deviations affecting subject eligibility and/or safety must be reviewed and/or approved by the IRB/IEC and regulatory authorities, as applicable, prior to implementation.

The investigator should document and explain any deviation from the approved protocol.

13.4 Protection of Confidentiality

Prior to study participation, the investigator shall inform the subject or the subject's legally acceptable representative that the monitor(s), auditor(s), IRB/IEC, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written ICF, the subject or the subject's legally acceptable representative is authorizing such access.

In addition, prior to study participation, the subject must be informed that the records identifying the subject will be kept confidential and, to the extent permitted by the

applicable laws and/or regulations, will not be made publicly available; if the results of the study are published, the subject's identity will remain confidential.

13.5 Disclosure of Study Results

The Sponsor will post the results of the study in a publicly accessible database in accordance with the applicable laws and regulations.

14 REGULATORY AND ADMINISTRATIVE CONSIDERATIONS

14.1 Quality Assurance

Quality assurance and quality control systems shall be implemented and maintained with written standard operating procedures (SOPs) to ensure that the study is conducted, data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s). Quality control shall be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

An agreement must be secured from all involved parties to ensure direct access to all study related sites, source documents, and reports for the purpose of monitoring and auditing by the Sponsor, and of inspection by regulatory authorities.

14.1.1 Monitoring

On-site monitoring visits will be conducted before, at regular intervals during, and after the study, as appropriate, by Sponsor-approved monitors. At a minimum, the accuracy and completeness of the eCRF entries, source documents, and other study-related records will be checked against one another during these visits. After each monitoring visit, a report of any significant findings/facts, deviations, and deficiencies will be communicated to the investigator. The actions taken to address the findings and secure compliance should be documented.

14.1.2 Audit

An audit may be performed independently of, and separately from, routine monitoring to evaluate clinical study conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

14.2 Clinical Research Organizations

A Clinical Research Organization (CRO) will be utilized to assist in the conduct of this study. Accredited central laboratories will be used for the analysis of safety laboratory samples and for the bioanalytical testing of PK samples.

14.3 Data Management

14.3.1 Case Report Forms

eCRFs must be completed for each subject enrolled in this study. These forms will be used to transmit information collected during the study to the Sponsor and regulatory authorities, as applicable. The eCRF data for this study is being collected with an eCRF. The documentation related to the validation of the eCRFs will be maintained in the Trial Master File (TMF). The TMF will be maintained by the CRO and the Sponsor.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study (see Section 14.3.2). All eCRF data required by this protocol will be recorded by investigative site personnel.

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which will be part of the electronic data capture system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness and acceptability by Sponsor personnel (or their representatives). The Sponsor (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Access to the electronic data capture system will be password-protected and will be removed from the study site at the end of the site's participation in the study. Data from the eCRF will be archived on appropriate data media and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

14.3.2 Source Documents

Source documents are defined as original documents, data, and records. These may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, ECGs, X-rays, ultrasounds, angiograms, venograms, computed tomography scans, and/or magnetic resonance imaging scans. Data collected during this study must be recorded on the appropriate source documents.

In some instances, the initial entry of data will be made by subjects and site personnel onto a hand-held device at the site and will be considered the source, e.g. eSource. This system is fully compliant with 21 Code of Federal Regulations (CFR) part 11 regulations.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data documents.

14.4 Premature Termination or Suspension of the Study

If the Sponsor terminates or suspends the study, the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension. If the IRB/IEC terminates or suspends its approval/favorable opinion of the study, the investigator/institution should promptly notify the Sponsor and provide the Sponsor with a detailed written explanation of the termination or suspension.

14.5 Clinical Study Report

Whether the study is completed or prematurely terminated, the clinical study report will be prepared and provided to the regulatory agencies as required by the applicable regulatory requirement(s).

14.6 Publication Policy

The publication policy is outlined in the Clinical Trial Agreement. The data generated in this clinical trial are the exclusive property of Ra Pharmaceuticals, Inc. and are confidential. Written approval from Ra Pharmaceuticals, Inc is required prior to disclosing any information related to this clinical trial.

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16 APPENDICES

Appendix 1: MG-Activities of Daily Living Scale

Appendix 2: Prohibited Concomitant Medications

Please consider the following list of prohibited medications for patients with MG (PNDS, 2015). Should you have any questions, please contact the Medical Monitor.

Absolute contraindications:

- Aminoglycosides, colomycin, polymyxin, telithromycine, injectable cyclin, macrolides, fluoroquinolones
- Quinines, quinidine, hydroxychloroquine, procainamide
- Beta-blockers (even in eye drops)
- Diphenylhydantoin, trimethadione
- Dantrolene
- D-penicillamine
- Magnesium

Relative contraindications:

- Curariform agents: use of non-depolarizing molecules of rapid degradation, such as atracurium, is possible, requires precise monitoring
- Benzodiazepines
- Neuroleptics (phenothiazine)
- Carbamazepine
- Lithium

SPONSOR SIGNATURE PAGE

Protocol Number: RA101495-02.301 (RAISE)

Protocol Title: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Confirm the Safety, Tolerability, and Efficacy of Zilucoplan in Subjects with Generalized Myasthenia Gravis

Protocol Version: Version 2.0/18.Dec.2020

Approval Signatures

Name: mg0010-protocol-amend-v2.0

Version: 1.0

Document Number: CLIN-000165911

Title: MG0010 RAISE Protocol Amendment v2.0

Approved Date: 18 Dec 2020

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 18-Dec-2020 08:27:09 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 18-Dec-2020 08:31:28 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 18-Dec-2020 11:44:00 GMT+0000