RA PHARMACEUTICALS, INC.

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Preliminary Efficacy of RA101495 in Subjects with Generalized Myasthenia Gravis

Protocol Number:	RA101495-02.201
Protocol Version/Date:	Version 3.0/10-Apr-2019
Indication Studied:	Generalized Myasthenia Gravis
Developmental Phase of Study:	2
Sponsor Address:	Ra Pharmaceuticals, Inc. 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

SPONSOR SIGNATURE PAGE

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[redacted] [redacted]

Signature of Ra Pharmaceuticals, Inc. Medical Officer Date

[redacted], MD FACC
Chief Medical Officer

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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.

_____ _____

Signature of Investigator Date

_____

Name of Investigator (Typed or Printed)

1 SYNOPSIS

Protocol Title	A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Preliminary Efficacy of RA101495 in Subjects with Generalized Myasthenia Gravis
Protocol Number	RA101495-02.201
Phase of Clinical Development	Phase 2
Investigational Medicinal Product	RA101495 administered by daily subcutaneous (SC) injection
Study Population	Adults with generalized myasthenia gravis (gMG)
Investigative Sites	Approximately 30 centers are planned worldwide
Planned Number of Subjects	Approximately 36 subjects (12 per treatment arm)

Study Objectives

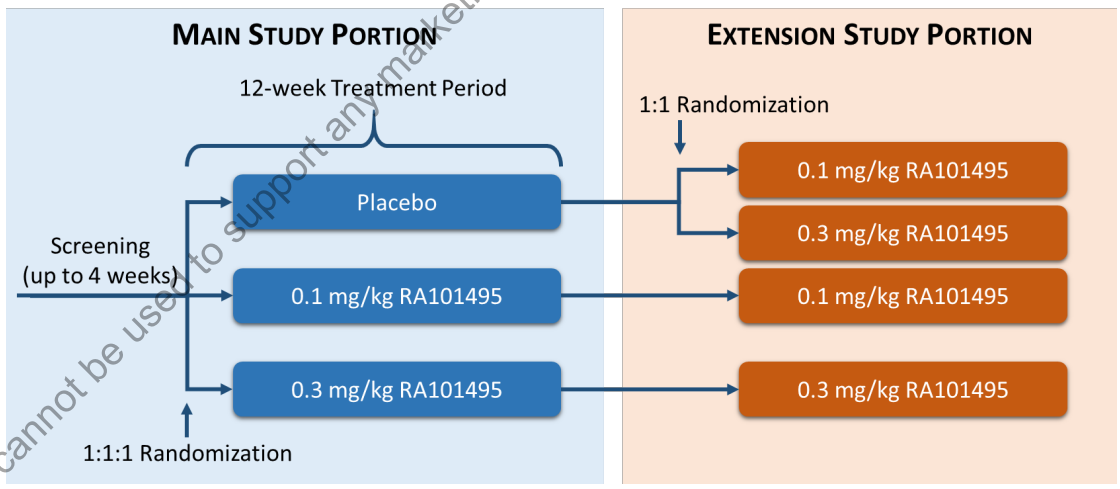
- To assess the safety and tolerability of RA101495 in subjects with gMG
- To assess preliminary efficacy of RA101495 in subjects with gMG

Study Design

Study RA101495-02.201 is a multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and preliminary efficacy of RA101495 in subjects with gMG. The planned enrollment is approximately 36 subjects.

Subjects will be randomized in a 1:1:1 ratio to receive daily SC doses of 0.1 mg/kg RA101495, 0.3 mg/kg RA101495, or matching placebo. Randomization will be stratified based on the screening Quantitative Myasthenia Gravis (QMG) Score (≤ 17 versus ≥ 18).

Design of RA101495-02.201 Study



The Main Portion of 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 weekly for the first 2 visits (Day 8 and Day 15) after the Day 1 visit, followed by visits at Week 4 (Day 29), Week 8 (Day 57), and Week 12 (Day 84) to evaluate safety, tolerability, and preliminary efficacy. Additional assessments will include quality of life (QOL) questionnaires, biomarker samples, pharmacokinetics, pharmacodynamics, and optional pharmacogenomics. Safety assessments will include physical examinations, vital signs, electrocardiogram (ECG), clinical laboratory tests, adverse events (AEs), and immunogenicity.

Randomized subjects will receive 0.1 mg/kg RA101495, 0.3 mg/kg RA101495, 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. An injection device will be provided for use during the study.

Subjects are expected to remain on stable doses of standard of care (SOC) therapy for gMG throughout the study, including pyridostigmine, corticosteroids, or immunosuppressive drugs. If, in the opinion of the investigator, escalation of gMG therapy (i.e., 'rescue therapy') becomes necessary due to deterioration of a subject's clinical status, the subject may receive immunoglobulin or plasma exchange treatment.

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.

The risk of *Neisseria meningitidis* infection will be closely monitored during the study. All subjects who have not been previously vaccinated against *Neisseria meningitidis* prior to study entry must be vaccinated 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.

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, will be provided to each subject.

At the conclusion of the Treatment Period in the Main Portion of the study, all subjects will have the option to receive RA101495 in the Extension Portion of the study provided they meet the Extension Portion selection criteria. Subjects assigned to a RA101495 treatment arm during the Main Portion of the study will continue to receive the same dose of study drug during the Extension Portion. Subjects assigned to the placebo arm during the Main Portion of the study will be randomized in a 1:1 ratio to receive daily SC doses of 0.1 mg/kg RA101495 or 0.3 mg/kg RA101495. Visits during the first 12 weeks of the Extension Portion will be identical to Main Portion of the study for all subjects to ensure appropriate monitoring of subjects transitioning from placebo to active treatment and to maintain blinding of treatment assignment. The study will remain double-blinded during the Extension Portion until after the data from the Main Portion of the study have been cleaned, locked, and unblinded.

Following implementation of the present Amendment (v.3.0), and upon appropriate reconsent, all subjects ongoing in the Extension Portion will receive the 0.3 mg/kg dose that has been selected for the pivotal Phase 3 study (See Section 5.5.3 for details).

If a subject discontinues study drug treatment prior to the Day 84 visit for any reason, he/she will not be eligible for the Extension Portion. Subjects who undergo rescue treatment and continue receiving study drug are eligible for participation in the Extension Portion. For subjects who do not participate in the Extension Portion, a safety follow-up telephone call 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 (SAEs) since the last study visit.

Duration of Study Participation

During the Main Portion of the study, the total duration of study participation for all subjects will include a Screening Period of up to 4 weeks and a 12-week Treatment Period for a total of up to approximately 16 weeks.

During the Extension Portion of the study, RA101495 will continue to be provided by the Sponsor until RA101495 is approved and available in the territory, or the Sponsor terminates development of RA101495 for gMG. In countries where RA101495 is not approved or marketed, but in which sponsored clinical studies have been conducted, subjects may continue to receive RA101495 through a compassionate use pathway.

Inclusion/Exclusion Criteria

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

1. Male or female ≥ 18 years and < 85 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-IVa] at Screening.
4. Positive serology for acetylcholine receptor (AChR) autoantibodies.
5. QMG score ≥ 12 at Screening and baseline (off acetylcholinesterase inhibitor therapy for at least 10 hours) with ≥ 4 test items scored at ≥ 2.
6. No change in corticosteroid dose for at least 30 days prior to baseline or anticipated to occur during the 12-week Treatment Period.
7. 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.
8. 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.
9. 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.

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

1. Thymectomy within 6 months prior to baseline or scheduled to occur during the 12-week Treatment Period.
2. Abnormal thyroid function as determined by local standard.
3. Known positive serology for muscle-specific kinase (MuSK) or lipoprotein receptor-related peptide 4 (LRP4).
4. Minimal Manifestation Status of myasthenia gravis based on the clinical judgement of the investigator.
5. Calculated glomerular filtration rate of < 60 mL/min/1.73 m^2 based on the Modification of Diet in Renal Disease (MDRD) equation at Screening.

   $$\text{GFR}\left(\frac{\text{mL}/\text{min}}{1.73\ \text{m}^2}\right) = 175 \times (S_{cr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742\ if\ female) \times (1.212\ if\ African\ American)$$
6. Elevated liver function tests defined as total bilirubin or transaminases [aspartate aminotransferase (AST)/alanine aminotransferase (ALT)] > 2 times the upper limit of normal (× ULN).

7. History of meningococcal disease.
8. Current or recent systemic infection within 2 weeks prior to baseline or infection requiring intravenous (IV) antibiotics within 4 weeks prior to baseline.
9. Pregnant, planning to become pregnant, or nursing female subjects.
10. Recent surgery requiring general anesthesia within 2 weeks prior to Screening or surgery expected to occur during Screening or the 12-week Treatment Period.
11. Treatment with an experimental drug or another complement inhibitor within 30 days or 5 half-lives of the experimental drug (whichever is longer) prior to baseline.
12. Treatment with rituximab within 6 months prior to baseline.
13. Ongoing treatment with IVIG or plasma exchange or treatment within 4 weeks prior to baseline.
14. Active neoplasm (other than benign thymoma) 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. Fixed weakness ['burnt out' myasthenia gravis (MG)] based on the clinical judgement of the investigator.
16. History of any significant medical or psychiatric disorder that in the opinion of the investigator would make the subject unsuitable for participation in the study.
17. Participation in another concurrent clinical trial involving an experimental therapeutic intervention (participation in observational studies and/or registry studies is permitted).
18. Unable or unwilling to comply with the requirements of the study.

Endpoints and Assessments for the Main Portion

Safety and Tolerability:

Safety assessments will include reporting of AEs and SAEs, clinical laboratory tests, ECGs, vital signs, and physical examination.

Primary Efficacy Endpoint:

- Change from baseline to Week 12 (Day 84) in QMG score.

Secondary Efficacy Endpoints:

- Change from baseline to Week 12 in the Myasthenia Gravis-Activities of Daily Living (MG-ADL) scale
- Change from baseline to Week 12 in the MG-QOL15r survey
- Change from baseline to Week 12 in the MG Composite
- Subjects with ≥ 3-point reduction in QMG score at Week 12
- Subjects requiring rescue therapy over the 12-week Treatment Period

Pharmacokinetic (PK):

- Plasma concentrations of RA101495 and its major metabolites
- Maximum plasma concentration (C_{max}) on Day 1
- Time corresponding to C_{max} (t_{max}) on Day 1

Pharmacodynamic (PD):

- Sheep red blood cell (sRBC) lysis assay for evaluation of classical complement pathway activation
- Complement component 5 (C5) levels

Exploratory:

- Mechanistic biomarkers pertinent to MG pathophysiology [e.g., complement fixation, complement function, complement pathway proteins, autoantibody characterization (titer and immunoglobulin class) and inflammatory markers]
- Pharmacogenomic analyses (optional)

Endpoints and Assessments for Extension Portion

Endpoints in the Extension Portion will be similar to those in the Main Portion and detailed in the statistical analysis plan (SAP).

Statistical Considerations

Study Populations: The following study populations are defined:

- *Intention-to-Treat (ITT) Population:* All subjects randomized
- *Modified ITT (mITT) Population:* All subjects in the ITT Population who have received at least 1 dose of study drug
- *Per Protocol Population*: All subjects in the mITT Population who have completed the 12-week Treatment Period and have no major protocol deviations
- *Safety Population*: All subjects who have received at least 1 dose of study drug (i.e., mITT Population), with subjects to be analyzed based on the actual study treatment received
- *PK Population*: All subjects in the mITT Population who have at least 1 evaluable PK assessment. All PK analyses will be performed using this population.
- *PD Population*: All subjects in the mITT Population who have at least 1 evaluable PD assessment. All PD analyses will be performed using this population.

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

Continuous variables will be summarized using the number of observations, number of observations above the limit of quantification (if applicable), mean, standard deviation (SD), median, and range. Categorical variables will be summarized using frequency counts and percentages.

Stratification of Randomization: Subjects will be randomized in a 1:1:1 ratio to receive daily SC doses of 0.1 mg/kg RA101495, 0.3 mg/kg RA101495, or matching placebo.

Randomization will be stratified based on the screening QMG Score (≤ 17 versus ≥ 18).

Safety: AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; Version 18.0 or higher). Incidence rates for treatment-emergent AEs 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, QT interval, QT interval corrected by Bazett's formula (QTcB), and QT interval corrected by Fridericia's formula (QTcF)] 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.

The complete set of physical examination findings will be provided in listings. Clinically significant physical examination abnormalities will be reported as AEs, when appropriate.

Efficacy: For the primary efficacy endpoint, change from baseline to Week 12 (Day 84) in QMG score, treatment group differences will be assessed using an Analysis of Covariance (ANCOVA) model, with treatment as a factor and baseline QMG score as a covariate. The primary efficacy analysis will be the comparison of the 0.3 mg/kg RA101495 dose group versus placebo based on the ANCOVA model at a 1-sided 0.10 significance level.

The secondary efficacy endpoints, Week 12 change from baseline in MG-ADL, MG-QOL15r, and MG Composite, will be analyzed by an ANCOVA model similar to the primary endpoint analysis, with treatment as a factor and the corresponding baseline value as a covariate. Each of the active doses will be compared to the placebo group based on the ANCOVA model at the 1-sided 0.10 level.

For the 'Subjects with ≥ 3-point reduction in QMG score at Week 12' and 'Subjects requiring rescue therapy over the 12-week Treatment Period' secondary efficacy endpoints, the rate of subjects meeting the endpoint for each of the active treatment groups will be compared to the placebo group using a Fisher's exact test at the 1-sided 0.10 level.

Pharmacokinetics: Drug exposure will be evaluated using PK parameters derived from non-compartmental methods. All calculations for the final analysis will be based on actual sampling times. Individual PK parameters will be presented in listings and summarized using descriptive statistics.

Pharmacodynamics: Pharmacodynamic endpoints will be summarized using descriptive statistics.

Determination of Sample Size: For the primary efficacy endpoint, change from baseline to Week 12 (Day 84) in QMG score, assuming a difference in treatment group means of 4.5, an SD of 5.0, and 12 subjects per group, the study has approximately 81% power to detect a difference between an active and placebo treatment group based on a 1-sided t-test with a 0.10 type I error rate.

2 TIME AND EVENTS TABLES

Assessments to be performed during the study are shown in Table 1 and Table 2.

Table 1 MAIN PORTION: Time and Events Table

Study Procedure	Screening Days -28 to -1	Day 1	Day 8 (± 2 days)	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 57 (± 7 days)	End of Study[a] Day 84 (± 2 days)	Safety Follow-up Call (last dose + 40d)	Rescue Therapy Visit[b] (*if applicable*)
Informed consent[c]	X								
Review eligibility and randomization[c]	X								
Medical history[d] and demographics	X								
Height[e] and weight	X				X		X		
Prior and concomitant medications[f]	X	X	X	X	X	X	X		X
Safety									
Physical examination[g]	X	X	X	X	X	X	X		X
Vital signs[h]	X	X	X	X	X	X	X		X
12-Lead electrocardiogram	X						X		X
Neisseria meningitidis vaccination[i]	X								
Hematology/Chemistry[j]	X	X	X	X	X	X	X		X
Coagulation[k]	X	X	X	X	X	X	X		X
Urinalysis	X	X	X	X	X	X	X		X
Pregnancy test[l]	X	X					X		
Adverse events[m]		X	X	X	X	X	X	X[m]	X
Anti-drug antibody	X				X		X		X
Efficacy									
QMG Test/Score[n]	X	X	X	X	X	X	X		X
MG-ADL		X	X	X	X	X	X		X
MG-QOL15r		X	X	X	X	X	X		X
MG Composite		X	X	X	X	X	X		X
Pharmacokinetic/Pharmacodynamic									
RA101495 plasma PK[o]		X[o]	X	X	X	X	X[o]		X[o]
Pharmacodynamic analysis[o]		X[o]	X	X	X	X	X[o]		X[o]
Exploratory									
Additional biomarker samples[p]		X	X	X	X	X	X		
Pharmacogenomic analysis *(optional)*	X								
Study Drug									
RA101495 or placebo administration[q]		X	X	X	X	X	X		X[q]

See footnotes on following page.

1-a. If a subject prematurely discontinues study drug at any time prior to completion of the Day 84 visit during the Treatment Period, the subject should return to clinic for an End of Study Visit.

1-b. 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.

1-c. 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.

1-d. Screening includes disease history with diagnosis of gMG by the MGFA criteria (Class II-IVa), serology for AChR autoantibodies.

1-e. Height will be measured only at Screening.

1-f. All prescriptions and over-the-counter medications taken during the 30 days prior to baseline (i.e., Day 1) through the last study visit will be documented. NOTE: A complete history of medications taken for the treatment of gMG will be collected.

1-g. A full physical examination will be performed on all subjects at Screening. On all other study visit days, the physical examination will be symptom-directed.

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

1-i. All subjects must have documentation of prior *Neisseria meningitidis* vaccination (and booster, if appropriate) prior to study entry. If the subject has not been vaccinated, he/she must be vaccinated with a quadrivalent meningococcal vaccine at least 14 days prior to the first dose of study drug on Day 1 and should have a booster vaccination as indicated by SOC. Subjects should bring their patient safety card to every study visit. If the subject does not bring their card with them they will be given a new one.

1-j. All laboratory samples should be obtained prior to administration of study drug at applicable visits unless otherwise noted for PK, PD, and biomarker samples.

1-k. Coagulation tests should be performed only in subjects who are receiving anticoagulant therapy.

1-l. 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.

1-m. 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. 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. This Safety Follow-up Call will only be required for subjects who choose not to receive RA101495 in the Extension Portion.

1-n. The assessment of QMG 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) 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 QMG test.

1-o. Blood samples for PK and PD analysis will be obtained at the following time points:

<table>
<tr><th rowspan="2">Day 1</th><th rowspan="2">Day 84</th><th colspan="2">During Rescue Therapy</th></tr>
<tr><th>At sites where rescue therapy is administered locally</th><th>At sites where rescue therapy is NOT administered locally</th></tr>
<tr><td>predose (within 1 hour before first dose of study drug)</td><td>predose (any time prior to Day 84 study drug administration)</td><td>Within 1 hour before administration of rescue therapy</td><td>Prior to administration of the first course of rescue therapy</td></tr>
<tr><td>1 hour postdose (± 30 minutes)</td><td rowspan="3">1 hour postdose (± 30 minutes)</td><td>For PLEX only: PK will be measured in the exchanged plasma</td><td rowspan="3">After administration of the last course of rescue therapy</td></tr>
<tr><td>3 hours postdose (± 30 minutes)</td><td rowspan="2">Within 1 hour after administration of rescue therapy</td></tr>
<tr><td>6 hours postdose (± 90 minutes)</td></tr>
</table>

On all other study visit days, PK/PD samples should be collected prior to administration of study drug.

1-p. Blood samples for biomarker testing will be obtained prior to administration of study drug (within 1 hour of dosing) and at 6 hours postdose (± 90 minutes) on Day 1. On all other study visit days, biomarkers samples should be collected prior to administration of study drug.

1-q. Dosing on study visit days should be held until QMG scoring, PK, and PD sample blood collection has 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.

Table 2 EXTENSION PORTION: Time and Events Table

Study Procedure	Day E1[a] (Day 84)	Day E8 (± 2 days)	Day E15 (± 2 days)	Day E29 (± 2 days)	Day E57 (± 7 days)	Day E84 (± 7 days)	Rescue Therapy Visit[b] (*if applicable*)	Please refer to Appendix 2: Extension Portion Visits after Day E84	Final Study Visit[c]
Informed consent	X								
Review eligibility and randomization	X								
Weight	X			X		X			X
Prior and concomitant medications	X	X	X	X	X	X	X		X
Safety									
Physical examination (symptom directed)	X	X	X	X	X	X	X		X
Vital signs[d]	X	X	X	X	X	X	X		X
12-Lead electrocardiogram						X	X		X
Neisseria meningitidis vaccination[e]	SOC[e]								
Hematology/Chemistry[f]	X	X	X	X	X	X	X		X
Coagulation[g]	X	X	X	X	X	X	X		X
Urinalysis	X	X	X	X	X	X	X		X
Pregnancy test[h]	X					X			X
Adverse events[i]	X	X	X	X	X	X	X		X
Anti-drug antibody	X			X		X	X		X
Efficacy									
QMG Test/Score[j]	X	X	X	X	X	X	X		X
MG-ADL	X	X	X	X	X	X	X		X
MG-QOL15r	X	X	X	X	X	X	X		X
MG Composite	X	X	X	X	X	X	X		X
Pharmacokinetic/Pharmacodynamic									
RA101495 plasma PK[k]	X[k]	X	X	X	X	X	X[k]		X
Pharmacodynamic analysis[k]	X[k]	X	X	X	X	X	X[k]		X
Exploratory									
Additional biomarker samples[l]	X[l]	X	X	X	X	X			X
Study Drug									
RA101495 administration[m]	X	X	X	X	X	X	X[m]		X

See footnotes on following page.

2-a. For subjects that decide and are eligible to continue in the Extension Portion, the Day 84 visit from the Main Portion will serve as the Day E1 visit and will also include review of eligibility to continue, treatment group assignment (see Section 8.3), signing of an informed consent for the Extension Portion, and an additional biomarker blood sample.

2-b. 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.

2-c. If a subject discontinues study drug treatment at any time during the Extension Period, the subject should return to clinic for a Final Study Visit.

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

2-e. During the Extension Portion, all subjects should have *Neisseria meningitidis* booster vaccinations as indicated by SOC. Subjects should bring their patient safety card to every study visit. If the subject does not bring their card with them they will be given a new one.

2-f. All laboratory samples should be obtained prior to administration of study drug at applicable visits unless otherwise noted for PK, PD, and biomarker samples.

2-g. Coagulation tests should be performed only in subjects who are receiving anticoagulant therapy.

2-h. Urine pregnancy tests will be conducted in female subjects of childbearing potential.

2-i. 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.

2-j. The assessment of QMG 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) 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 QMG test.

2-k. Blood samples for PK and PD analysis will be obtained at the following time points:

Day E1 (Day 84 from the Main Portion)	**During Rescue Therapy**	
	At sites where rescue therapy is administered locally	**At sites where rescue therapy is NOT administered locally**
predose (any time prior to Day 84 study drug administration)	Within 1 hour before administration of rescue therapy	Prior to administration of the first course of rescue therapy
1 hour postdose (± 30 minutes)	For PLEX only: PK will be measured in the exchanged plasma	After administration of the last course of rescue therapy
	Within 1 hour after administration of rescue therapy	

On all other study visit days, PK/PD samples should be collected prior to administration of study drug.

2-l. Biomarkers samples should be collected prior to administration of study drug.

2-m. Dosing on study visit days should be held until QMG scoring, PK, and PD sample blood collection has 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.

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AChR	acetylcholine receptor
ADA	anti-drug antibody
AE	adverse event
aHUS	atypical hemolytic uremic syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	Analysis of Covariance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
$AUC_{(0-24)}$	area under the drug concentration-time curve from 0 to 24 hours
BUN	blood urea nitrogen
C5	complement component 5
C_{max}	maximum plasma concentration
CPK	creatine phosphokinase
CRO	Clinical Research Organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
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
LRP4	lipoprotein receptor-related peptide 4
MAC	membrane attack complex
MCV	mean corpuscular volume
MD	multiple dose
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MG	myasthenia gravis
MG-ADL	Myasthenia Gravis-Activities of Daily Living
MGFA	Myasthenia Gravis Foundation of America
MG-QOL	Myasthenia Gravis-Quality of Life
mITT	Modified Intention-to-Treat
MuSK	muscle-specific kinase
MSE	Minimum Symptom Expression
NCI	National Cancer Institute
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PLEX	plasma exchange
PNH	paroxysmal nocturnal hemoglobinuria
PT	prothrombin time
PTT	partial thromboplastin time
QMG	quantitative myasthenia gravis
QOL	quality of life
QTcB	QT interval corrected by Bazett's formula
QTcF	QT interval corrected by Fridericia's formula
SAD	single ascending dose
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
TEAE	treatment-emergent adverse event
t_{max}	time to corresponding C_{max}
TMF	Trial Master File
ULN	upper limit of normal
WBC	white blood cell

5 INTRODUCTION

Ra Pharmaceuticals, Inc. is developing RA101495, a subcutaneously (SC) administered 15-amino acid cyclic peptide that inhibits the cleavage of complement component 5 (C5).

Please refer to the Investigator's Brochure (IB) for additional information on the chemistry, toxicology, pharmacology, and safety of RA101495.

5.1 OVERVIEW OF GENERALIZED MYASTHENIA GRAVIS

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 electrical signals from nerves to muscles. The prevalence of MG in the United States is estimated at approximately 36,000 to 60,000 cases [Howard, 2016]. In approximately 15% of patients with MG, symptoms are confined to the ocular muscles. The remaining patients have MG that affects multiple muscle groups throughout the body, which is defined as 'generalized' myasthenia gravis (gMG) [Gilhus, 2016].

Patients with gMG present with muscle weakness that characteristically becomes more severe with repeated use and recovers with rest. Muscle weakness can be localized to specific muscles, but often progresses to more diffuse muscle weakness [Gilhus, 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 2 years of diagnosis [Ramizuddin, 2014].

The most common target of autoantibodies in gMG is the nicotinic acetylcholine receptor (AChR), located at the neuromuscular junction, the point at which a motor neuron transmits chemical signals to a skeletal muscle fiber. Current 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, which is the only approved therapy for MG. Although usually adequate for control of mild ocular symptoms, pyridostigmine monotherapy is usually insufficient for the treatment of generalized weakness, and dosing of this therapy may be limited by cholinergic side effects. Therefore, in patients who remain symptomatic despite pyridostigmine therapy, corticosteroids with or without systemic immunosuppressives are indicated [Sanders, 2016]. Immunosuppressives used in gMG include azathioprine, cyclosporine, mycophenylate mofetil, methotrexate, tacrolimus, cyclophosphamide, and rituximab. To date, efficacy data for these agents are sparse and no steroidal or immunosuppressive therapy has been approved for the treatment of gMG. Moreover, all of these agents are associated with well-documented long-term toxicities. Surgical removal of the thymus may be recommended in patients with nonthymomatous gMG and moderate to severe symptoms in an effort to reduce the production of AChR autoantibodies [Wolfe, 2016]. Intravenous (IV) immunoglobulin and plasma exchange are restricted to short-term use in patients with myasthenic crisis or life-threatening signs

such as respiratory insufficiency or dysphagia [Sanders, 2016]. There is, therefore, a substantial unmet medical need for novel therapies to treat patients with gMG.

5.2 ROLE OF COMPLEMENT IN GENERALIZED MYASTHENIA GRAVIS

There is substantial evidence that supports the role of terminal complement cascade in the pathogenesis of AChR autoantibody-positive gMG. Results from animal models of experimental autoimmune MG have demonstrated that immune complex formation at the neuromuscular junction triggers activation of the classical complement pathway, resulting in local activation of C3 and deposition of the membrane attack complex (MAC) at the neuromuscular junction, resulting in loss of signal transduction and eventual muscle weakness [Kusner, 2012].

In addition, inhibition of C5 has been recently validated as a target for the treatment of refractory gMG based on clinical studies with the C5-blocking antibody, eculizumab. Eculizumab is currently approved for use in 2 other complement-driven rare diseases, paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS). In a Phase 2, randomized, double-blind, placebo-controlled trial, eculizumab was tested in 14 AChR autoantibody-positive patients with refractory gMG, who had a quantitative myasthenia gravis (QMG) score ≥ 12 and previously failed treatment with at least 2 immunosuppressant therapies (ISTs) [Howard, 2013]. Patients were randomized in a 1:1 ratio to receive either eculizumab or placebo. Patients on eculizumab received 600 mg per week for 4 weeks, followed by 900 mg every other week by IV infusion, for a total of 16 weeks of treatment. After a 5-week washout period, patients were crossed over to the opposite arm of the study. Patients who received placebo for the first 16 weeks of the study were treated with eculizumab and vice versa. The primary endpoints were safety and efficacy, as measured by the percentage of patients who achieved a ≥ 3-point reduction in QMG score. The impact of C5 inhibition by eculizumab in QMG score occurred rapidly (within 1 week of initiating treatment) and favored eculizumab compared with placebo across all study visits ($p = 0.0144$). Following the initial 16-week treatment period, 6 out of 7 patients on eculizumab achieved a ≥ 3-point improvement in QMG score, compared with 4 out of 7 patients in the placebo arm. Of those patients who responded to eculizumab, 4 achieved an 8-point reduction in QMG score compared with only 1 in the placebo arm.

A Phase 3 trial was also recently completed that enrolled 125 AChR autoantibody-positive patients with a Myasthenia Gravis-Activities of Daily Living (MG-ADL) score ≥ 6, who had previously failed 2 ISTs or had failed 1 IST and required chronic plasma exchange or IV immunoglobulin therapy [Alexion, 2017]. Patients were randomized 1:1 to receive either placebo or eculizumab for a 26-week treatment period, followed by an extension study. Patients receiving eculizumab were treated with 900 mg per week for 4 weeks followed by 1200 mg every other week by IV infusion. Eculizumab treatment was not associated with a statistically significant benefit relative to placebo in the primary endpoint of change from baseline in MG-ADL ($p = 0.0698$) in this study [Alexion, 2016]. However, statistically significant results were observed in 18 of 22 prespecified analyses, including the secondary endpoint of change from baseline in QMG score ($p = 0.0129$). Taken together, the results of these 2 clinical trials establish that

inhibition of the terminal complement cascade by blocking cleavage of C5 is a clinically validated target for the treatment of gMG.

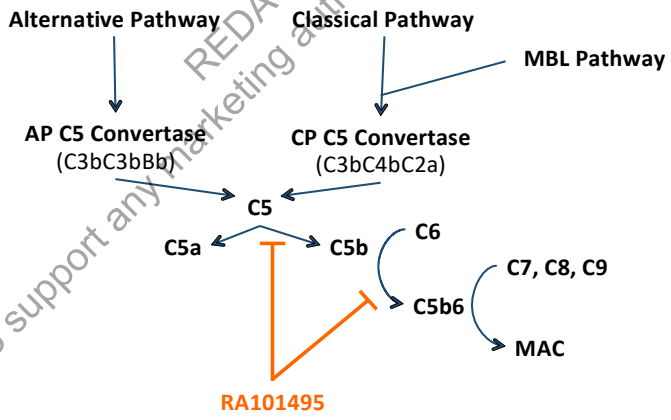
5.3 MECHANISM OF ACTION OF RA101495

RA101495 is a macrocyclic peptide designed to inhibit complement activation at the level of C5, the same molecular target as eculizumab. RA101495 binds to C5 with high affinity and prevents its cleavage by the C5 convertase into both cleavage products C5a and C5b (Figure 1). Inhibition of C5 cleavage therefore prevents the downstream assembly and activity of the MAC, which has been detected in the post-junctional membrane of the neuromuscular junction of patients with gMG. Distinct from eculizumab, RA101495 binds to the portion of C5 that corresponds to the C5b domain. In binding to this region of C5, should any C5b be formed, RA101495 will also block binding to C6, which further prevents the subsequent assembly of the MAC (C5b-9). Using surface plasmon resonance and analysis of a high-resolution co-crystal structure, RA101495 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.

Thus, RA101495 inhibits MAC formation by a dual mechanism:

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

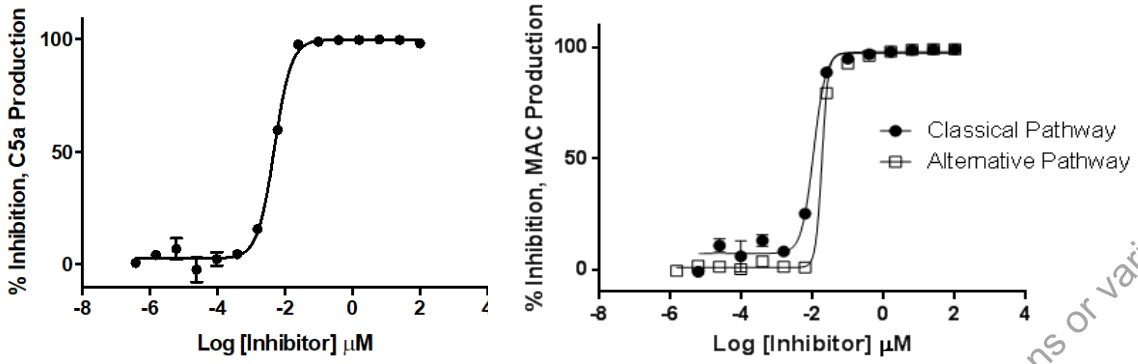
Figure 1 Mechanism of Action of RA101495 in the Complement System



Abbreviations: AP=alternative pathway; C5=complement component 5; CP=complement pathway; MAC=membrane attack complex; MBL= mannose-binding lectin.

The dose-dependent inhibition by RA101495 of C5a formation upon activation of the classical pathway is depicted in the left panel of Figure 2. The right panel of Figure 2 shows the inhibition by RA101495 of C5b formation (as measured by C5b-9 or MAC deposition on a complement activating surface) upon activation of the classical and alternative complement pathways. In these experiments, the relative levels of both C5a and MAC were measured by enzyme-linked immunosorbent assays (ELISAs) using antibodies specific for C5a and C5b-9.

Figure 2 Inhibition of C5a (left) and C5b-9 (MAC; right) Formation by RA101495



Note: Inhibitor is RA101495.
Abbreviations: C5=complement component 5; MAC=membrane attack complex.

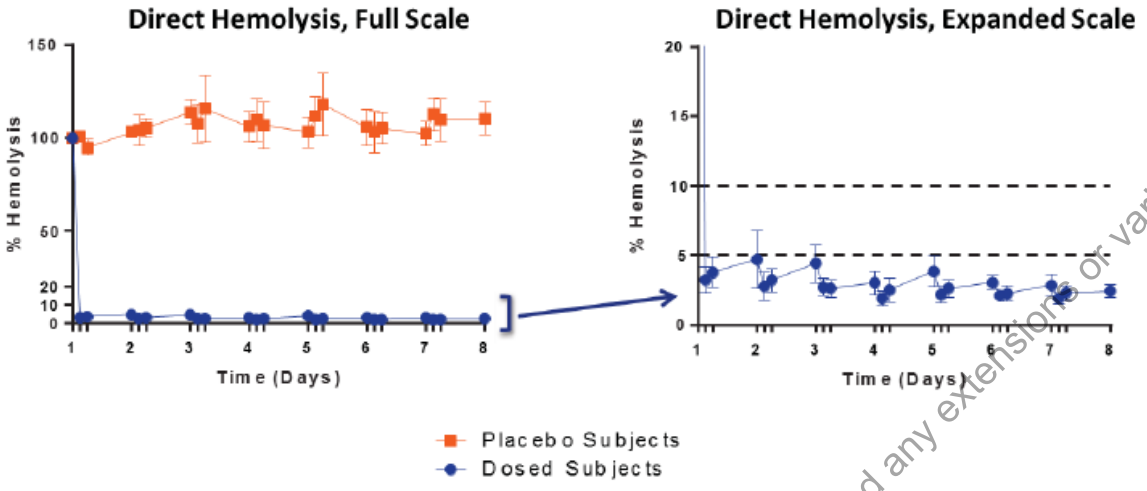
5.4 CLINICAL TRIAL EXPERIENCE WITH RA101495

Clinical trial experience with RA101495 to date includes a single Phase 1 study (RA101495-1001) in healthy volunteers. Study RA101495-1001 was a randomized, double-blind, placebo-controlled, single ascending dose (SAD) and multiple dose (MD) study designed to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of RA101495.

The first part of the RA101495-1001 study (SAD) evaluated a single dose of RA101495 versus placebo at 4 dose levels (0.05, 0.1, 0.2, and 0.4 mg/kg) in separate cohorts. Twenty-two subjects were enrolled; 14 subjects received RA101495 (0.05 mg/kg in 2 subjects; 0.1, 0.2, and 0.4 mg/kg in 4 subjects each) and 8 subjects received placebo (2 subjects per each dose level). The second part of the study (MD) evaluated 7 daily doses of RA101495 versus placebo at a single dose level (0.2 mg/kg). A total of 6 subjects were enrolled; 4 subjects received RA101495 and 2 subjects received placebo.

The results of this study showed that RA101495 had highly predictable, dose-dependent PK after single- and multiple-dose SC injections over the dose range investigated. RA101495 demonstrated robust ex vivo hemolysis suppression and complement inhibition with daily SC dosing compared with placebo treatment (Figure 3).

Figure 3 Robust Suppression of Hemolytic Activity by RA101495 in the Multiple Dose Cohort (Study RA101495-1001)



Note: Dosed subjects were treated with 0.2 mg/kg RA101495 daily for 7 days.

Administration of RA101495 in this study was also associated with an acceptable safety and tolerability profile with no serious adverse events (SAEs) reported. The most common adverse events (AEs) in subjects who received single doses of RA101495, regardless of causality, were injection site erythema (3 subjects, 0.4 mg/kg), upper respiratory tract infection (1 subject, 0.05 mg/kg; 2 subjects, 0.4 mg/kg), and headache (2 subjects, 0.4 mg/kg). The most common AEs in subjects who received multiple doses of 0.2 mg/kg RA101495, regardless of causality, were injection site erythema (3 subjects) and headache (2 subjects). A complete overview of results from the RA101495-1001 study is provided in the RA101495 IB.

5.5 RATIONALE FOR THE CURRENT STUDY

Current therapies for gMG focus on either augmenting the AChR signal or nonspecifically suppressing the autoimmune response, and none of these treatments target the injury to the post-synaptic muscle endplate caused by complement attack. Inhibition of terminal complement activity with RA101495 may block complement-mediated damage to the motor endplate, thereby preserving responsiveness to signaling and potentially reversing or preventing muscle weakness. The current study will evaluate the safety and efficacy of 12 weeks of treatment with 2 different doses of RA101495 (0.1 mg/kg daily and 0.3 mg/kg daily) compared with placebo, as well as the long-term effects of administration of RA101495, in subjects with gMG.

5.5.1 RATIONALE FOR BLINDING AND PLACEBO CONTROL

The primary objective of this study is the evaluation of efficacy based on functional assessment of weakness measured by the QMG 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 have stable disease and will be allowed to continue their standard of care (SOC) therapy, including escalation of treatment as medically necessary (see Section 10.1.3.1 Rescue Therapy). 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 ([redacted]) 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 RA101495-02.201 is not anticipated to cause undue burden or risk for study subjects.

Following the completion of the 12-week Treatment Period in the Main Portion of the study, all subjects will have the option to receive RA101495 in the Extension Portion of the study. Therefore, subjects originally randomized to placebo will eventually have the opportunity to receive active study drug. The study will remain double-blinded during the Extension Portion until after the data from the Main Portion of the study have been cleaned, locked, and unblinded.

Following implementation of the present Amendment (v.3.0), and upon appropriate reconsent, all subjects ongoing in the Extension Portion will receive the 0.3 mg/kg dose that has been selected for the pivotal Phase 3 study (See Section 5.5.3 for details).

5.5.2 DOSE SELECTION AND PRESENTATION

Study drug will be provided in prefilled syringes for self-injection using weight bracketed dosing (i.e., subjects will be provided prefilled syringes containing fixed amounts of RA101495 based on their weight, and each fixed amount will cover a range of subject weights). This weight-bracketed dosing strategy will result in the potential for a range of doses to be received at each dose level (see Section 9.1.3).

The doses to be used in this Phase 2 study were selected based on the following:

- Preliminary data from ongoing Phase 2 studies in adult subjects with PNH indicates that daily dosing of RA101495 at both 0.1mg/kg and 0.3mg/kg is well-tolerated.
- The predicted steady state C_{max} and $AUC_{(0-24)}$ achieved at both doses are expected to be within the range of those achieved in the Phase 1 RA101495 study in healthy volunteers and/or in Phase 2 studies in subjects with PNH.
- Based on pharmacodynamic data from the ongoing Phase 2 studies in PNH, both doses have been shown to achieve rapid and sustained inhibition of complement activity.
- Additional information on pharmacokinetics, pharmacodynamics, and experience in other clinical trials is available in the Investigators' Brochure.

5.5.3 DOSE SELECTION FOR OPEN LABEL PORTION

After analysis of the results of the Main Portion of this Phase 2 Study, the dose of 0.3 mg/kg daily was selected for the Open Label Extension Portion based on its superior

efficacy, greater inhibition of the terminal complement pathway, and similar safety profile as compared with the 0.1 mg/kg and placebo arms.

In the Main Portion of the Phase 2 Study RA101495-02.201, the magnitude and speed of improvement on the primary (QMG) and key secondary (MG-ADL) endpoints were greater with the 0.3 mg/kg dose than the 0.1 mg/kg dose, and both active doses were superior to placebo. The superior efficacy of the 0.3 mg/kg dose was further demonstrated by the complete freedom from the need for rescue therapy with IVIG or PLEX in the 0.3mg/kg arm, as compared with a 7% rescue rate in the 0.1 mg/kg arm, and a 20% rescue rate in the placebo arm. A higher proportion of subjects achieved MSE (Vissing 2018), defined as an MG-ADL of 0 or 1, in the 0.3mg/kg arm (35.7%) as compared with the 0.1 mg/kg arm (26.7%) and placebo (13.3%).

The dose response seen in the clinical outcome measures is consistent with the known pharmacodynamic effect of zilucoplan that resulted, as expected, in rapid, sustained and complete (97%) inhibition of the terminal complement pathway in all gMG subjects receiving the 0.3 mg/kg dose while the 0.1 mg/kg group achieved only submaximal (88%) inhibition of the terminal complement pathway.

The once daily dosing interval will be retained because pharmacokinetic simulations indicate that longer dosing intervals cannot achieve adequate exposures and fail to maintain the depth of complement inhibition needed for maximum therapeutic benefit. For example, once every other day dosing is estimated to reduce the zilucoplan trough concentration by approximately 50%, resulting in inadequate pharmacodynamic effect.

The same weight brackets for the 0.3 mg/kg dose will continue to be used in the Open Label Extension Portion. Study drug will continue to be provided in prefilled syringes for self-injection using weight bracketed dosing (i.e., subjects will be provided prefilled syringes containing fixed amounts of zilucoplan based on their weight, and each fixed amount will cover a range of subject weights). This weight-bracketed dosing strategy will result in the potential for a range of doses to be received at each dose level (see Section 9.1.3).

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 OBJECTIVES

The objectives of the study are:

- To assess the safety and tolerability of RA101495 in subjects with gMG
- To assess preliminary efficacy of RA101495 in subjects with gMG

6.2 ENDPOINTS

6.2.1 SAFETY AND TOLERABILITY ENDPOINTS

Safety assessments will include evaluations of AEs and SAEs, clinical laboratory tests, electrocardiograms (ECGs), vital signs, and physical examinations.

6.2.2 EFFICACY ENDPOINTS

Primary efficacy:

The primary efficacy endpoint is the change from baseline to Week 12 (Day 84) in QMG score. The primary endpoint comparison will be between the 0.3 mg/kg RA101495 group and the placebo group.

Secondary efficacy:

The secondary efficacy endpoints are:

- Change from baseline to Week 12 in the MG-ADL scale
- Change from baseline to Week 12 in the MG-Quality of Life 15r (MG-QOL15r) survey
- Change from baseline to Week 12 in the MG Composite
- Subjects with ≥ 3-point reduction in QMG score at Week 12
- Subjects requiring rescue therapy over the 12-week Treatment Period

6.2.3 PHARMACOKINETIC ENDPOINTS

The PK endpoints are:

- Plasma concentrations of RA101495 and its major metabolites
- Maximum plasma concentration (C_{max}) on Day 1
- Time corresponding to C_{max} (t_{max}) on Day 1

6.2.4 PHARMACODYNAMIC ENDPOINTS

The PD endpoints are:

- Sheep red blood cell (sRBC) lysis assay for evaluation of classical complement pathway activation
- C5 levels

6.2.5 EXPLORATORY ENDPOINTS

The following exploratory endpoints will also be examined during the study:

- Mechanistic biomarkers [e.g., MG pathophysiology, complement fixation, complement function, complement pathway proteins, autoantibody characterization (titer and immunoglobulin class) and inflammation]
- Pharmacogenomic analyses (optional)

7 STUDY DESIGN

7.1 OVERVIEW OF STUDY DESIGN

Study RA101495-02.201 is a multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and preliminary efficacy of RA101495 in subjects with gMG. The planned enrollment is approximately 36 subjects.

Subjects will be randomized in a 1:1:1 ratio to receive daily SC doses of 0.1 mg/kg RA101495, 0.3 mg/kg RA101495, or matching placebo. Randomization will be stratified based on the screening QMG Score (≤ 17 versus ≥ 18).

The Main Portion of the study includes a Screening Period of up to 4 weeks and a 12-week Treatment Period (Figure 4). During the Treatment Period, subjects will return to the clinic weekly for the first 2 visits (Day 8 and Day 15) after the Day 1 visit, followed by visits at Week 4 (Day 29), Week 8 (Day 57), and Week 12 (Day 84) to evaluate safety, tolerability, and preliminary efficacy. Additional assessments will include quality of life (QOL) questionnaires, biomarker samples, pharmacokinetics, pharmacodynamics, and optional pharmacogenomics. Safety assessments will include physical examinations, vital signs, ECGs, clinical laboratory tests, AEs, and immunogenicity.

Randomized subjects will receive 0.1 mg/kg RA101495, 0.3 mg/kg RA101495, 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. An injection device will be provided for use during the study.

Subjects are expected to remain on stable doses of SOC therapy for gMG throughout the study, including pyridostigmine, corticosteroids, or immunosuppressive drugs. If, in the opinion of the investigator, escalation of gMG therapy (i.e., 'rescue therapy') becomes necessary due to deterioration of a subject's clinical status, the subject may receive immunoglobulin or plasma exchange treatment.

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 (see Section 11.3.2.1).

The risk of *Neisseria meningitidis* infection will be closely monitored during the study. All subjects who have not been previously vaccinated against *Neisseria meningitidis* prior to study entry must be vaccinated 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.

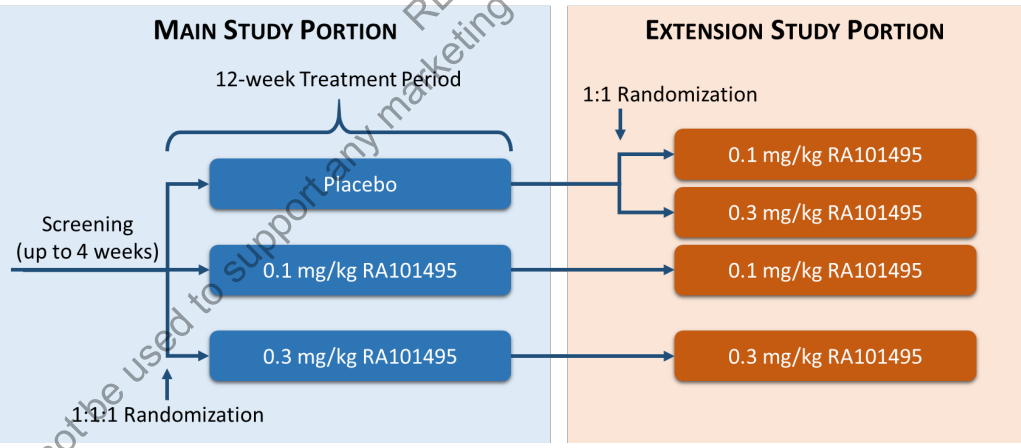
During the Treatment Period, to mitigate the risk of infection, subjects will be counseled and reminded of the early signs and symptoms of *Neisseria meningitidis* infection. A patient safety card detailing the signs and symptoms of infection, with instructions to seek immediate medical attention, will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

At the conclusion of the Treatment Period in the Main Portion of the study, all subjects will have the option to receive RA101495 in the Extension Portion of the study provided they meet the Extension Portion selection criteria (Section 8.3). Subjects assigned to a RA101495 treatment arm during the Main Portion of the study will continue to receive the same dose of study drug during the Extension Portion. Subjects assigned to the placebo arm during the Main Portion of the study will be randomized in a 1:1 ratio to receive daily SC doses of 0.1 mg/kg RA101495 or 0.3 mg/kg RA101495. Visits during the first 12 weeks of the Extension Portion will be identical to Main Portion of the study for all subjects to ensure appropriate monitoring of subjects transitioning from placebo to active treatment and to maintain blinding of treatment assignment. The study will remain double-blinded during the Extension Portion until after the data from the Main Portion of the study have been cleaned, locked, and unblinded.

Following implementation of the present Amendment (v.3.0), and upon appropriate reconsent, all subjects ongoing in the Extension Portion will receive the 0.3 mg/kg dose that has been selected for the pivotal Phase 3 study (See Section 5.5.3 for details).

If a subject discontinues study drug treatment prior to the Day 84 visit for any reason, he/she will not be eligible for the Extension Portion. Subjects who undergo rescue treatment and continue receiving study drug are eligible for participation in the Extension Portion. For subjects who do not participate in the Extension Portion, a safety follow-up telephone call 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 (SAEs) since the last study visit.

Figure 4 Design of RA101495-02.201 Study



7.2 STUDY PERIODS

During the Main Portion of the study, 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.

During the Extension Portion of the study, RA101495 will continue to be provided by the Sponsor until RA101495 is approved and available in the territory, or the Sponsor terminates development of RA101495 for gMG. In countries where RA101495 is not

approved or marketed, but in which sponsored clinical studies have been conducted, subjects may continue to receive RA101495 through a compassionate use pathway.

Following implementation of the present Amendment (v.3.0), and upon appropriate reconsent, all subjects ongoing in the Extension Portion will receive the 0.3 mg/kg dose that has been selected for the pivotal Phase 3 study (See Section 5.5.3 for details).

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 3 months. 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
- Review of eligibility criteria
- Review of medical history and demographics, including collection of disease history with diagnosis of gMG according to Myasthenia Gravis Foundation of America (MGFA) criteria (Class II-IVa), serology for AChR autoantibodies, and QMG score assessment
- 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.
- Full physical examination
- Vital signs [heart rate (HR), body temperature, blood pressure in the sitting position]
- 12-lead ECG
- *Neisseria meningitidis* vaccination for all subjects who do not have documentation of prior *Neisseria meningitidis* vaccination (and booster, if appropriate). A booster should also be administered, in applicable subjects, as indicated by SOC. All eligible subjects must have documentation of prior *Neisseria meningitidis* vaccination (and booster, if appropriate) prior to study entry.
- 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 ADA testing
- Collection of blood sample for pharmacogenomic analysis (optional)

- Enrollment and randomization

7.2.2 TREATMENT PERIOD (MAIN AND EXTENSION PORTIONS)

Subjects will receive treatment with 0.1 mg/kg RA101495, 0.3 mg/kg RA101495, or matching placebo, according to randomization, from Day 1 to Day 84 during the Treatment Period of the Main Portion of the study. In consultation with the treating physician, subjects who complete the Day 84 visit (including those randomized to the placebo arm) will have the option to continue treatment with RA101495 in the Extension Portion of the study. Subjects assigned to a RA101495 treatment arm during the Main Portion of the study will continue to receive the same dose of study drug during the Extension Portion. Subjects assigned to the placebo arm during the Main Portion of the study will be randomized in a 1:1 ratio to receive daily SC doses of 0.1 mg/kg RA101495 or 0.3 mg/kg RA101495. If a subject chooses not to participate in the Extension Portion, the subject will receive standard-of-care treatment off-study, as recommended by the treating physician.

Please refer to the Time and Events Tables (Table 1 and Table 2) for details regarding assessments that must be completed at visits during the Treatment Period for both the Main and Extension Portions of the study.

7.2.2.1 RANDOMIZATION AND BLINDING

Subjects who meet all entry criteria will be randomized in a 1:1:1 ratio to receive daily SC doses of 0.1 mg/kg RA101495, 0.3 mg/kg RA101495, or matching placebo. Subjects will be assigned to study arms in a blinded fashion using a computerized randomization algorithm. Randomization will be stratified based on the screening QMG Score (≤ 17 versus ≥ 18).

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

Instructions for emergency unblinding, if warranted, for safety reasons are provided in Section 11.3.3.

7.2.2.2 DISCONTINUATION OF INVESTIGATIONAL MEDICINAL PRODUCT

Upon completion of the 12-week Treatment Period, if a subject chooses not to participate in the Extension Portion then they should return to the clinic for the Day 84 (or End of Study) visit. If a subject prematurely discontinues study drug at any time prior to completion of the Day 84 (see Section 8.3.2), the subject should return to clinic for an End of Study Visit. During the Extension Portion, if a subject prematurely discontinues study drug at any time (see Section 8.3.2), the subject should return to clinic for a Final Study Visit.

The following procedures will be completed at the End of Study and Final Study Visits:

- Measurement of weight

- Review and documentation of concomitant medications
- Symptom-directed 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
- Collection of blood samples for the following assessments:
  - ADA sampling
  - PK analysis
  - PD analyses
  - Additional biomarker analysis
- QMG score assessment
- Completion of the following efficacy assessments:
  - MG-ADL
  - MG-QOL15r
  - MG Composite
- Return of all used and unused study drug syringes to site

All subjects who prematurely discontinue study treatment during the Main Portion of the study will receive a safety follow-up telephone call 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.

7.3 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. If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

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

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 < 85 years.
2. Able to provide informed consent, including signing and dating the informed consent form (ICF).
3. Diagnosis of gMG (MGFA Class II-IVa) at Screening.

4. Positive serology for AChR autoantibodies.
5. QMG score ≥ 12 at Screening and baseline (off acetylcholinesterase inhibitor therapy for at least 10 hours) with ≥ 4 test items scored at ≥ 2.
6. No change in corticosteroid dose for at least 30 days prior to baseline or anticipated to occur during the 12-week Treatment Period.
7. 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.
8. 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.
9. 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 (see Section 10.2.4.3).

8.2 EXCLUSION CRITERIA

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

1. Thymectomy within 6 months prior to baseline or scheduled to occur during the 12-week Treatment Period.
2. Abnormal thyroid function as determined by local standard.
3. Known positive serology for muscle-specific kinase (MuSK) or lipoprotein receptor-related peptide 4 (LRP4).
4. Minimal Manifestation Status of myasthenia gravis based on the clinical judgement of the investigator.
5. Calculated glomerular filtration rate of < 60 mL/min/1.73 m^2 based on the Modification of Diet in Renal Disease (MDRD) equation at Screening.

$$\text{GFR}\left(\frac{\text{mL}/\text{min}}{1.73\ \text{m}^2}\right) = 175 \times (\text{S}_{\text{cr}})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742\ if\ female) \times (1.212\ if\ African\ American)$$

6. Elevated liver function tests (LFTs) defined as total bilirubin or transaminases [aspartate aminotransferase (AST)/alanine aminotransferase (ALT)] > 2 times the upper limit of normal (× ULN).
7. History of meningococcal disease.
8. Current or recent systemic infection within 2 weeks prior to baseline or infection requiring IV antibiotics within 4 weeks prior to baseline.
9. Pregnant, planning to become pregnant, or nursing female subjects.
10. Recent surgery requiring general anesthesia within 2 weeks prior to Screening or surgery expected to occur during Screening or the 12-week Treatment Period.
11. Treatment with an experimental drug or another complement inhibitor within 30 days or 5 half-lives of the experimental drug (whichever is longer) prior to baseline.
12. Treatment with rituximab within 6 months prior to baseline.

13. Ongoing treatment with IV immunoglobulin G (IVIG) or plasma exchange or treatment within 4 weeks prior to baseline.
14. Active neoplasm (other than benign thymoma) 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. Fixed weakness ('burnt out' MG) based on the clinical judgement of the investigator.
16. History of any significant medical or psychiatric disorder that in the opinion of the investigator would make the subject unsuitable for participation in the study.
17. Participation in another concurrent clinical trial involving an experimental therapeutic intervention (participation in observational studies and/or registry studies is permitted).
18. Unable or unwilling to comply with the requirements of the study.

8.3 SELECTION CRITERIA FOR THE EXTENSION PORTION:

1. Completion of the Main Portion of the study.
2. Continues to meet inclusion criteria 2, 4, 8, and 9 from the Main Portion of the study.
   - *2. Able to provide informed consent, including signing and dating the informed consent form (ICF).*
   - *4. Positive serology for AChR autoantibodies.*
   - *8. 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.*
   - *9. 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 (see Section 10.2.4.3).*
3. Did not start any disallowed medication per the exclusion criteria from the Main Portion of the study or alter the dose of any other concomitant medication, unless medically indicated.
4. Unable or unwilling to comply with the requirements of the study.
5. Any new medical condition (since entry into the Main Portion) or any other reason that, in the opinion of the investigator, would disqualify the subject from participation in the Extension Portion of this study.

8.4 REMOVAL AND REPLACEMENT OF SUBJECTS IN THE STUDY

8.4.1 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).

8.4.2 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 of consent
- 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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)
- Loss to follow-up

Subjects may also be withdrawn from study treatment due to unacceptable or intolerable AEs (see Section 11.1.3 for additional details).

8.4.3 REPLACEMENT OF SUBJECTS

Subjects who prematurely discontinue participation prior to the Day 84 visit may be replaced in order to obtain at least 12 evaluable subjects per treatment arm.

9 INVESTIGATIONAL MEDICINAL PRODUCTS AND TREATMENTS

9.1 STUDY TREATMENT ADMINISTRATION

9.1.1 INVESTIGATIONAL MEDICINAL PRODUCT AND MATCHING PLACEBO

The investigational medicinal product (IMP), RA101495, and the matching placebo will be supplied as a sterile, preservative-free, aqueous solution prefilled into 1 mL glass syringes with a 29 gauge, ½ inch, staked needle placed within a self-administration device. Subjects will be instructed to self-administer SC doses daily.

9.1.2 DOSING SCHEDULE

During the Main Portion of the study, all eligible subjects will be randomized 1:1:1 to receive 0.1 mg/kg RA101495, 0.3 mg/kg RA101495, or matching placebo administered SC at the Day 1 visit, which will be performed by the site staff at the study 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. An injection device will be provided for use during the Main Portion.

During the Extension Portion of the study, subjects assigned to a RA101495 treatment arm during the Main Portion of the study will continue to receive the same dose of study drug. Subjects assigned to the placebo arm during the Main Portion of the study will be randomized in a 1:1 ratio to receive daily SC doses of 0.1 mg/kg RA101495 or 0.3 mg/kg RA101495.

Following implementation of the present Amendment (v.3.0), and upon appropriate reconsent, all subjects ongoing in the Extension Portion will receive the 0.3 mg/kg dose that has been selected for the pivotal Phase 3 study (See Section 5.5.3 for details).

Dosing on study visit days should be held until QMG scoring, PK, and PD sample blood collection has 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.

9.1.3 DOSE PRESENTATION

Doses of RA101495 will be determined by a target dose and weight, accomplished using a fixed dose by weight brackets. These brackets are grouped by body weight category such that each subject will receive the no less than the target minimum dose to avoid sub-therapeutic dosing. For the 0.1 mg/kg dose, subjects will receive, at a minimum, a fixed dose of 0.1 mg/kg (range: 0.10 to 0.14 mg/kg). For the 0.3 mg/kg dose, subjects will receive a minimum dose of 0.3 mg/kg (range: 0.30 to 0.42 mg/kg). Table 2 summarizes the dose presentations for RA101495 0.1 and 0.3 mg/kg doses. Subjects who present with a higher body weight (≥ 109 kg) will be accommodated on a case-by-case basis, in consultation with the medical monitor.

Matching placebo will be provided in 2 presentations, 0.220 mL for the 0.1 mg/kg dose and 0.574 mL for the 0.3 mg/kg dose.

Table 3 RA101495 Dose Presentations by Weight Brackets

Target Dose (mg/kg)	Dose Presentation		Weight Range (kg)	Dose Range (mg/kg)
	Fill Volume	Dose		
	mL	mg		
0.1	0.150	6	≥ 43 to < 61	0.10 to 0.14
0.1	0.220	8.8	≥ 61 to < 88	0.10 to 0.14
0.1	0.310	12.4	≥ 88 to < 109	0.11 to 0.14
0.3	0.416	16.6	≥ 43 to < 56	0.30 to 0.39
0.3	0.574	23	≥ 56 to < 77	0.30 to 0.41
0.3	0.810	32.4	≥ 77 to < 109	0.30 to 0.42

9.1.3.1 MISSED DOSES

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.

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 prefilled syringes and the injection device.

9.2.2 STUDY DRUG SUPPLY, STORAGE, AND HANDLING

Investigational medicinal product (IMP) will be provided as a sterile, preservative-free, aqueous solution for injection containing 40 mg/mL of RA101495 or placebo in a [redacted] prefilled into a 1 mL glass syringe with a ½ inch, 29 gauge, staked needle. Six dosage strengths of RA101495 will be supplied as shown in Table 2.

The IMP should be stored at 2°C to 8°C at the study site. Once dispensed to subjects, the IMP may be stored at controlled 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 IMP 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. The subjects will be provided with an injection device for use during the study. The subject may inject study drug into the abdomen (preferred site), thigh, or upper arm.

All subjects will receive a study drug kit that will include prefilled syringes (pre-loaded into self-injection devices) containing study drug (according to randomization), a syringe disposal container, alcohol wipes, and adhesive dressings.

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) should be retained by the subject.

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 on the Main Portion or Final Study Visit on the Extension Portion).

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 and Table 2 for the timing of study assessments. Please also refer to Appendix 2 for study visits after Week E36 on the Extension Portion.

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-IVa), serology for AChR autoantibodies, and QMG score (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 and Table 2.

10.1.3 PRIOR AND CONCOMITANT MEDICATIONS

All prescriptions and over-the-counter medications taken during the 30 days prior to baseline (i.e., Day 1) 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. All concomitant medications necessary for the health and well-being of a subject will be permitted.

Subjects are expected to remain on stable doses of SOC therapy for gMG throughout the Main Portion of the study and through the Day E84 visit of the Extension Portion, including pyridostigmine, corticosteroids, and immunosuppressive drugs. If after that period the investigator determines that dose reduction of SOC therapy for gMG may be a reasonable course of action, dose reduction should be initiated after a study visit, and the new dosing regimen should be stable for at least 4 weeks prior to the next study visit.

Dose of standard of care treatment should not be increased during the study. Instead, rescue therapy as described in 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 concomitant medications eCRF.

10.1.3.1 RESCUE THERAPY

Subjects are expected to remain on stable doses of SOC therapy for gMG throughout the Main Portion of the study and through the Day E84 visit of the Extension Portion, including pyridostigmine, corticosteroids, or immunosuppressive drugs. If, in the opinion of the investigator, escalation of gMG therapy (i.e., 'rescue therapy') becomes necessary due to deterioration of a subject's clinical status, the subject may receive immunoglobulin or plasma exchange treatment. If such rescue therapy becomes necessary, the choice of immunoglobulin vs. plasma exchange, as well as the frequency and duration of such therapy, will be determined by the investigator. Escalation of doses of pyridostigmine, corticosteroids, or immunosuppressive drugs 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 and Table 2 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 retain 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. However, for the purpose of the primary efficacy analyses, the last observation prior to initiation of rescue therapy will be used as the final assessment (see Section 12 for details). 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 full physical examination will be performed on all subjects at the Screening visit and will include the following assessments:

- General inspection
- Examination of the injection site and draining nodes
- Head/ears/eyes/nose/throat examination
- Mucosal examination
- Cardiac examination
- Auscultation of lungs
- Abdominal examination (liver, spleen, and lower abdomen)
- Musculoskeletal assessment
- Neurological assessment

Any abnormalities found will be recorded in the eCRF.

At all other study visits, the physical examination will be symptom-directed.

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 all the subjects.

10.2.3 ELECTROCARDIOGRAM

12-lead ECGs will be assessed as normal or abnormal by the investigator; 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.

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 3 and should be performed as specified in the Time and Events Tables (Table 1 and Table 2). All laboratory samples should be collected prior to the administration of study drug at applicable visits, unless otherwise noted for PK, PD, or biomarker samples.

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

Table 4 Chemistry, Hematology, and Coagulation Analytes

Chemistry	Hematology
Alanine aminotransferase (ALT) Albumin Alkaline phosphatase (ALP) Amylase Aspartate aminotransferase (AST) Bicarbonate Bile acids Bilirubin (total, direct, and indirect) Blood urea nitrogen (BUN) Calcium Chloride Creatinine Gamma-glutamyl transferase (GGT) Glucose Lipase Potassium Sodium Total protein Uric acid	Hematocrit Hemoglobin Mean corpuscular volume (MCV) Platelet count White blood cell (WBC) count and differential (%)
	Coagulation
	International normalized ratio (INR)/prothrombin time (PT) Fibrinogen Partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT)
	Other
	C-reactive protein (CRP) Creatine phosphokinase (CPK)

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 the Time and Events Tables (Table 1 and Table 2).

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. 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 4 weeks after the last dose of study drug.

- Double-barrier birth control (e.g., male condom, female condom, diaphragm sponge, or cervical cap together with spermicidal foam/gel/film/suppository) starting at the Screening visit, throughout the study, and for 4 weeks after the last dose of study drug.
- Intrauterine contraception/device starting at the Screening visit, throughout the study, and for 4 weeks 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 4 weeks 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 assessment will be collected as specified in the Time and Events Tables (Table 1 and Table 2) in all enrolled subjects. These samples will be banked and used to investigate and characterize any ADA response over time in the general study population.

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

10.3 EFFICACY ASSESSMENTS

10.3.1 QUANTITATIVE MYASTHENIA GRAVIS SCORE

The primary efficacy endpoint is the change from baseline to Week 12 (Day 84) in QMG score. The QMG is a standardized and validated quantitative strength scoring system that was developed specifically for MG and has been used previously in clinical trials. Higher scores are representative of more severe impairment. Recent data suggest that improvements in the QMG score of 2 to 3 points may be considered clinically meaningful, depending upon disease severity [Barohn, 1998; Katzberg, 2014].

QMG evaluators must be adequately trained prior to conducting any QMG score assessments. The QMG assessment will be performed at Screening to assess subject eligibility and at each study visit according to the Time and Events Tables (Table 1 and Table 2). The QMG assessment 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) 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 QMG test.

Detailed instructions regarding the administration of the QMG test will be provided to sites.

10.3.2 OTHER EFFICACY ASSESSMENTS

Efficacy assessments will also include an evaluation of the MG-ADL, MG-QOL15r, and MG Composite assessments.

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. The MG-ADL has been shown to correlate with other validated MG outcome measures (e.g., MG-QOL15r), and a 2-point improvement in MG-ADL score is considered clinically meaningful [Wolfe, 1999; Muppidi, 2011].

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, 2010; Burns, 2016].

The MG Composite 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 MG Composite indicate more severe impairment due to the disease. A 3-point change in this instrument is considered clinically meaningful [Benatar, 2012; Sadjadi, 2012].

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

10.4 PHARMACOKINETIC ASSESSMENTS

During the Main Portion of the study, blood samples for PK analysis will be collected from all subjects at the following time points:

Day 1	Day 84	During Rescue Therapy*	
		At sites where rescue therapy is administered locally	**At sites where rescue therapy is NOT administered locally**
predose (within 1 hour before first dose of study drug)	predose (any time prior to Day 84 study drug administration)	Within 1 hour before administration of rescue therapy	Prior to administration of the first course of rescue therapy
1 hour postdose (± 30 minutes)	1 hour postdose (± 30 minutes)	For PLEX only: PK will be measured in the exchanged plasma	After administration of the last course of rescue therapy
3 hours postdose (± 30 minutes)		Within 1 hour after administration of rescue therapy	
6 hours postdose (± 90 minutes)			

* See Appendix 1 for details on PK/PD sampling during Rescue Therapy

During the Extension Portion of the study, blood samples for PK analysis will be collected from all subjects at the following time points:

During Rescue Therapy*		Week E36 *(See Appendix 2)*
At sites where rescue therapy is administered locally	**At sites where rescue therapy is NOT administered locally**	
Within 1 hour before administration of rescue therapy	Prior to administration of the first course of rescue therapy	predose (within 1 hour before first dose of study drug)
For PLEX only: PK will be measured in the exchanged plasma	After administration of the last course of rescue therapy	1 hour postdose (± 30 minutes)
Within 1 hour after administration of rescue therapy		3 hours postdose (± 30 minutes)
		6 hours postdose (± 90 minutes)

* See Appendix 1 for details on PK/PD sampling during Rescue Therapy

On all other study visit days, a single PK sample will be collected prior to administration of study drug. Plasma concentrations of RA101495 and its metabolites will be measured and reported in all subjects receiving active RA101495. All samples will be sent to a central laboratory for analysis. Detailed instructions regarding PK sample collection, processing, and shipping will be provided to sites.

10.5 PHARMACODYNAMIC ASSESSMENTS

During the Main Portion of the study, blood samples for PD analysis will be collected from all subjects at the following time points:

Day 1	Day 84	During Rescue Therapy*	
		At sites where rescue therapy is administered locally	**At sites where rescue therapy is NOT administered locally**
predose (within 1 hour before first dose of study drug)	predose (any time prior to Day 84 study drug administration)	Within 1 hour before administration of rescue therapy	Prior to administration of the first course of rescue therapy
1 hour postdose (± 30 minutes)	1 hour postdose (± 30 minutes)		
3 hours postdose (± 30 minutes)		Within 1 hour after administration of rescue therapy	After administration of the last course of rescue therapy
6 hours postdose (± 90 minutes)			

* See Appendix 1 for details on PK/PD sampling during Rescue Therapy

During the Extension Portion of the study, blood samples for PD analysis will be collected from all subjects at the following time points:

During Rescue Therapy* (ONLY through Day 167 visit)		Week E36 *(See Appendix 2)*
At sites where rescue therapy is administered locally	**At sites where rescue therapy is NOT administered locally**	
Within 1 hour before administration of rescue therapy	Prior to administration of the first course of rescue therapy	predose (within 1 hour before first dose of study drug)
For PLEX only: PK will be measured in the exchanged plasma	After administration of the last course of rescue therapy	1 hour postdose (± 30 minutes)
Within 1 hour after administration of rescue therapy		3 hours postdose (± 30 minutes)
		6 hours postdose (± 90 minutes)

* See Appendix 1 for details on PK/PD sampling during Rescue Therapy

On all other study visit days, a single PD sample will be collected prior to administration of study drug. All samples will be sent to a central laboratory for analysis. Detailed instructions regarding PD sample collection, processing, and shipping will be provided to sites.

10.6 EXPLORATORY ASSESSMENTS

10.6.1 BIOMARKERS

Blood samples for analysis of biomarkers will be collected at the following time points on Day 1: (i) predose (within 1 hour before first dose administration of study drug) and (ii) 6 hours postdose (± 90 minutes).

At all other study visits, biomarker samples will be collected prior to the administration of study drug (Table 1 and Table 2).

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 RA101495 in subjects with gMG. Complement protein levels and complement activity will be tested to evaluate response to RA101495 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 RA101495. 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.

During the Extension Portion of the study, if a subject undergoes a thymectomy, lymphadenectomy, or other surgical excision in which a biopsy was obtained, a section of the biopsy may be sent for exploratory immunohistochemical and biomarker analysis provided the subject has given their consent. Processing and preservation of the tissue should be discussed with the Sponsor prior to the intervention if possible.

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.

10.6.2 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 pharmacogenomics studies, a blood sample will be obtained at Screening. 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, DNA copy number analysis, and ribonucleic acid expression profiling], 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 11.3.

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.

11.1.3 STOPPING RULES

For all ≥ Grade 3 AEs that are considered related to study drug (except for hepatic and pancreatic AEs described in Section 11.1.3.1 and Section 11.1.3.2, respectively), study drug should be permanently discontinued.

11.1.3.1 MONITORING OF LIVER FUNCTION TESTS

All subjects will be monitored for signs and symptoms of hepatic or biliary dysfunction. LFT parameters [alkaline phosphatase (ALP), ALT, AST, gamma-glutamyl transferase (GGT), and bilirubin] will be evaluated as part of the chemistry laboratory assessments performed at each study visit, as shown in Table 1 and Table 2 (see also Table 4 for a list of chemistry analytes). The following guidelines should be followed for all subjects during study participation:

- Subjects with isolated ALT or AST elevation > 2 × ULN with no other explanation for the elevation(s): contact the medical monitor to review the case details and determine whether or not the subject should continue study treatment. The subject should be monitored until the elevated enzymes return to ≤ 2 × ULN.
- Subjects with isolated total bilirubin elevation > 2 × ULN with no other explanation for the elevation(s): contact the medical monitor to review the case details and determine whether or not the subject should continue study treatment. The subject should be monitored until the total bilirubin returns to ≤ 2 × ULN.
- Subjects with isolated ALT or AST elevations > 3 × ULN concurrently with total bilirubin elevation > 2 × ULN and a normal ALP with no other explanation for the elevation: study drug should be permanently discontinued. The medical monitor should be contacted as soon as possible to review the case. The subject should be monitored until the elevated enzymes return to Grade 1 [National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03] or lower, and the total bilirubin is ≤ 2 × ULN.

11.1.3.2 MONITORING OF PANCREATIC ENZYMES

Subjects will be monitored during the study for symptoms of pancreatitis or cholecystitis. Pancreatic enzymes (amylase and lipase) will be evaluated as part of the hematology/chemistry laboratory assessments performed at each study visit, as shown in Table 1 and Table 2 (see also Table 4 for a list of chemistry analytes). The following guidelines should be followed for all subjects during study participation:

- Subjects with elevations of amylase or lipase to NCI CTCAE (Version 4.03) Grade 3 (> 2 × ULN): study drug treatment should be interrupted. The subject should be monitored until amylase and/or lipase returns to Grade 1 or lower. The medical monitor should be contacted to review the case.
- Subjects with elevations of amylase or lipase to NCI CTCAE (Version 4.03) Grade 4 (> 5 × ULN): study drug should be permanently discontinued. The subject should be monitored until amylase and/or lipase returns to Grade 1 or lower. The medical monitor should be contacted to review the case.

11.1.3.3 MONITORING OF SKIN AND ORAL MUCOSA

Subjects should be monitored at each study visit for adverse events due to skin or oral lesions. The medical monitor should be contacted to discuss any skin or oral lesions, regardless of causality, to determine whether the subject should interrupt or discontinue study treatment. Study drug must be permanently discontinued in the event of any moderate or severe skin or oral lesions considered related to study drug (e.g., mucous membrane inflammation, oral ulceration, blistering, abrasions, and dermatitis).

11.1.3.4 INFECTION

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

To reduce the risk of infection, all subjects must have documentation of prior *Neisseria meningitidis* vaccination (and booster, if appropriate) prior to study entry. All subjects who have not been previously vaccinated will be vaccinated against *Neisseria meningitidis* at least 14 days prior to the first dose of study drug on Day 1 and should have a booster vaccination as indicated by 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, will be provided to each subject.

Any subject receiving antibiotics for suspected *Neisseria meningitidis* infection should interrupt study drug administration until *Neisseria meningitidis* infection can be ruled out. If *Neisseria meningitidis* infection is confirmed the subject should permanently discontinue study drug.

11.1.4 MONITORING OF INJECTION SITE REACTIONS

The investigator should assess the injection site (included as part of the physical examination) at each scheduled visit for:

- Pain, tenderness, erythema, and induration severity (Table 5)
  - Erythema and induration: record the maximum linear diameter
- Blisters, ulceration, necrosis: record the maximum linear diameter and severity
- Lymphadenopathy

In addition, the investigator will, whenever possible, take de-identified photos of the injection site reaction (ISR).

Table 5 Grading the Severity of Local Injection Site Reactions

Local Reaction to Injectable Product	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life Threatening)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema/ redness	2.5 to 5.0 cm	5.1 to 10.0 cm	> 10.0 cm	Necrosis or exfoliative dermatitis
Induration/ swelling	2.5 to 5.0 cm and does not interfere with activity	5.1 to 10.0 cm or interferes with activity	> 10.0 cm or prevents daily activity	Necrosis

11.2 EVALUATION AND CLASSIFICATIONS

11.2.1 SEVERITY

The investigator should determine the severity of the reported AE by using the NCI CTCAE (Version 4.03).

For any reported AE not described in the NCI 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.

11.2.2 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., ISR) 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.

11.3 RECORDING, REPORTING, AND MONITORING

11.3.1 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 11.2.1
- The relationship of the event to study treatment as defined in Section 11.2.2

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.

11.3.1.1 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, Day 84 visit, or Final Study 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 11.3.1.2 for SAE reporting instructions). This Safety Follow-up Call will only be required for subjects who choose not to participate in the Extension Portion of the study.

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., [redacted]).

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA; Version 18.0 or higher) after the eCRFs have been monitored and signed by the investigator.

11.3.1.2 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. This Safety Follow-up Call will only be required for subjects who do not participate in the Extension Portion.

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.

11.3.1.3 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 11.3.1.2. Any autopsy or other postmortem findings (including a coroner's report) should be provided if available.

11.3.1.4 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.

11.3.2 SAFETY MONITORING

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

11.3.2.1 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 RA101495.02.201, 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.

11.3.2.2 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 11.3.1.2. These SAEs should be recorded in the eCRF. Sites will call subjects 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 11.3.1.2 for SAE reporting instructions). This Safety Follow-up Call will only be required for subjects who do not participate in the Extension Portion.

11.3.3 EMERGENCY UNBLINDING DURING THE BLINDED PORTION

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.

11.4 SPECIAL CIRCUMSTANCES

11.4.1 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.

11.4.2 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 more than 1.5 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 MODIFIED ITT POPULATION

The modified ITT (mITT) Population will include all subjects in the ITT Population who have received at least 1 dose of study drug.

12.1.3 PER PROTOCOL POPULATION

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

12.1.4 SAFETY POPULATION

The Safety Population will include all subjects who have received at least 1 dose of study drug (i.e., mITT Population), with subjects to be analyzed based on the actual treatment received.

12.1.5 PHARMACOKINETIC POPULATION

The PK Population will include all subjects in mITT Population who have at least 1 evaluable PK assessment. All PK analyses will be performed using this population.

12.1.6 PHARMACODYNAMIC POPULATION

The PD Population will include all subjects in mITT Population who have at least 1 evaluable PD assessment. All PD analyses will be performed using this population.

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, number of observations above the limit of quantification (if applicable), mean, standard deviation

(SD) median, and range. Categorical variables will be summarized using frequency counts and percentages.

Once all patients have completed the Main Portion of the study, the study database will be locked, unblinded, and efficacy analyses for the Main Portion will be performed.

12.2.2 SUBJECT DISPOSITION

Disposition of all consented subjects will be provided overall and by treatment group. This will include a breakdown of subjects who consented, were randomized, were treated, discontinued treatment, and were lost to follow-up, or withdrew consent. Additionally, a summary of subjects included in the analysis populations defined in Section 12.1 will be provided.

12.2.3 DEMOGRAPHY AND BASELINE DISEASE CHARACTERISTICS

Quantitative variables will be summarized using mean, median, and range. Categorical variables will be summarized using counts and proportions.

12.2.4 SAFETY ANALYSIS

Safety analyses will be performed on the Safety Population.

12.2.4.1 ADVERSE EVENTS

AEs will be coded using the MedDRA (Version 18.0 or higher).

For each treatment group, incidence rates for TEAEs will be summarized overall, by maximum severity, and by relationship to study drug. SAEs will also be summarized by treatment group. A TEAE is defined as:

- An AE that occurs after study treatment start that was not present at the time of treatment start.
- An AE that increases in severity after treatment start, if the event was present at the time of treatment start.

AEs occurring before the first dose of study drug will be summarized separately.

12.2.4.1.1 HEPATIC ADVERSE EVENTS

Hepatic and biliary AEs will be summarized by treatment group, system organ class, and preferred term. LFT laboratory values will be summarized by changes from baseline and graded in severity using the NCI CTCAE criteria.

12.2.4.1.2 PANCREATIC ENZYME ELEVATIONS

Pancreatic AEs will be summarized by treatment group, system organ class, and preferred term. Elevations in pancreatic function parameters will be summarized by changes from baseline and graded in severity using the NCI CTCAE criteria.

12.2.4.1.3 INJECTION SITE REACTIONS

ISRs will be summarized by treatment group, system organ class, and preferred term. The summary will include additional details on these events as described in Section 11.1.4.

12.2.4.1.4 INFECTION

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

12.2.4.2 CLINICAL LABORATORY EVALUATION

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

12.2.4.3 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters [i.e., HR, PR interval, RR interval, QRS interval, QT interval, QT interval corrected by Bazett's formula (QTcB), and QT interval corrected by Fridericia's formula (QTcF)] at each assessment time point will be presented by treatment group.

12.2.4.4 VITAL SIGNS

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

12.2.4.5 PHYSICAL EXAMINATION

The complete set of physical examination findings will be provided in listings. Clinically significant physical examination abnormalities will be included and summarized as AEs, when appropriate.

12.2.5 EFFICACY ANALYSIS

Additional efficacy endpoints and analyses beyond what is specified in this protocol may be identified in the SAP.

Unless otherwise specified, if a subject receives rescue therapy (as defined in Section 10.1.3.1), efficacy endpoints occurring after rescue therapy will be imputed using last observation carried forward (LOCF) methodology using the closest non-missing endpoint value prior to the initiation of rescue therapy.

12.2.5.1 PRIMARY EFFICACY ANALYSIS

For the primary efficacy endpoint, the change from baseline to Week 12 (Day 84) in QMG score, treatment group differences will be assessed by an Analysis of Covariance (ANCOVA) model, with treatment as a factor and baseline QMG score as a covariate.

The primary efficacy analysis will be the comparison of the 0.3 mg/kg dose group versus the placebo dose group based on the ANCOVA model at a 1-sided 0.10 significance level.

The comparison of the 0.1 mg/kg dose group versus the placebo dose group will be a secondary efficacy analysis tested at the 1-sided 0.10 level. A test of linear trend for the across the 3 treatment groups will also be performed.

12.2.5.2 SECONDARY ENDPOINT ANALYSES

The secondary efficacy endpoints: Week 12 change from baseline in MG-ADL, MG-QOL15r, and MG Composite will be analyzed by an ANCOVA model similar to the primary efficacy endpoint analysis, with treatment as a factor and the corresponding baseline value as a covariate. Each of the active doses will be compared to the placebo group based on the ANCOVA model at the 1-sided 0.10 level.

For the 'Subjects with ≥ 3-point reduction in QMG score at Week 12' and 'Subjects requiring rescue therapy over the 12-week Treatment Period' secondary efficacy endpoints, the rate of subjects meeting the endpoint for each of the active treatment groups will be compared to the placebo group using a Fisher's exact test at the 1-sided 0.10 level.

12.2.6 CLINICAL PHARMACOLOGY ANALYSIS

12.2.6.1 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Drug exposure will be evaluated using PK parameters derived from non-compartmental methods. All calculations for the final analysis will be based on actual sampling times. Individual PK parameters will be presented in listings and summarized using descriptive statistics.

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

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

12.2.7 INTERIM ANALYSIS

No interim analysis is planned for the Main Portion of the study. Interim analyses during the Extension Portion of the study may be performed.

12.3 SAMPLE SIZE DETERMINATION

For the primary efficacy endpoint, change from baseline to Week 12 (Day 84) in QMG score, assuming a difference in treatment group means of 4.5, an SD of 5.0, and

12 subjects per group, the study has approximately 81% power to detect a difference between an active and placebo treatment group based on a 1-sided t-test with a 0.10 type I error rate.

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.

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 and 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 screened/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 data for this study are 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. All eCRF data required by this protocol will be recorded by investigative site personnel. All data entered into the eCRF will be supported by source documentation.

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.

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.

15 REFERENCES

Alexion Pharmaceuticals. Safety and Efficacy of Eculizumab in Refractory Generalized Myasthenia Gravis (REGAIN Study). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). [cited 2017 March 15]. Available from: https://clinicaltrials.gov/ct2/show/study/NCT01997229?term=NCT01997229&rank=1. NLM Identifier: NCT01997229.

Alexion Pharmaceuticals. (07 July 2016). New Data from Phase 3 REGAIN Study of Eculizumab (Soliris®) in Patients with Refractory Generalized Myasthenia Gravis (gMG) Presented at ICNMD Annual Congress. [Press release]. Retrieved from: http://news.alexionpharma.com/press-release/product-news/new-data-phase-3-regain-study-eculizumab-soliris-patients-refractory-gene. Accessed: 15 March 2017.

Barohn RJ, McIntire D, Herbelin L, Wolfe GI, Nations S, Bryan WW. Reliability testing of the quantitative myasthenia gravis score. *Ann N Y Acad Sci.* 1998;841:769-772.

Benatar M, Sanders DB, Burns TM, Cutter GR, Guptill JT, Baggi F, et al; Task Force on MG Study Design of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Recommendations for myasthenia gravis clinical trials. *Muscle Nerve.* 2012;45(6):909-917.

Burns, TM, Grouse CK, Conway MR, Sanders DB, and MG Composite and MG-QOL 15 study group. Construct and concurrent validation of the MG-QOL 15 in the practice setting. *Muscle Nerve.* 2010;41(2):219-226.

Burns TM, Sadjadi R, Utsugisawa K, Gwathmey KG, Joshi A, Jones S, et al.International clinimetric evaluation of the MG-QOL15, resulting in slight revision and subsequent validation of the MG-QOL15r. *Muscle Nerve.* 2016;54(6):1015-1022.

Gilhus NE. Myasthenia gravis: subgroup classification and therapeutic strategies. *Lancet Neurol*. 2015;14(10):1023-1036.

Gilhus NE. Myasthenia gravis. *N Engl J Med.* 2016;37(26):2570-2581.

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

Howard JF. Myasthenia Gravis Foundation of America. Clinical Overview of MG. Available from: http://www.myasthenia.org/HealthProfessionals/ClinicalOverviewofMG.aspx. Accessed: 28 February 2017.

Katzberg HD, Barnett C, Merkies IS, Bril V. Minimal clinically important difference in myasthenia gravis: outcomes from a randomized trial. *Muscle Nerve.* 2014;49(5):661-665.

Kusner LL, Kaminski HJ. The role of complement in experimental autoimmune myasthenia gravis. *Ann N Y Acad Sci.* 2012;1274(1):127-132.

Muppidi S, Wolfe GI, Conaway M, Burns TM; MG Composite and MG-QOL15 study group. MG ADL: still a relevant outcome measure. *Muscle Nerve.* 2011;44(5):727-731.

Ramizuddin MK. Review on: Myasthenia gravis and telithromycin-myasthenia crisis. *IOSR J Dent Med Sci*. 2014;13(7):67-97.

Sadjadi R, Conaway M, Cutter G, Sanders DB, Burns TM; MG Composite MG-QOL15 Study Group. Psychometric evaluation of the myasthenia gravis composite using Rasch analysis. *Muscle Nerve.* 2012;45(6):820-825.

Sanders DB, Wolfe GI, Benatar M, Evoli A, Gilhus NE, Illa I, et al. International consensus guidance for management of myasthenia gravis. Neurology. 2016;87(4):419-425.

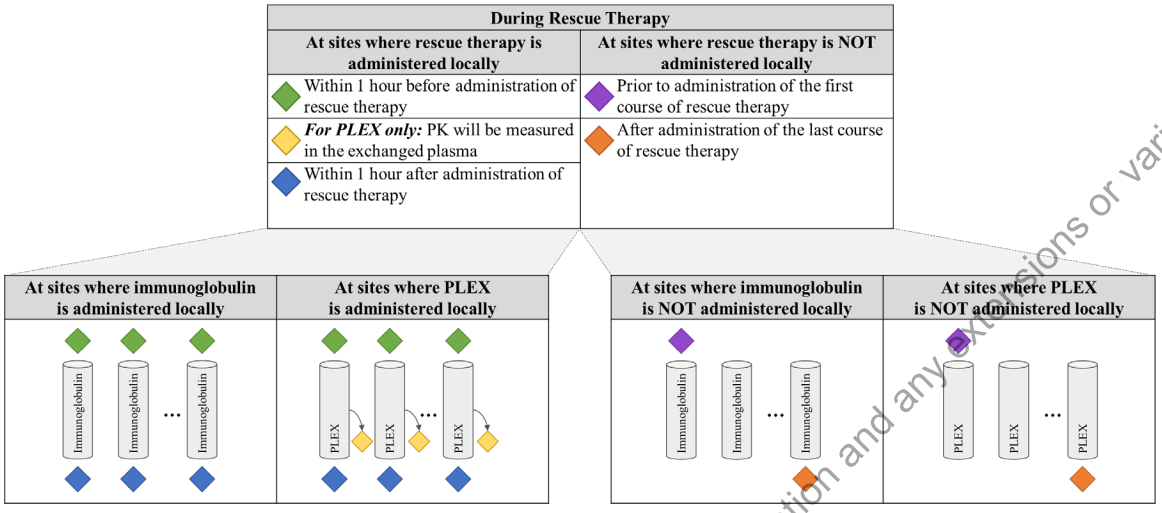
Vissing J, J. S. (2018). 'Minimal Symptom Expression' with Eculizumab in Myasthenia Gravis. *AANEM*. Washington, DC.

Wolfe GI, Herbelin L, Nations SP, Foster B, Bryan WW, Barohn RJ. Myasthenia gravis activities of daily living profile. *Neurology.* 1999;52(7):1487-1489.

Wolfe GI, Kaminski IB, Minisman G, Kuo H-C, Marx A, Strobel P, et al. Randomized trial of thymectomy in myasthenia gravis. N Engl J Med. 2016;375(6):511-522.

16 APPENDIX 1: RESCUE THERAPY PK/PD SAMPLING

Blood samples for PK and PD analysis will be obtained at the following time points during rescue therapy:



NOTE: On days when rescue therapy is concurrently administered, study drug dosing should be held until ***after*** administration of rescue therapy and PK/PD sampling

17 APPENDIX 2: EXTENSION PORTION VISITS AFTER DAY E84

Table 6 EXTENSION PORTION: Time and Events after Day E84 through Week E36

Nominal Visit relative to Main Portion			Week 28	Week 32	Week 36	Week 40	Week 44	Week 48		
Nominal Visit on Extension Portion			Week E16 (± 7 days)	Week E20 (± 7 days)	Week E24 (± 7 days)	Week E28 (± 7 days)	Week E32 (± 7 days)	Week E36 (± 7 days)	Rescue Therapy Visit[a] (*if applicable*)	Final Study Visit[b]
Study Procedure										
Weight					X			X		X
Prior and concomitant medications			X	X	X	X	X	X	X	X
Safety										
Physical examination (symptom directed)					X			X	X	X
Vital signs[c]					X			X	X	X
12-Lead electrocardiogram								X	X	X
Neisseria meningitidis vaccination[d]			SOC[d]	SOC[d]	SOC[d]	SOC[d]	SOC[d]	SOC[d]		
Hematology/Chemistry[e]					X			X	X	X
Coagulation[f]					X			X	X	X
Urinalysis					X			X	X	X
Pregnancy test[g]					X			X		X
Adverse events[h]			X	X	X	X	X	X	X	X
Anti-drug antibody					X			X	X	X
Efficacy[m]										
QMG Test/Score[i]					X			X	X	X
MG-ADL					X			X	X	X
MG-QOL15r					X			X	X	X
MG Composite					X			X	X	X
Pharmacokinetic/Pharmacodynamic										
RA101495 plasma PK[j]					X			X[j]	X[j]	X
Pharmacodynamic analysis[j]					X			X[j]	X[j]	X
Exploratory										
Additional biomarker samples[k]					X			X		X
Study Drug										
RA101495 administration[l]			X	X	X[l]	X	X	X[l]	X[l]	X[l]

See footnotes on following page.

6-a. 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.

6-b. If a subject discontinues study drug treatment at any time during the Extension Period, the subject should return to clinic for a Final Study Visit.

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

6-d. During the Extension Portion, all subjects should have *Neisseria meningitidis* booster vaccinations as indicated by SOC. Subjects should bring their patient safety card to every study visit. If the subject does not bring their card with them they will be given a new one.

6-e. All laboratory samples should be obtained prior to administration of study drug at applicable visits unless otherwise noted for PK, PD, and biomarker samples.

6-f. Coagulation tests should be performed only in subjects who are receiving anticoagulant therapy.

6-g. Urine pregnancy tests will be conducted in female subjects of childbearing potential.

6-h. 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.

6-i. The assessment of QMG 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) 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 QMG test.

6-j. Blood samples for PK and PD analysis will be obtained at the following time points:

Week E36 ***Approximately 1 year (48 weeks) after Day 1***	**During Rescue Therapy**	
	At sites where rescue therapy is administered locally	**At sites where rescue therapy is NOT administered locally**
predose (within 1 hour before study drug dosing)	Within 1 hour before administration of rescue therapy	Prior to administration of the first course of rescue therapy
1 hour postdose (± 30 minutes)	For PLEX only: PK will be measured in the exchanged plasma	After administration of the last course of rescue therapy
3 hours postdose (± 30 minutes)	Within 1 hour after administration of rescue therapy	
6 hours postdose (± 90 minutes)		

On all other study visit days, PK/PD samples should be collected prior to administration of study drug.

6-k. Biomarkers samples should be collected prior to administration of study drug.

6-l. Dosing on study visit days should be held until QMG scoring, PK, and PD sample blood collection has 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.

6-m. If a subject consents to the Open Label Portion of the study, the subject will be required to complete the QMG, MG-ADL, MG-QOL15r, and MGC assessments, even if their visit lands on a monthly visit.

Table 7 EXTENSION PORTION: Time and Events for each year after Week E36

The table below provides an example for a year's visit schedule on the Extension Portion after Week E36.
11 monthly visits (4-week months) followed by a yearly visit and will be repeated each year (48-week year) on the Extension Portion.
After Week E84, subjects will return to the study site monthly for study drug dispensation.

Nominal Visit relative to Main Portion	Week 52	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80	Week 84	Week 88	Week 92	Week 96		
	Monthly Visits											Yearly Visit		
Nominal Visit on Extension Portion / Study Procedure	Week E40 (± 7 days)	Week E44 (± 7 days)	Week E48 (± 7 days)	Week E52 (± 7 days)	Week E56 (± 7 days)	Week E60 (± 7 days)	Week E64 (± 7 days)	Week E68 (± 7 days)	Week E72 (± 7 days)	Week E76 (± 7 days)	Week E80 (± 7 days)	Week E84 (± 7 days)	Rescue Therapy Visit[a] (*if applicable*)	Final Study Visit[b]
Weight			X			X			X			X		X
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety														
Physical examination (symptom directed)			X			X			X			X	X	X
Vital signs[c]			X			X			X			X	X	X
12-Lead electrocardiogram												X	X	X
Neisseria meningitidis vaccination[d]	SOC[d]	SOC[d]	SOC[d]	SOC[d]	SOC[d]	SOC[d]	SOC[d]	SOC[d]	SOC[d]	SOC[d]	SOC[d]	SOC[d]		
Hematology/Chemistry[e]			X			X			X			X	X	X
Coagulation[f]			X			X			X			X	X	X
Urinalysis			X			X			X			X	X	X
Pregnancy test[g]			X			X			X			X		X
Adverse events[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-drug antibody												X	X	X
Efficacy[m]														
QMG Test/Score[i]			X			X			X			X	X	X
MG-ADL			X			X			X			X	X	X
MG-QOL15r			X			X			X			X	X	X
MG Composite			X			X			X			X	X	X
Pharmacokinetic/Pharmacodynamic														
RA101495 plasma PK[j]												X[j]	X[j]	X
Pharmacodynamic analysis[j]												X[j]	X[j]	X
Exploratory														
Additional biomarker samples[k]												X		X
Study Drug														
RA101495 administration[l]	X	X	X	X	X	X	X	X	X	X	X	X[l]	X[l]	X[l]

See footnotes on following page.

7-a. 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.

7-b. If a subject discontinues study drug treatment at any time during the Extension Period, the subject should return to clinic for a Final Study Visit.

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

7-d. During the Extension Portion, all subjects should have *Neisseria meningitidis* booster vaccinations as indicated by SOC. Subjects should bring their patient safety card to every study visit. If the subject does not bring their card with them they will be given a new one.

7-e. All laboratory samples should be obtained prior to administration of study drug at applicable visits unless otherwise noted for PK, PD, and biomarker samples.

7-f. Coagulation tests should be performed only in subjects who are receiving anticoagulant therapy.

7-g. Urine pregnancy tests will be conducted in female subjects of childbearing potential.

7-h. 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.

7-i. The assessment of QMG 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) 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 QMG test.

7-j. Blood samples for PK and PD analysis will be obtained at the following time points:

Yearly Visit (e.g., Week E84)	During Rescue Therapy	
	At sites where rescue therapy is administered locally	At sites where rescue therapy is NOT administered locally
predose (within 1 hour before study drug dosing)	Within 1 hour before administration of rescue therapy	Prior to administration of the first course of rescue therapy
	For PLEX only: PK will be measured in the exchanged plasma	After administration of the last course of rescue therapy
	Within 1 hour after administration of rescue therapy	

On all other study visit days, PK/PD samples should be collected prior to administration of study drug.

7-k. Biomarkers samples should be collected prior to administration of study drug.

7-l. Dosing on study visit days should be held until QMG scoring, PK, and PD sample blood collection has 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.

7-m. If a subject consents to the Open Label Portion of the study, the subject will be required to complete the QMG, MG-ADL, MG-QOL15r, and MGC assessments, even if their visit lands on a monthly visit.