RA PHARMACEUTICALS, INC.

STATISTICAL ANALYSIS PLAN

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

RA101495-02.201

Statistical Analysis Plan Version:	Date of Statistical Analysis Plan:
Version 1.0	05Nov2018
Version 2.0	05Mar2020

SIGNATURE PAGE

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DOCUMENT HISTORY

Version	Author	Description
1.0	[redacted]	Original Version
2.0	[redacted]	Updated to include Extension Period analyses in appendix

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LIST OF ABBREVIATIONS

Abbreviation	Full Term
ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
aPTT/APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
C5	complement component 5
cm	centimeter
C_{max}	maximum plasma concentration
CPK	creatine phosphokinase
CRP	C-reactive protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
eCRF	electronic case report form
GGT	gamma-glutamyl transferase
HR	heart rate
ICF	informed consent form
ICH	International Conference on Harmonization
INR	international normalized ratio
ISR	injection site reaction
ITT	intent-to-treat
kg	kilogram
LOCF	last observation carried forward
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MG-ADL	myasthenia gravis activities of daily living
mg	milligram
mITT	modified intent-to-treat
MMRM	mixed model repeated measures
NCI	National Cancer Institute
PD	pharmacodynamics
PK	pharmacokinetics

PNH	paroxysmal nocturnal hemoglobinuria
PT	prothrombin time
PT	preferred term
PTT	partial thromboplastin time
QMG	quantitative myasthenia gravis
QOL	quality of life
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneously
SOC	system organ class
sRBC	sheep red blood cell
TEAE	treatment-emergent adverse event
t_{max}	time to corresponding Cmax
ULN	upper limit of normal
WBC	white blood cell

1 INTRODUCTION

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

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.

This Statistical Analysis Plan (SAP) describes data-handling and statistical procedures to be used for the analysis and reporting of efficacy and safety data collected under Study RA101495-02.201 (version 2.0 19 October 2017) and presented in the clinical study report (CSR). The methods are based on those presented in Section 12 of the study protocol. Any post-hoc or exploratory analyses not specified in this SAP will be identified as such when they are presented in the CSR. This SAP has been developed and finalized prior to locking the clinical database for the Main Portion of the study.

The analyses involving the Main Portion and the first 12 Weeks of the Extension Portion (i.e., through study day E84) will be included in the main section of this SAP document. Analyses involving the whole study, including the entire open-label Extension Portion beyond study day E84 will be in the appendix of this document. The reason for the analyses being separated into two distinct sections of the SAP document is to allow for the analysis methods relating to the randomized double-blind portion of the study to be finalized while allowing for future modifications to the analyses of the open-label Extension Portion (note: this method is consistent with the study protocol in that the schedule of assessments after day E84 is in the Protocol Appendix).

This SAP was written in accordance with the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled “Guidance for Industry: Statistical Principles for Clinical Trials” and the most recent ICH-E3 Guideline, entitled “Guidance for Industry: Structure and Content of Clinical Study Reports.”

2 STUDY SUMMARY

2.1 STUDY 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

2.2 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).

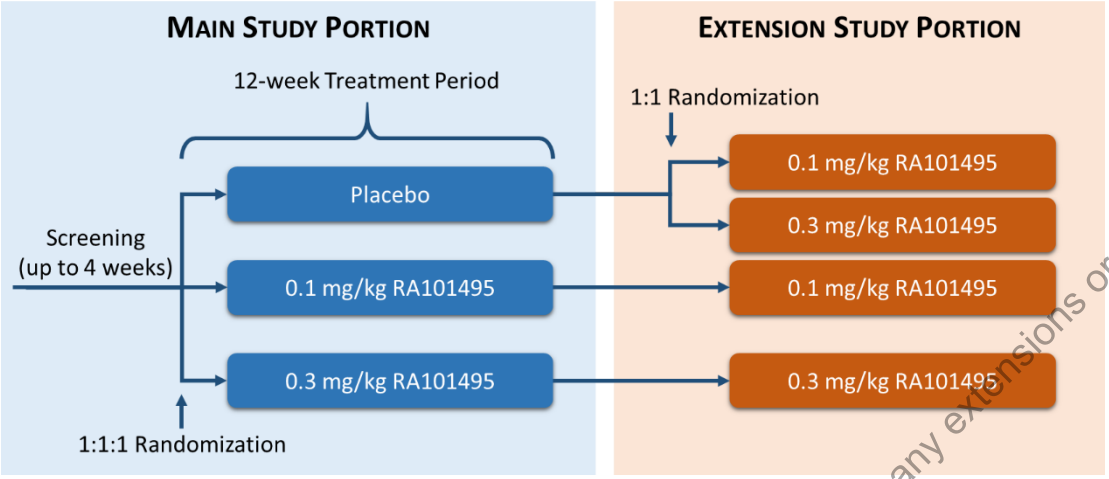
The Main Portion of the study includes a Screening Period of up to 4 weeks and a 12-week Treatment Period (Figure 1). During the Treatment Period, subjects will return to the clinic weekly for the first 2 visits (Day 8 and Day 15) after the Day 1 visit, followed by visits at Week 4 (Day 29), Week 8 (Day 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, 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. A single-use, disposable, injection device will be provided for use during the study.

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 (Protocol 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. Assessments and visits during the first 12 weeks of the Extension Portion will be identical to the 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.

Figure 1 provides an illustration of the study design.

Figure 1: Design of RA101495-02.201



2.2.1 Number of Subjects

Approximately 36 subjects will be randomized (i.e., 12 per treatment arm):

2.2.2 Randomization and Blinding Procedures

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).

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. This randomization will occur at the screening visit when the subject is initially randomized to the Main Portion of the study.

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.

The procedure for emergency unblinding of study drug treatment for an individual subject is discussed in protocol section 11.3.3.

2.3 Safety Assessments

Safety assessments will include physical examinations, vital signs, ECGs, clinical laboratory tests, AEs, and immunogenicity.

2.3.1 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 electronic case report form (eCRF).

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

2.3.2 Vital Signs

Vital signs (Heart Rate (HR), body temperature, and blood pressure) will be measured in the sitting position. 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.

2.3.3 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.

2.3.4 Laboratory 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.

2.3.4.1 Hematology, Chemistry, and Coagulation

Hematology, chemistry, and coagulation analytes that will be assessed during the study are identified in Table 1. Coagulation tests should only be performed in subjects receiving anticoagulant therapy.

Table 1: Clinical Chemistry, Hematology, and Coagulation Analytes

Clinical 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 (%) • basophils • eosinophils • lymphocytes • monocytes • neutrophils
	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)

2.3.4.2 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.

2.3.4.3 Pregnancy Test

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 9 and Table 10).

2.3.5 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 had been scheduled prior to study participation (i.e., signing of the informed consent form (ICF))

A serious adverse event (SAE) is any untoward medical occurrence 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 scheduled prior to study participation (i.e., signing of the ICF) should not be reported as SAEs.

2.3.6 Immunogenicity

Blood samples for anti-drug antibody (ADA) assessment will be collected as specified in the Time and Events Tables (Table 9 and Table 10) 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.

2.4 Efficacy Assessments

2.4.1 Quantitative Myasthenia Gravis Score

The primary efficacy assessment is the Quantitative Myasthenia Gravis (QMG) score. The QMG is a standardized and validated quantitative muscle strength scoring system that was developed specifically for MG and has been used widely in prior 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].

Table 2 presents the scoring scale for the 13 individual assessments, each scored on a 0-3 point scale (i.e., 0=none, 1=mild, 2=moderate, and 3=severe). The total score is the sum of the individual scores; range 0 – 39.

If a subject is missing a response for one of the 13 individual QMG items, the subject's corresponding item score from the previously scheduled QMG assessment will be imputed for the missing item score (and the total score calculated using this imputed value and the non-missing item scores). If the item response is also missing from the previously scheduled QMG, the QMG total score will be set to missing for that visit. If the subject is missing responses to more than one of the 13 items, the QMG total score will be set to missing for that visit (note: the LOCF algorithm will still be applied, as appropriate).

2.4.2 Myasthenia Gravis Activities of Daily Living Score

The MG-ADL is a brief 8-item survey designed to evaluate MG symptom severity. Higher scores are associated with more severe symptoms of MG. 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].

Table 3 presents the 8 items with corresponding response scale, each scored on a 0 – 3 point scale (i.e., 0=none, 1=mild, 2=moderate, and 3=severe). The total score is the sum of the 8 individual scores; range 0 – 24.

If a subject is missing a response for one of the 8 individual MG-ADL items, the subject's corresponding item score from the previously scheduled MG-ADL assessment will be imputed for the missing item score (and the total score calculated using this imputed value and the non-missing item scores). If the item response is also missing from the previously scheduled MG-ADL, the MG-ADL total score will be set to missing for that visit. If the subject is missing responses to more than one of the 8 items, the MG-ADL total score will be set to missing for that visit (note: the LOCF algorithm will still be applied, as appropriate).

2.4.3 Myasthenia Gravis Quality of Life

The MG-QOL15r is a 15-item survey that was designed to assess quality of life in subjects with MG. Higher scores indicate more severe impact of the disease on aspects of the subject's life [Burns, 2010; Burns, 2016].

The following are the 15 questions and the corresponding response scales, each scored on a 0-2 point scale (0=Not much at all, 1=Somewhat, 2=Very Much).

1. I'm frustrated by my myasthenia gravis.
2. I have trouble using my eyes because of my myasthenia gravis.
3. I have trouble eating because of my myasthenia gravis.
4. I have limited my social activity because of my myasthenia gravis.
5. My myasthenia gravis limits my ability to enjoy hobbies and activities.
6. I have trouble meeting the needs of my family because of my myasthenia gravis.
7. I have to make plans around my myasthenia gravis.
8. My occupational skills and job status have been negatively affected by my myasthenia gravis.
9. I have difficulty speaking due to my myasthenia gravis.
10. I have trouble driving due to my myasthenia gravis.
11. I am depressed about my myasthenia gravis
12. I have trouble walking due to my myasthenia gravis
13. I have trouble getting around public places because of my myasthenia gravis.
14. I feel overwhelmed by my myasthenia gravis.
15. I have trouble performing my personal grooming needs because of myasthenia gravis.

The MG-QOL15r total score is the sum of the 15 individual item scores with a range of 0 – 30.

If a subject is missing a response for one of the 15 individual MG-QOL15r items, the subject's corresponding item score from the previously scheduled MG-QOL15r assessment will be imputed for the missing item score (and the total score calculated using this imputed value and the non-missing item scores). If the item response is also missing from the previously scheduled MG-QOL15r, the MG-QOL15r total score will be set to missing for that visit. If the subject is missing responses to more than one of the 10 items, the MG-QOL15r total score will be set to missing for that visit (note: the LOCF algorithm will still be applied, as appropriate).

2.4.4 MG Composite

The MG Composite is a 10-item scale that has been used to measure the clinical status of subjects 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].

Table 4 presents the 10 items with corresponding response scale scores. The total score is the sum of the 10 individual scores; range 0 – 50.

If a subject is missing a response for one of the 10 individual MG Composite items, the subject's corresponding item score from the previously scheduled MG Composite assessment will be imputed for the missing item score (and the total score calculated using this imputed value and the non-missing item scores). If the item response is also missing from the previously scheduled MG Composite assessment, the MG Composite total score will be set to missing for that visit. If the subject is missing responses to more than one of the 10 items, the MG Composite total score will be set to missing for that visit (note: the LOCF algorithm will still be applied, as appropriate).

Table 2: QMG Items and Scoring

* Circle as appropriate

Test Item		Measured value, if applicable	Grade				
			None 0	Mild 1	Moderate 2	Severe 3	Score (0-3)
1.	Double vision on lateral gaze *right / left / both *glasses removed: Y / N / NA	____ seconds	≥61	11-60	1-10	Spontaneous	
2.	Ptosis (upward gaze)	____ seconds	≥61	11-60	1-10	Spontaneous	
3.	Facial Muscles	NA	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete	
4.	Swallowing 4oz. (½ cup) water	NA	Normal	Minimal coughing or throat clearing	Severe coughing/choking or nasal regurgitation	Cannot swallow (test not attempted)	
5.	Speech after counting aloud from #1 to 50	Number ____	None at #50	Dysarthria at #30-49	Dysarthria at #10-29	Dysarthria at 9	
6.	Right arm outstretched (90°, sitting, away from back of chair)	____ seconds	240	90-239	10-89	0-9	
7.	Left arm outstretched (90°, sitting, away from back of chair)	____ seconds	240	90-239	10-89	0-9	

8.	Forced vital capacity FVC % predicted [%p] FVC [L]	Best of 3-5 attempts _____ %p _____ FVC [L] Normal Range used: NHANES III	≥80%	65-79%	50-64%	<50%	
9.	Right hand grip Men Women	*Setting: 2 3 ____ kg	 ≥45 ≥30	 15-44 10-29	 5-14 5-9	 0-4 0-4	
10.	Left hand grip Men Women	*Setting: 2 3 ____ kg	 ≥35 ≥25	 15-34 10-24	 5-14 5-9	 0-4 0-4	
11.	Head, lifted (45°, supine)	____ seconds	120	30-119	1-29	0	
12.	Right leg outstretched (45°, supine)	____ seconds	100	31-99	1-30	0	
13.	Left leg outstretched (45°, supine)	____ seconds	100	31-99	1-30	0	

Table 3: MG-ADL Items and Scoring

Grade	0	1	2	3	Score
Talking	Normal	Intermittent slurring of nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	

Total score _____

Table 4: MG-Composite Assessments and Scoring

		Item	Seconds, if applicable					Score
Transcribe from QMG	1.	Ptosis upward ease, seconds (physician examination)	____ seconds	>45 seconds =0	11-45 =1	1-10 =2	Immediate =3	
	2.	Double vision on lateral gaze left/right/both, seconds (physical examination)	____ seconds	>45 seconds =0	11-45 =1	1-10 =3	Immediate =4	
	3.	Eye closure (physician examination)	NA	Normal =0	Mild weakness (can be forced open with effort) =0	Moderate weakness (can be forced open easily) =1	Severe weakness (unable to keep eye closed) =2	
Transcribe from MG-ADL	4.	Talking (patient history)	NA	Normal =0	Intermittent slurring or nasal speech =2	Constant slurring or nasal but can be understood = 4	Difficult to understand speech =6	
	5.	Chewing (patient history)	NA	Normal =0	Fatigue with solid food =2	Fatigue with soft food =4	Gastric tube =6	
	6.	Swallowing (patient history)	NA	Normal =0	Rare episode of choking or trouble swallowing =2	Frequent trouble swallowing =5	Gastric Tube =6	

	7.	Breathing thought to be caused by MG (patient history)	NA	Normal =0	Shortness of breath with exertion =2	Shortness of breath at rest =4	Ventilator dependence =9	
	8.	Neck flexion or extension (weakest) (physician examination)	NA	Normal =0	Mild weakness =1	Moderate weakness =3	Severe weakness =4	
	9.	Shoulder abduction (physician examination)	NA	Normal =0	Mild weakness =2	Moderate weakness =4	Severe weakness =5	
	10.	Hip Flexion (physician examination)	NA	Normal =0	Mild weakness =2	Moderate weakness =4	Severe weakness =5	

2.5 Pharmacokinetic Assessments

The following are the Pharmacokinetic (PK) endpoints:

- 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
- Ratio of parent to metabolites (i.e., 2 metabolites).

Table 5 and Table 6 present the schedule of PK blood samples for the Main Portion and Extension Portion, respectively.

Table 5: Main Portion: Pharmacokinetic Schedule of Assessments

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)			

Table 6: Extension Portion: Pharmacokinetic Schedule of Assessments

During Rescue Therapy*		Week E36 *(see Study Protocol 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)

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 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.

2.6 Pharmacodynamic Assessments

The following are the Pharmacodynamic assessments:

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

Table 7 and Table 8 present the schedule of Pharmacodynamic (PD) blood samples for the Main Portion and Extension Portion, respectively.

Table 7: Main Portion: Pharmacodynamic Schedule of Assessments

<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 rowspan="3">Within 1 hour after administration of rescue therapy</td><td rowspan="3">After administration of the last course of rescue therapy</td></tr>
<tr><td>3 hours postdose
(± 30 minutes)</td></tr>
<tr><td>6 hours postdose
(± 90 minutes)</td></tr>
</table>

Table 8: Extension Portion: Pharmacodynamic Schedule of Assessments

<table>
<tr><th colspan="2">During Rescue Therapy*
(ONLY through Day 167 visit)</th><th rowspan="2">Week E36
(see Study Protocol Appendix 2)</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>Within 1 hour before administration of rescue therapy</td><td>Prior to administration of the first course of rescue therapy</td><td>predose (within 1 hour before first dose of study drug)</td></tr>
<tr><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><td>1 hour postdose (± 30 minutes)</td></tr>
<tr><td rowspan="2">Within 1 hour after administration of rescue therapy</td><td>3 hours postdose (± 30 minutes)</td></tr>
<tr><td>6 hours postdose (± 90 minutes)</td></tr>
</table>

2.7 Rescue Therapy

Subjects are expected to remain on stable doses of standard of care 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.

A Rescue Therapy Visit should be performed prior to initiation of rescue therapy (see Table 9 and Table 10 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.

2.8 Schedule of Assessments

The following are the time and events tables for the Main Portion (Table 9) and the Extension Portion (Table 10).

Table 9: 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 Protocol 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 10: 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 **Study Protocol Appendix 2**	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 Protocol 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 Protocol 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.
NOTE: For those subjects that consent to the Extension Portion an additional blood sample for biomarker testing will be taken at 6 hours postdose (± 90 minutes) on Day 84.

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.

3 STATISTICAL METHODS

3.1 General Methods

3.1.1 Computing Environment

All statistical analyses will be performed using SAS® Version 9.1.3 or higher for Windows.

3.1.2 Reporting of Numerical Values

All clinical study data will be presented in subject data listings. Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be calculated by treatment group for continuous variables. Confidence intervals will be provided where appropriate. For continuous endpoints, the confidence interval for the mean will be based on the t-distribution (e.g., CLM in the SAS Proc Means procedure).

Frequencies and percentages will be presented by treatment group for categorical and ordinal variables. If there are missing values, the number of missing values will be presented, but without a percentage and the number of non-missing values used as the denominator.

Means, medians, standard deviations, and confidence intervals will be reported to one decimal place more than the data reported on the CRF or by the laboratory/vendor. Minimum and maximum will be reported to the same number of decimal places displayed on the CRF or by the laboratory/vendor. P-values will be reported to 4 decimal places.

3.1.3 Baseline Value and Change from Baseline

Unless otherwise specified, for the Main Portion analyses, the baseline value is defined as the most recent non-missing value obtained prior to the subject receiving the first dose of study drug. For most endpoints this will be the Day 1 visit assessment.

For analyses which include the Extension Portion, some analyses may utilize a "baseline" defined as the value obtained prior to receiving the first administration of RA101495 (i.e., first dose of active treatment). For subjects who received RA101495 during the Main Portion, the baseline remains the same, the most recent non-missing value obtained prior to the subject receiving the first dose of study drug. For subjects who received placebo in the Main Portion, the value obtained prior to receiving the first administration of RA101495 will generally occur on the Day E1 (Day 84) visit, and will be the baseline value.

The cases where baseline is defined as the value obtained immediately prior to receiving the first administration of RA101495 will be explicitly defined.

3.2 Handling of Missing Values

3.2.1 Efficacy Endpoints: Main Portion

The primary method for handling missing data in the efficacy analyses will be last observation carried forward (LOCF). For the LOCF algorithm, if a patient is missing a value, the closest non-missing endpoint value prior to the missing value will be imputed for the missing value (note: this includes the baseline value and values from unscheduled visits).

Additionally, if a subject receives rescue therapy (see Section 2.7), efficacy endpoints occurring after rescue therapy will be censored and imputed using the LOCF method. The LOCF method is such that the closest non-missing endpoint value prior to the initiation of rescue therapy will be imputed, (note: this includes the baseline value and values from unscheduled visits).

For selected efficacy endpoints, observed case analyses will be presented as a sensitivity analysis.

- Observed Case Method: analyses censoring observations post-rescue therapy medication. Observations occurring post-rescue therapy will be censored and not imputed. Otherwise, missing values will not be imputed. Note that the imputation of individual efficacy assessment items to create a total score, as discussed in Section 2.4 will still be applied in the Observed Case Method.

3.2.2 Efficacy Endpoints: Extension Portion

For analyses which involve the Extension Portion (i.e., analyses of the Extension Period data or analyses combining the Main and Extension Periods), the following methods will be applied to the Extension Portion efficacy analyses:

- LOCF method in Extension Period:

  If a subject is missing values for a scheduled assessment the subject's previous non-missing value will be imputed (note: this includes the baseline value and values from unscheduled visits).

  Handling of Values Post-Rescue Medication Use:

  If the subject was in one of the active treatment groups in the Main Portion of the study:

  - If the subject had received rescue medication in the Main Portion of the study (see Section 2.7), then the subject will continue to have post-rescue medication observations censored and imputed using LOCF method in the Extension Period.

    If the subject had not received rescue medication in the Main Portion of the study but receives rescue medication in the Extension Period, the post-rescue medication observations will be censored and imputed

via LOCF method (i.e., using the methodology described in Section 3.2.1).

If the subject was in the placebo treatment group in the Main Portion of the study:

- If the subject had received rescue medication in the Main Portion of the study (see Section 2.7), the subject will stop having the post-rescue medication observations censored after, but not including, the Day 84 visit (i.e., LOCF in the Main Portion will not carry over into the Extension Portion).

  If the subject receives rescue medication in the Extension Period, the post-rescue medication observations will be censored and imputed via LOCF method (i.e., using the methodology described in Section 3.2.1).

- Observed Case Method in Extension Portion:
  Missing values will not be imputed, and analyses will be performed on the observed cases (with the exception of observations occurring post-rescue medication use). Note that the imputation of individual efficacy assessment items to create a total score, as discussed in Section 2.4, will still be applied in the Observed Case Method.

  Handling of Values Post-Rescue Medication Use:

  If the subject was in one of the active treatment groups in the Main Portion of the study:

  - If the subject had received rescue medication in the Main Portion of the study (see Section 2.7), then the subject will continue to have post-rescue medication observations censored in the Extension Period.

    If the subject had not received rescue medication in the Main Portion of the study but receives rescue medication in the Extension Period, the post-rescue medication observations will be censored.

  If the subject was in the placebo treatment group in the Main Portion of the study:

  - If the subject had received rescue medication in the Main Portion of the study (see Section 2.7), the subject will stop having the post-rescue medication observations censored after, but not including, the Day 84 visit (i.e., the censoring of observations in the Main Portion will not carry over into the Extension Portion).

If the subject receives rescue medication in the Extension Period, the post-rescue medication observations will be censored.

3.2.3 Safety, PK and PD Endpoints

Missing data for safety, PK, and PD endpoints will not be imputed; observed cases will be used. This will include observations occurring after a subject receives rescue-medication.

3.3 Analysis Populations

Analysis populations in this study are defined in the sections that follow. If any of the analysis populations are identical, duplicate results may not be presented for the identical populations.

3.3.1 Intention-to-Treat Population

The Intention-to-Treat (ITT) Population will include all randomized subjects. ITT population analyses will be based on the randomized treatment.

3.3.2 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. mITT population analyses will be based on the randomized treatment.

3.3.3 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 during the 12-week Treatment Period.

If, in the Main Portion of the study, a patient received multiple doses of different study drug levels (i.e., placebo, 0.1 mg/kg, and 0.3 mg/kg), the patient will be assigned to the dose group which they received at the highest frequency within the Main Portion of the study.

Similarly, if in the Extension Portion of the study, a patient received multiple doses of different study drug levels (i.e., 0.1 mg/kg, and 0.3 mg/kg), the patient will be assigned to the dose group which they received at the highest frequency within the Extension Portion of the study.

3.3.4 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.

If, in the Main Portion of the study, a patient received multiple doses of different study drug levels (i.e., placebo, 0.1 mg/kg, and 0.3 mg/kg), the patient will be assigned to the dose group which they received at the highest frequency within the Main Portion of the study.

Similarly, if in the Extension Portion of the study, a patient received multiple doses of different study drug levels (i.e., 0.1 mg/kg, and 0.3 mg/kg), the patient will be assigned to the dose group which they received at the highest frequency within the Extension Portion of the study.

3.3.5 RA101495 Safety Population

The RA101495 Safety Population will include all subjects who are assigned to an active treatment group in the Main Portion of the study in the Safety Population or received at least 1 dose of RA10495 in the Extension Portion (i.e., this population would not include subjects who, in the Safety Population, were assigned to the placebo group in the Main Portion and dropped out of the study prior to receiving RA101495).

If, in the Main Portion of the study, a patient received multiple doses of different study drug levels (i.e., placebo, 0.1 mg/kg, and 0.3 mg/kg), the patient will be assigned to the dose group which they received at the highest frequency within the Main Portion of the study.

Similarly, if in the Extension Portion of the study, a patient received multiple doses of different study drug levels (i.e., 0.1 mg/kg, and 0.3 mg/kg), the patient will be assigned to the dose group which they received at the highest frequency within the Extension Portion of the study.

3.3.6 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.

3.3.7 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.

3.4 Combining RA101495 Data Across Study Portions

For many of the efficacy and safety endpoints, the data from the Main Portion and the Extension Portion will be combined and summarized. Specifically, the Main Portion data for subjects in the 0.1 mg/kg dose group will be combined with the Extension Portion data for subjects in the placebo−0.1 mg/kg group (i.e., subjects in the placebo group for the Main Portion who receive 0.1 mg/kg in the Extension Portion). For the efficacy and safety data, the schedule of assessments between the Main Portion and Extension Portion are such that the scheduled assessments match up as is indicated by the “E1”, “E8”,…,“E84” naming convention used for the Extension Portion visit

dates (see Table 10). The same combining of data procedure will be applied to the 0.3 mg/kg dose group as well.

In these analyses, the baseline value for the subjects where the data is coming from the Extension Portion, will be the value obtained prior to receiving first administration of RA101495 (see Section 3.1.3).

3.5 Efficacy Endpoints

The following are the primary and secondary efficacy endpoints. For these endpoints baseline will be based on Day 1 value.

3.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline to Week 12 (Day 84) in QMG score.

3.5.2 Secondary Efficacy Endpoints

The key secondary efficacy endpoint is change from baseline to Week 12 in the MG-ADL scale.

Additional secondary efficacy endpoints are:

- Change from baseline to Week 12 in the MG-ADL scale
- Minimal symptom expression at Week 12, defined as an MG-ADL scale score of 0 or 1
- 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
- A ≥ 3-point reduction in QMG score at Week 12
- Requiring rescue therapy over the 12-week Treatment Period.

3.6 Pharmacodynamic Endpoints

The PD assessments are:

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

3.7 Exploratory Endpoints

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

- Responder analysis for changes in QMG, MG-ADL, MG-QOL, and MG-Composite Scores from baseline to Week 12.
- Functional sub-scores of the QMG, MG-ADL, MG-QOL, and MG-Composite scores

- Items for the functional scales are defined in Table 11. The functional sub-score for a subject is defined as the total score of the corresponding items (or the value of the item if it is a single score).

Table 11: Functional Sub-Scores

	Scales			
Function	QMG	MG ADL	QOL	MG Composite
Ocular	1-3	7-8	2	1-3
Bulbar	4-5	1-3	3, 9	4-6
Respiratory	8	4		7
Limb/Axial	6-7, 9-13	5-6	12, 15	8-10

If an item response has a missing value, the methods defined in Section 2.4 for imputing missing values will be used. Specifically, if a subject is missing a response for one of the items, the subject's corresponding item score from the previously scheduled assessment will be imputed for the missing item score (and the total score calculated using this imputed value and the non-missing item scores). If the item response is also missing from the previously scheduled assessment, the corresponding function sub-score will be set to missing.

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

- Pharmacogenomic analyses (optional)

3.8 Patient Disposition and Evaluability

3.8.1 Patient Disposition

A disposition of all randomized subjects will be provided. This will include the number and percentage of subjects evaluated for each of the analysis populations (Section 3.3), which will be presented by treatment group and overall. Percentages will be based on the number of subjects in the ITT population in the respective treatment group and overall unless otherwise specified.

The number of subjects completing the Main Portion, entering the Extension Portion, completing study Visit Day E84 (i.e., Day 84 of the Extension Portion), discontinuing from the study, and the primary reason for discontinuation will also be summarized.

3.8.2 Protocol Deviations

A listing of protocol deviations will be presented by treatment group.

3.9 Demographics and Baseline Characteristics

3.9.1 Demographics

Subject demographics and baseline characteristics will be summarized by treatment group and overall for the ITT, mITT, Safety, and PP Populations.

Descriptive statistics will be provided for age, height, weight, and body mass index (BMI, calculated as weight in kilograms divided by height in meters squared). Frequencies and percentages will be tabulated for sex, race, and ethnicity. Age will also be summarized by <65, 65-<75, and ≥75.

Age will be calculated as (informed consent date – date of birth + 1)/365.25, truncated and displayed as years. BMI will be calculated as weight (kg)/height^2 (m^2), using the weight and height measurements obtained at screening.

Baseline and Screening QMG scores will be summarized. Additionally, for Screening QMG, the number and percentage of patients with scores ≤ 17 / ≥18 will be presented. Baseline MG-ADL will also be summarized.

Note: If the day and month are missing for date of birth, impute January 1st, if only the day is missing impute the 1st.

Two-sided p-values will be calculated comparing the similarity of the distribution of the demographics and baseline characteristics across the treatment groups. For the continuous endpoints, the p-value from the overall F-test from an analysis of variance (ANOVA) with treatment group as the factor will be presented. (Note: the set of continuous endpoints are: age, weight, BMI, Screening QMG score, Baseline QMG Score, Baseline ADL score). For categorical variables the p-value from the 3×2 Fisher's exact test will be presented, with the multi-response categories dichotomized. (Note: the set of categorical endpoints are: sex, race [dichotomized as white/non-white], ethnicity [dichotomized as 'Hispanic or Latino' or not].

3.9.2 Medical History

Medical history will be coded using MedDRA version 19.1 (or higher). The coded Preferred Terms (PT) will be summarized by treatment group and overall for the mITT Population. A subject will be counted only once for each preferred term. The summary will present the results alphabetically by System Organ Class (SOC) and, within SOC, by decreasing frequency for the Preferred Terms (PT).

3.9.3 Myasthenia Gravis History

The following gMG disease history data will be summarized by treatment group and overall for the mITT Population.

- Age at onset (years)
- Duration of disease (years)
  = (Date of Study Day 1 – Date of Diagnosis)/(365.25)

Note: If the Date of Diagnosis day and month are missing impute July 2nd, if only the day is missing impute the 15th. If the imputed Date of Diagnosis date is later than the date of Study Day 1, impute Study Day 1.

- Symptoms at onset (Ocular/Generalized)
- MGFA Disease Class at Screening (Class II, III, or IV)
- Ever had a Crisis (Yes/No)
- Time since most recent crisis (months)
  - Time since most recent crisis will be calculated as (Date of Study Day 1– Date of Crisis)/(365.25/12)
    Note: If the Date of Crisis day and month are missing impute July 2nd, if only the day is missing impute the 15th. If the imputed Date of Crisis date is later than the date of Study Day 1, impute the date of Study Day 1.
- Most Recent Crisis Intervention Required (Hospitalization, ICU, Tracheostomy)
- Family members have MG (Yes, No)
- Number of Family members with MG
- Closest relation with MG (Parent, Sibling, Child, Other) *note: more than 1 relation may be selected*
- Diagnosed with Thymoma (Yes, No)
- Prior Thymectomy (No: Yes [Total Thymectomy, Subtotal Thymectomy])
- Time from Thymectomy (months)
  - Time since thymectomy will be calculated as (Date of Study Day 1 – Date of Thymectomy)/(365.25/12)

Note: If the Date of Thymectomy day and month are missing impute July 2nd, if only the day is missing impute the 15th. If the imputed Date of Thymectomy date is later than the date of Study Day 1 impute the date of Study Day 1.

Additionally, a categorical summary of the age at disease onset overall and by gender will be performed by treatment group and overall.

3.10 Prior and Concomitant Medications

Prior and concomitant medications will be coded using WHO Drug (Version: v.2017JUN01 DDE B2 (enhanced)) and summarized by treatment group and overall for the Safety Population. MG specific medication will be summarized and listed separately (see Section 3.11 below) and not included in these summaries.

Incidence of prior and concomitant medication will be presented by treatment group, therapeutic class, and preferred (generic) drug name for the Safety Population. A subject is counted only once for each therapeutic class and for each preferred drug name. Separate tables will be created for the following study periods:

A. Prior medications:
   Prior medications are those that started and stopped before the Baseline visit

B. Concomitant Medications in the Main Portion
   Concomitant medications in the Main Portion of the study are those concomitant medications taken during the Main Portion of the study (up to,

but not including Day 84), including those started before and ongoing at first dose.

C. Concomitant Medications in the Main and Extension Portions:
This analysis will be performed on the RA10495 Safety Population. This combines the Main Portion and the first 12 weeks of the Extension Portion. Concomitant medication in the Extension Portion of the study are those concomitant medications taken during the Extension Potion of the study (i.e., the Extension Portion starting on Day E1/Day 84), including those started before and ongoing into the Extension Portion.

The summaries will be performed for the 0.1 mg/kg and 0.3 mg/kg dose groups separately and combined, summarizing concomitant medications occurring in both the Main Portion and Extension Portion based on the following groups:

- 0.1 mg/kg Group: The subjects in the Main Portion 0.1 mg/kg group and the subjects in the Extension Portion in the placebo−0.1 mg/kg group.
- 0.3 mg/kg Group: The subjects in the Main Portion 0.3 mg/kg group and the subjects in the Extension Portion in the placebo−0.3 mg/kg group.
- Combined 0.1 and 0.3 mg/kg Group: Combining the 0.1 mg/kg and 0.3 mg/kg groups.

Results will be presented in the following time-frames:

- Within the First 12 Weeks:
This will include concomitant medications in in the Main Portion for subjects receiving active treatment in the Main Portion and in the first 12 weeks of the Extension Portion for subjects who received placebo in the Main Portion.

- Within the First 24 Weeks: This will include concomitant medications in the Main Portion or the first 12 weeks of the Extension Study Period for subjects receiving active treatment in the Main Portion.

The following definitions will be used:

- Prior medications are those that started and stopped before the Baseline visit

- Concomitant medications are all medications taken during the study period, including those started before and are ongoing at first dose.

    - Concomitant medication in the Main Portion of the study are those concomitant medications taken during the Main Portion of the study (up to, but not including Day 84), including those started before and ongoing at first dose.

- Concomitant medication in the Extension Portion of the study are those concomitant medications taken during the Extension Potion of the study (i.e., the Extension Portion starting on Day E1/Day 84), including those started before and ongoing into the Extension Portion.

Where a medication start date is partially or fully missing, and it is unclear as to whether the medication is prior or concomitant, it will be assumed that it is concomitant and taken in the Main Portion.

3.11 MG Specific Prior and Concomitant Medications

MG specific medication will be presented separately from the other prior and concomitant medications (for both tables and listings). An MG specific mediation is defined by the "indication" value on the Prior and Concomitant Medication eCRF form ="Prior therapy for MG".

The following tables summarizing the incidence of MG medication use will be created based on the Safety population: The following 2 tables will be created:

1) MG specific prior medications:
   MG specific prior medications are those that started prior to the Baseline visit

2) MG specific medications taken at baseline:
   MG specific medications taken at baseline are those where the subject was on the medication at baseline (i.e., start date on or prior to Day 1 and stop date on or after Day 1 [or ongoing]).

Where an MG medication start date is partially or fully missing, and it is unclear as to whether the medication is prior or taken at baseline, it will be assumed that it is taken at baseline.

Note that a patient's MG medication may be in both of these categories.

In addition, a listing of MG specific medications which change from baseline through Day E84 will be produced.

Additionally, the number and percentage of patients who are taking one or more of the sets of MG specific medications presented in Table 12 (i.e., Groups A-E) will be summarized using the same 2 sets of tables:

1) MG specific prior medications
2) MG specific medications taken at baseline.

Table 12: List of MG Medication Groups

Group	Concomitant Medication	Preferred Term
A	prednisone for MG	PREDNISONE

	other corticosteroids for MG	*TBD**
B	Azathioprine	AZATHIOPRINE
	Mycophenolate	MYCOPHENOLATE MOFETIL
C	IV Ig	IMMUNOGLOBULINS NOS
	SC Ig	IMMUNOGLOBULINS NOS
D	Cyclosporine	CICLOSPORIN
	Cyclophosphamide	CYCLOPHOSPHAMIDE
	Methotrexate	METHOTREXATE
	Tacrolimus	TACROLIMUS
	Rituximab	RITUXIMAB
	other third line immunosuppressants	*TBD**
E	plasma exchange	ALL OTHER NON-THERAPEUTIC PRODUCTS
* *TBD:* to be determined; a list of corresponding medications and preferred terms will be provided by RA prior to database lock.		

3.12 Exposure to Study Treatment

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).

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.

The location and time of the study drug administrations will be presented in the listings for those visits where this information is collected for the Safety Population.

3.13 Safety Analysis

Safety analysis results will be presented using the Safety Population by dose group and overall.

For safety analyses, summary results for the 0.1 mg/kg and 0.3 mg/kg dose groups will be presented individually and also combining the two dose groups.

Listings for all safety data will be presented.

3.13.1 Adverse Events

All AEs will be coded using the Medical Dictionary of Regulatory Activities (MedDRA) Version 20.0 and will be classified by MedDRA system organ class (SOC) and preferred term (PT). Analyses of AEs will be performed using the Safety Population.

Treatment emergent AEs (TEAEs) are defined as follows:

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

TEAE Analyses:

The following are the set of TEAE summaries to be provided:

A. Overall summary of Treatment Emergent Adverse Events
B. Incidence of Treatment Emergent Adverse Events by System Organ Class and Preferred Term
C. Incidence of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity
D. Incidence of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug
E. Incidence of Treatment Emergent Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term

For these summaries, the number and percentage of subjects who experienced at least one of the TEAE as well as the number and percentage of subjects who experienced each specific SOC and PT will be presented by treatment group. The corresponding number of TEAEs will also be presented for the Overall Summary of TEAEs table.

For the presentation of TEAE incidences, the SOCs will be sorted alphabetically, and within SOC, the preferred term (PT) will be used and presented by decreasing total frequency based on the total population.

For the overall summary of TEAEs, the following information will be provided

- Number of subjects with TEAEs
- Number of subjects with TEAE of Grade 2 or higher
- Number of subjects with a drug related TEAE
- Number of subjects with a TEAE leading to study discontinuation
- Number of subjects with an SAE.

For reporting, each TEAE will be assigned to either the Main Portion or the Extension Portion based on the AE start date:

- If the start date of the TEAE is prior to Study Day 84 (i.e., the day the subject receives RA101495 in the Extension Portion) the TEAE will be assigned to the Main Portion.
- If the start date of the TEAE is on or after Study Day 84 (i.e., the day the subject receives RA101495 in the Extension Portion) the TEAE will be assigned to the Extension Portion.

Additionally, a listing of Serious Adverse Events by System Organ Class and Preferred Term will be provided as well as a Listing of Deaths.

The following are Study Period and Treatment Groups for which the set of TEAE analyses (listed as **A**-**E** above) will be performed.

1. Main Portion:
   The set of TEAE analyses will be performed for each of the 3 treatment groups (and the RA101495 group combined) summarizing TEAEs occurring in the Main Portion.

2. Main Portion and Extension Portion:
   This combines the Main Portion and the first 12 weeks of the Extension Portion. The set of TEAE analyses will be performed for the 0.1 mg/kg and 0.3 mg/kg dose groups separately and combined, summarizing TEAEs occurring in both the Main Portion and Extension Portion based on the following groups:

   - 0.1 mg/kg Group: The subjects in the Main Portion 0.1 mg/kg group and the subjects in the Extension Portion in the placebo−0.1 mg/kg group.
   - 0.3 mg/kg Group: The subjects in the Main Portion 0.3 mg/kg group and the subjects in the Extension Portion in the placebo−0.3 mg/kg group.
   - Combined 0.1 and 0.3 mg/kg Group: Combining the 0.1 mg/kg and 0.3 mg/kg groups.

   Results will be presented in the following time-frames:

   - Within the First 12 Weeks: This will include AEs with a start date within the Main Portion for subjects receiving active treatment in the Main Portion and in the first 12 weeks of the Extension Portion for subjects who received placebo in the Main Portion.
   - Within the 24 Weeks: This will include AEs with a start date in Main Portion or the first 12 weeks of the Extension Study Period for subjects receiving active treatment in the Main Portion.

   Note: This is combining the RA101495 data from the Main Portion with the RA101495 data from the Extension Portion as described in Section 3.4.

3.13.1.1 Treatment Emergent with Adverse Event Date Imputation

The following rules apply when determining if an AE is treatment-emergent in the scenario where the start date is missing or partially missing. These rules provide an algorithm to "impute" a complete AE start date which will then be used to determine if the AE is treatment emergent.

AE start date missing day and month:

- If the year is the same as the year of the treatment start date, the day and month of the date of treatment start date will be assigned to the missing fields.
- If the year is prior to the year of the treatment start date, December 31 will be assigned to the missing fields.
- If the year is after the year of the date of the treatment start date, January 1 will be assigned to the missing fields.

AE start date missing month only:

- The day will be treated as missing, and both month and day will be replaced according to the above procedure.

AE start date missing day only:

- If the month and year are the same as the month and year of the treatment start date, the day of the treatment start date will be assigned to the missing day.
- If either the year is before the year of the date of the treatment start date or if both years are the same, but the month is before the month of the treatment start date, the last day of the month will be assigned to the missing day.
- If either the year is after the year of the treatment start date or if both years are the same, but the month is after the month of the treatment start date, the first day of the month will be assigned to the missing day.

AE start date completely missing:

- If the AE end date is complete and after the treatment start date, the treatment start date will be assigned to the missing start date.
- If the end date is complete and before the treatment start date, the end date will be assigned to the missing start date
- Otherwise the AE start date will be assigned the treatment start date.

If the end date is complete and the imputed start date as above is after the end date, the start date will be imputed by the end date.

3.13.1.2 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 13)
  - Erythema and induration: record the maximum linear diameter
- Blisters, ulceration, necrosis: record the maximum linear diameter and severity

- Lymphadenopathy

Table 13: 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

Analysis of injection site reactions (ISRs) will include by treatment summaries of the following assessments using the subject's maximum grade over the corresponding study period as well as the number of times a grade was reported for a particular ISR.

- Any ISR, Pain, tenderness, erythema, and induration severity, and lymphadenopathy (categorical variables with grades 1 – 4, and absent).

This analysis will be performed for the:

- The Main Portion based on the Safety Population
- RA10495 Safety Population Within the First 12 Weeks: This will include ISRs with an assessment date within the Main Portion for subjects receiving active treatment in the Main Portion and in the first 12 weeks of the Extension Portion for subjects who received placebo in the Main Portion.
- RA10495 Safety Population Within the 24 Weeks: This will include ISRs with an assessment date in Main Portion or the first 12 weeks of the Extension Study Period for subjects receiving active treatment in the Main Portion.

3.13.2 Clinical Laboratory Evaluation

A list of the clinical chemistry, hematology, and coagulation analytes are listed in Table 1.

Quantitative laboratory endpoints will be summarized (including the value and change from baseline) at each scheduled assessment time point using descriptive statistics by dose group and combining the active dose groups for the Main Portion.

For the Extension Portion results will be summarized for the scheduled visits based on for the combined 0.1 and 0.3 mg/kg dose groups as defined in Section 3.4.

Laboratory parameters which do not lend themselves to analyses (e.g., Urinalysis "Color") will be presented in the listings only.

3.13.2.1 Hepatic Laboratory Tests: NCI CTCAE Grading

The liver functions test to be summarized via the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) criteria are provided in Table 14.

The number and percentage of subjects meeting these criteria at each scheduled visit will be presented for the Main Portion by individual dose group and the combining the 0.1 and 0.3 mg/kg dose groups.

For the Extension Portion, active-dose results will be summarized for the scheduled visits based on the individual and combined 0.1 and 0.3 mg/kg dose groups as defined in Section 3.3 including results through 24 weeks of active-treatment.

Table 14: CTCAE Grading Criteria for Selected Liver Function Tests

Lab Test	Grade/Criteria			
	1	2	3	4
alanine aminotransferase (ALT)	> 1.0 - 3.0 (x ULN)	>3.0 - 5.0 (x ULN)	>5.0 - 20.0 (x ULN)	> 20.0 (x ULN)
alkaline phosphatase (ALP)	>1.0 - 2.5 (x ULN)	>2.5 - 5.0 (x ULN)	>5.0 - 20.0 (x ULN)	> 20.0 (x ULN)
direct bilirubin	> 1.0 – 1.5 (x ULN)	>1.5 – 3.0 (x ULN)	>3.0 - 10.0 (x ULN)	> 10.0 (x ULN)
gamma-glutamyl transferase (GGT)	>1.0 - 2.5 (x ULN)	>2.5 - 5.0 (x ULN)	>5.0 - 20.0 (x ULN)	>20.0 (x ULN)
Grading criteria based on Common Terminology Criteria for Adverse Events (CTCAE) v4.03				

3.13.2.2 Pancreatic Enzymes: NCI CTCAE Grading

Amylase and lipase values will be summarized via the NCI CTCAE criteria provided in Table 15.

The number and percentage of subjects meeting these criteria at each scheduled visit will be presented for the Main Portion by individual dose group and the combining the 0.1 and 0.3 mg/kg dose groups.

For the Extension Portion, active-dose results will be summarized for the scheduled visits based on for the combined 0.1 and 0.3 mg/kg dose groups as defined in Section 3.3 including results through 24 weeks of active-treatment.

Table 15: CTCAE Grading Criteria for Selected Pancreatic Enzyme Tests

Lab Test	Grade/Criteria

	1	2	3	4
amylase	> 1.0 – 1.5 (x ULN)	>1.5 – 2.0 (x ULN)	>2.0 - 5.0 (x ULN)	> 5.0 (x ULN)
lipase	> 1.0 – 1.5 (x ULN)	>1.5 – 2.0 (x ULN)	>2.0 - 5.0 (x ULN)	> 5.0 (x ULN)
Grading criteria based on Common Terminology Criteria for Adverse Events (CTCAE) v4.03				

3.13.3 Vital Signs and Other Physical Findings

Descriptive statistics for vital signs (i.e., heart rate, body temperature, and blood pressure) values and the change from baseline will be presented for each scheduled assessment time points by treatment group.

3.13.4 ECG

Descriptive statistics for ECG parameters (i.e., HR, PR interval, RR interval, QRS interval, QT interval, QTcB interval, and QTcF interval) at each assessment time point will be presented for the values and change from baseline scores by treatment group. QTc intervals will be calculated using both Fridericia's and Bazett's corrections.

Additionally, the ECG interpretation categorized as Normal, Abnormal – Clinically Significant, Abnormal – Not Clinically Significant, Not Evaluable, or Not Done will also be provided for each assessment time point (note: ECG interpretations of "Abnormal – Clinically Significant" would be recorded as AEs).

Note: ECG is not performed at Day 1, baseline values will be based on the Screening visit.

3.13.5 Physical Examination

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

3.14 Efficacy Analyses

Listings for all efficacy data will be presented.

3.14.1 Primary Efficacy Endpoint 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 one-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. Least-square means for

each treatment group will also be presented. The following additional tests will be performed:

- A test of linear trend across the 3 treatment groups: This will be performed by an ANCOVA model with treatment as a continuous variable with values of 0, 0.1, and 0.3 for the placebo, 0.1 mg/kg, and 0.3 mg/kg dose groups respectively, and baseline QMG score as a covariate. The test of linear trend will be testing the slope of the treatment effect versus 0 using a two-sided p-value.

- A test for treatment effect pooling the 0.1 mg/kg and 0.3 mg/kg dose groups versus placebo: This will be performed by repeating the primary efficacy analysis ANCOVA with the 0.1 mg/kg, and 0.3 mg/kg dose groups combined.

The primary analysis population will be the mITT Population and LOCF is the primary method for handling missing data.

3.14.2 Secondary Efficacy Endpoints Analysis

The secondary efficacy endpoints are:

- Change from baseline to Week 12 in the MG-ADL scale
- Minimal symptom expression at Week 12, defined as an MG-ADL scale score of 0 or 1
- 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
- A ≥ 3-point reduction in QMG score at Week 12
- Requiring rescue therapy over the 12-week Treatment Period.

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 categorical secondary endpoints: 'Minimal symptom expression at Week 12, defined as an MG-ADL scale score of 0 or 1', 'Subjects with ≥ 3-point reduction in QMG score at Week 12' and 'Subjects requiring rescue therapy over the 12-week Treatment Period', the rate of subjects meeting the endpoint for each of the active treatment groups will be compared to the placebo group using a one-sided Fisher's exact test.

For the secondary endpoints the primary analysis population will be the mITT Population and LOCF is the primary method for handling missing data.

3.15 Controlling for Multiplicity

This Phase 2 study will not control for multiple secondary endpoints.

3.15.1 Additional Analyses of Primary and Secondary Endpoints

The following are the set of additional analyses for the primary and secondary efficacy endpoint analyses:

a. The primary and secondary efficacy endpoint analyses will be performed on the PP population using the LOCF method.

b. The primary and secondary efficacy endpoints will also be performed on the PP and mITT populations using the Observed Case analysis method (i.e., as defined in Section 3.2).

c. The data from the placebo group Extension Portion (i.e., when the placebo group subjects are taking 0.1 mg/kg or 0.3 mg/kg RA101495) will be combined with the corresponding 0.1 mg/kg or 0.3 mg/kg RA101495 dose group data from the Main Portion following the method described in Section 3.4. Summary statistics will be provided for the values and change from baseline at each of the scheduled assessment time points for this combined data. These analyses will be done on the RA101495 Safety population. Note: no inferential analyses are planned. This analysis will be done for the change from baseline in QMG score and MG-ADL score using the LOCF methodology.

d. The ANCOVA model as defined in Section 3.14.1 will be performed on the mITT Population using the LOCF method for missing data (as described in Section 3.2) including each of the following variables as an additional covariate (i.e., a separate ANCOVA model for each variable listed).
   - Sex (dichotomous class variable)
   - Age (continuous variable)
   - Duration of disease (continuous variable)
   - Age at disease onset (continuous variable)
   - Ever had a crisis(dichotomous yes/no class variable)
   - Prior thymectomy (dichotomous yes/no class variable)
   - Prior/current steroid therapy[a]
   - Prior/current immunosuppressive therapy (nonsteroidal)[a]
   - Prior history of intravenous or subcutaneous Immunoglobulin (IvIg) or (plasma exchange) PLEX
     - Prior history of IvIg is defined in Concomitant Medications as “IMMUNOGLOBULINS NOS”; this is the ATC code via WhoDrug.
     - Prior history of PLEX is defined in Concomitant Medications as “ALL OTHER NON-THERAPEUTIC PRODUCTS”; this is the ATC code via WhoDrug.

a: Prior and concomitant medications will be reviewed and a list of those medications meeting this criteria will be finalized prior to database lock.

This analysis will be done for the change from baseline to Week 12 QMG score and MG-ADL score.

e. For the Main Portion, the frequency distribution of the change from baseline will be summarized categorically for the following endpoints:
   - Change from baseline to Week 12 in the QMG score (reduction levels from 0 to 20)
   - Change from baseline to Week 12 in the MG-ADL scale (reduction levels from 0 to 15)
   - Change from baseline to Week 12 in the MG-QOL15r survey (reduction levels from 0 to 15)
   - Change from baseline to Week 12 in the MG Composite (reduction levels from 0 to 15)

   Note: the tables may present reduction levels up to the maximum reduction level.

   For each of these endpoints the number and % of subjects that have a reduction at a particular level and ≥ that particular level (note: for these scales reduction from baseline indicates improvement) will be summarized. For each level a Fisher's exact test will be performed testing each active group versus the placebo group comparing the number of subjects with a change from baseline ≥ that particular level (and the combined active dose groups versus placebo).

   These analyses will be done on the mITT population using the LOCF method.
   Additionally, the data from the placebo group Extension Portion (i.e., when the placebo group subjects are taking 0.1 mg/kg or 0.3 mg/kg RA101495) will be combined with the corresponding 0.1 mg/kg or 0.3 mg/kg RA101495 dose group data from the Main Portion following the method described in Section 3.4. A summary of the change from baseline frequencies will be provided for the 0.1mg/kg and 0.3 mg/kg (and combined) dose groups.

   These analyses will be done on the RA10495 Safety population using the LOCF method.

f. A mixed model repeated measures (MMRM) analyzing the Main Portion. This analysis will be done on the following endpoints (i.e., a separate MMRM will be performed with each of these endpoints as the dependent variable):
   - Change from baseline in the QMG score
   - Change from baseline in the MG-ADL scale
   - Change from baseline in the MG-QOL15r survey

- Change from baseline in the MG Composite

Treatment, visit, treatment×visit interaction will be factors in the model and the corresponding baseline score will be a covariate. The model will adjust for repeated measures using a within-subject unstructured covariance matrix (note: the covariance matrix structure may be simplified if there are convergence issues). The analysis will use the post-baseline scheduled visits (Day 8, 15, 29, 57, and 84).

Based on the MMRM model, the treatment differences for each active dose group versus placebo as well as the treatment difference of the combined active doses versus placebo will be estimated for each of the post-baseline scheduled visits using LS means.

The MMRM model will be analyzed using SAS Proc Mixed, example SAS code for this MMRM is provided in the

Appendix. This analysis will be performed on the mITT population using the LOCF Method and Observed Case Method for missing data (as described in Section 3.2).

g. An MMRM analyzing the data from both the Main Portion and first 12 weeks of the Extension Portion will be performed. This analysis will be done on the following endpoints (i.e., a separate MMRM will be performed with each of these endpoints as the dependent variable):

   - Change from baseline in the QMG score
   - Change from baseline in the MG-ADL scale
   - Change from baseline in the MG-QOL15r survey
   - Change from baseline in the MG Composite

   Treatment, visit, treatment×visit interaction, and Study Portion, will be factors in the model and the corresponding baseline score will be a covariate (note: Study Portion is a categorical variable referring to the Main Portion and Extension Portion). For this analysis, the placebo subjects' Extension Study visit values will use the "matched" visits from the Main Portion. Specifically, the E*XX* visits (see Table 10) for the placebo subjects will map to Visit *XX* of the Main Portion (e.g., the Day E8 visit will map to Day 8 of the Main Portion). This has the Visits "matching" relative to the amount of time a subject has been on RA101495. For the extension period placebo data, the subject's baseline score (i.e., to be used when estimating change from baseline and used in the model as the baseline covariate) will be the Day 84 score.

   The model will be adjusted for repeated measures using a within-subject unstructured covariance matrix (note: the covariance matrix structure may be simplified if there are convergence issues). The analysis will use the post-baseline scheduled visits (Day 8, 15, 29, 57, 84/E1, E8, E15, E29, E57, and E84).

   Based on the MMRM model, the treatment difference of the combined active doses versus placebo will be estimated for each of the initial visits using LS means (Day 8, 15, 29, 57, and 84) and the LS-Means for the two active dose groups will be estimated for Visits: E1, E8, E15, E29, E57, and E84.

The MMRM model will be analyzed using SAS Proc Mixed, example SAS code for this MMRM is provided in the

Appendix. This analysis will be performed on the mITT population using the LOCF Method and Observed Case Method for missing data (as described in Section 3.2).

h. The primary and secondary efficacy endpoint analyses will be performed on the mITT and PP population using the LOCF and Observed Case methods for the other scheduled assessment time points in the Main Portion.

3.15.2 Pharmacodynamic Endpoints Analysis

Pharmacodynamic analyses will be performed on the PD Population.

The pharmacodynamic endpoints include:

- Sheep red blood cell (sRBC) lysis assay
- C5 levels

Summary statistics will be provided for the values, change from baseline, and percent change from baseline at each of the scheduled assessment time points.

For the Main Portion, the change from baseline for each of these endpoints will be assessed by an ANCOVA model 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.

Additionally, the data from the placebo group Extension Portion (i.e., when the placebo group subjects are taking 0.1 mg/kg or 0.3 mg/kg RA101495) will be combined with the corresponding 0.1 mg/kg or 0.3 mg/kg RA101495 dose group data from the Main Portion following the method described in Section 3.4. Summary statistics will be provided for the values, change from baseline, and percent change from baseline at each of the scheduled assessment time points for this combined data.

These analyses will be performed on the PD population using observed cases (i.e., no censoring or imputation of data).

3.15.3 Pharmacokinetic Endpoints Analysis

Pharmacokinetic analyses will be performed on the PK Population.

The following pharmacokinetic endpoints will be presented in listings and summarized in tables.

- Plasma concentrations of RA101495 and its two major metabolites ([redacted])
- Maximum plasma concentration (C_{max})
- Time corresponding to C_{max} (t_{max})
- Ratio of parent to metabolites (i.e., 2 metabolites).

These analyses will be performed on the PK population using observed cases (i.e., no censoring or imputation of data). Note: the PK parameters will be calculated by an external vendor and provided to PRA.

3.15.4 Exploratory Endpoints Analysis

For the functional sub-scores of the QMG, MG-ADL, QOL, and Composite scores (defined in Section 3.7) the endpoints will be summarized using descriptive statistics at each scheduled assessment time point. Additionally, an ANCOVA model, with treatment as a factor and corresponding baseline score as a covariate will be performed to assess treatment group differences. This will be performed on the mITT population using LOCF.

The following exploratory endpoints will be summarized using descriptive statistics at each scheduled assessment time point in the Main Portion:

- Mechanistic biomarkers pertinent to MG pathophysiology [e.g., complement fixation, complement function, complement pathway proteins, autoantibody characterization (titer and immunoglobulin class) and inflammatory markers]
- Anti-drug antibodies: The number and percentage of subjects with a positive confirmatory assay will be summarized for each of the scheduled assessment time points.

Pharmacogenomic analyses (optional) data collected will be presented in a listing.

3.16 Additional Analyses

3.16.1 Rescue Therapy

Subjects requiring rescue therapy over the 12-week Treatment Period is a secondary efficacy endpoint, with the analysis described in Section 3.14.2.

In addition to the secondary efficacy analyses the following analyses will be performed for the Main Portion on the mITT Population:

- For those subjects who receive rescue therapy during the Main Portion, the time to rescue therapy will be summarized using descriptive statistics, including the number and percentage of subjects receiving rescue therapy, and time to rescue therapy. Time to rescue therapy (in days), will be calculated as:

  Time to rescue therapy = (Date of Day 1 visit – Date of Rescue Therapy + 1)

- The frequency and type of rescue medication (Immunoglobulin or Plasma Exchange) a subject receives will be summarized.

These summaries will be provided by dose group and for the 0.1 and 0.3 mg/kg dose groups combined.

For those subjects who receive rescue therapy while on RA101495 (i.e., both in the Main Portion and the first 12 weeks of the Extension Portion) the following summaries will be performed on the RA101495 Safety population:

- The number and percentage of subjects receiving rescue therapy

- The time from first dose of RA101495 to rescue therapy (summarized for those subjects who received rescue therapy)
- The frequency and type of rescue medication (Immunoglobulin or Plasma Exchange) a subject received

The summaries will be provided by RA10495 dose group and the 0.1 and 0.3 mg/kg dose groups combined.

3.17 Interim Analysis

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

3.18 Timing of Primary Analysis

For the primary analyses of the Main Portion of the study, when all subjects have completed the Main Portion of the study, the Main Portion data in the study database will be "frozen" and the set of primary, secondary, and a subset of the additional efficacy analysis will be performed in addition to a subset of the safety analyses corresponding to the Main Portion of the study.

3.19 Sample Size Considerations

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.

3.20 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.

3.21 Protocol Violations

Protocol violations will be assessed as major or minor prior to database unblinding, in a blinded manner. A listing of protocol violations by treatment group will be presented.

4 References

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5 Appendix 1: Sample SAS code for Repeated Measures Mixed Models

The following is the sample code for the MMRM ANCOVA for the Main Portion described in Section 3.15.1, sub-section f. Note that this is an example to be used as a reference, the actual SAS code may differ from the sample provided below.

```
** MMRM ANCOVA Code **;
** Analysis of Main Portion of the Study **;
proc mixed data=XXXX;
  class usubjid visit trt(Ref='0');
  model y_chg = y_base visit trt trt*visit/s;
  repeated /subject=usubjid type=UN;
  lsmeans visit*trt/diff;
  ods output lsmeans=lsmeans;
  ods output diffs=diffs;
  ** Subset to Main Portion, Scheduled Assessment timepoints **;
  where visit in(8,15, 29, 57, 84);
run;

** this data step subsets the LS means comparisons to within a
visit, comparing against trt=0 **;
data diffs2;
  set diffs;
  where _trt=0 and visit=_visit;
run;

**-----------------------------------------------------------------**;
** MMRM ANCOVA Code                                               **;
** Analysis of Main and Extension Portion of the Study            **;
** 1) for subjects randomized to treatment in main portion:       **;
**   visit_x = visit                                              **;
** 2) for subjects randomized to placebo in main portion:         **;
**   visit_x = visit for main portion                             **;
**   visit_x = corresponding main portion visit for extension     **;
proc mixed data=simu4;
  class usubjid visit_x trt(Ref='0');
  model y_chg = y_base visit_x trt trt*visit_x/s;
  repeated /subject=usubjid type=UN;
  lsmeans visit_x*trt/diff;
  ods output lsmeans=xlsmeans;
  ods output diffs=diffs;
    where visit in(8,15, 29, 57, 84, 91, 98, 112, 140, 167);
run;

** this data step subsets the LS means comparisons to within a
visit, comparing against trt=0 **;
data diffs2;
  set diffs;
  where _trt=0 and visit_x=_visit_x;
run;
```

6 Appendix 2: Analyses Including Data After Day E84

The following are the set of tables to summarize the data collected after Day E84. The tables will provide descriptive summary statistics (i.e., no inferential analyses will be performed).

6.1 Additional Analysis Population: Extension Population

The Extension Population will include all subjects who entered the Extension Period of the study as indicated by having a Day E1 visit.

6.2 Disposition

The Extension Period Disposition table will be amended to provide the number of subjects who completed Week E84 of the study and the reasons for discontinuation.

6.3 Subject Switching From 0.1 mg/kg to 0.3 mg/kg

The date a subject in the 0.1 mg/kg group switched to 0.3 mg/kg (i.e., during the expansion phase of the study) will be presented in a listing.

Note: the date that a subject increased from the 0.1 mg/kg dose group to the 0.3 mg/kg dose group is recorded as "Date subject received first dose of open label study drug" in the eCRF form "Open Label Re-consent".

6.4 Exposure

The number of years a patient is on the 0.1 mg/kg dose and 0.3 mg/kg dose group will be calculated for each subject using the following algorithm:

- The beginning of the interval will be the first day the subject begins that dose level. This will one of 3 timepoints:
  - Day 1 of the Main Portion: the subject received this medication in the Main Portion)
  - Study Day 84/E1: the subject received placebo in the Main Portion and the dose of interest starting
  - The day the subject's dose increases from 0.1 mg/kg to 0.3 mg/kg: the subject was on 0.1 mg/kg and, during the Extension Period, the subject's dose was increased to 0.3 mg/kg.

- The end of the interval will be:
  - The day the subject either discontinues or completes the study
  - For the 0.1 mg/kg dose, the day prior to the subject taking the 0.3 mg/kg dose

The number of years for a subject on zilucoplan will be calculated (for the 0.1 mg/kg and 0.3 mg/kg dose groups separately) as:

Interval = (date of end of Interval – date of beginning of interval)/365.25

The total number of patient-years for a dose group will be the sum of the individual patient-years for that doses group within the corresponding population. This information will be presented in the adverse event table

6.5 Efficacy Endpoints

Efficacy endpoints will be summarized by the groups listed in Table 16.

Table 16: Extension Table Groups

Table Header	Treatment Group
Pbo/RA101495 0.1 mg/kg	These are the subjects randomized Placebo in the Main Portion and randomized to 0.1 mg/kg in the Extension Portion
RA101495/RA101495 0.1 mg/kg	These are the subjects randomized 0.1 mg/kg in the Main Portion and randomized to 0.1 mg/kg in the Extension Portion
Pbo/RA101495 0.3 mg/kg	These are the subjects randomized Placebo in the Main Portion and randomized to 0.3 mg/kg in the Extension Portion
RA101495/RA101495 0.3 mg/kg	These are the subjects randomized 0.3 mg/kg in the Main Portion and randomized to 0.3 mg/kg in the Extension Portion
Total	These are all subjects in the population.

Additional information for the efficacy tables:

- The analysis population for the tables will be the Extension Population (defined in Section 6.1)
- The endpoints will be summarized starting at Week E1 through Week E84 (i.e., the last scheduled visit for the study)
- The Observed Case method for the Extension Period, as described in Section 3.2.2, will be applied.
- The value and change from baseline values will be summarized. Baseline will be derived using the Extension Period definition of Baseline as described in Section 3.1.3.

The efficacy endpoints to be summarized include the primary and secondary change from baseline efficacy endpoints (i.e., QMG, MG-ADL, MG-QOL15r, and MG Composite).

6.6 Safety Endpoints

6.6.1 Adverse Events

TEAEs will be summarized across the entire study, excluding TEAEs occurring during the Main Portion of the study for those subjects on placebo during the Main Portion. Results will be summarized by the dose the subject was on (i.e., 0.1 mg/kg or 0.3 mg/kg) at the start date of the TEAE as well as "Overall".

The AE tables will include:

- TEAEs by SOC/PT
- Related TEAEs by SOC/PT
- Serious TEAEs by SOC/PT

In addition, an overall summary of TEAEs table will present the following:

- Any TEAEs
- Any Grade 2 or Greater, Grade 3 or Greater, and Grade 4 or Greater, TEAEs
- Any Treatment-Related TEAEs
- Any Grade 2 or Greater, Grade 3 or Greater, and Grade 4 or Greater, Treatment-Related TEAEs
- Any TEAEs with Outcome of Death
- Any Serious TEAEs
- Any Treatment-Related Serious TEAEs

The AE, SAE, and TEAEs with an outcome of Death listings will be updated to include the dose the subject is on at the start of the event. As the subject-years exposure will be notably different between the 0.1 mg/kg group and the 0.3 mg/kg group a footnote will be provided to provide context to the AE frequencies and percentages. The subject-years will be calculated using the method described in Section 6.3.

For each of these AE tables the total number of patient-years for each treatment group (and overall) as defined in Section 6.3 will be presented.

6.6.2 Labs and Vital Signs

Labs and vital sign endpoints will be summarized in the same manner as the efficacy endpoints (defined in Section 6.5).