RA PHARMACEUTICALS, INC.

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Efficacy of Zilucoplan in Subjects with Immune-Mediated Necrotizing Myopathy

Protocol Number:	RA101495-02.202 (UCB study IMNM01)
Protocol Version/Date:	Version 2.0/16 February 2021
Indication Studied:	Immune-Mediated Necrotizing Myopathy (IMNM)
Developmental Phase of Study:	2
EudraCT Number:	2019-001497-29
Sponsor Address:	Ra Pharmaceuticals, Inc. (now part of UCB) 87 Cambridge Park Drive Cambridge, MA, 02140 | USA

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

CONFIDENTIAL

CENTER INVESTIGATOR SIGNATURE PAGE

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

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

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

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

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

_____ _____

Signature of Investigator Date

_____

Name of Investigator (Typed or Printed)

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Protocol Version**	**Date**
Original Protocol	1.0	05 Apr 2019
Protocol Amendment (United Kingdom)	GB.1.1	25 Jul 2019
Protocol Amendment (France)	FR.1.1	20 Feb 2020
Protocol Amendment (Global)	2.0	16 Feb 2021

PROTOCOL AMENDMENT (GLOBAL) VERSION 2.0 (16 FEB 2021)

The purpose of this protocol amendment is to make the following changes to the original protocol (Version 1.0 dated 05 Apr 2019):

- Changes made in earlier United Kingdom (25 Jul 2019) and France (20 Feb 2020) country-specific protocol amendments have been consolidated into a single global protocol.
- The objectives and endpoints were revised to reflect current UCB practices for the categorization and description of study objectives, estimands, and endpoints.
- The protocol was updated to include provisions for the coronavirus disease 2019 (COVID-19) pandemic.
- To clarify that the snapshot will be taken after the Week 8 visit.
- Additional administrative updates were made in the protocol.

Section # and Name	Description of Change	Brief Rationale
Title Page	Updated version number and date; added UCB study number.	Updated.
Section 1, Synopsis, Study Objectives	Notes added that the long-term safety, tolerability, and efficacy will be evaluated during the open-label Extension Portion of the study.	Consolidation of earlier country-specific (UK) protocol amendment into global protocol.
Section 1, Synopsis, Study Design, paragraph 8	Text regarding safety data review has been updated.	Consolidation of earlier country-specific (France) protocol amendment into global protocol.
Section 1, Synopsis, Study Design, paragraph 9	The last sentence has been updated to specify Week 8 of the Main Portion of the study.	To clarify that the snapshot will be taken after the Week 8 visit.

Section # and Name	Description of Change	Brief Rationale
Section 1, Synopsis, Duration of Study Participation	The study duration for the Extension Portion has been amended from the France protocol amendment from 4 months to 18 months.	Consolidation of earlier country-specific (France) protocol amendment into global protocol. Extending the duration in France of the open-label extension from 4 months to 18 months to allow for enrolled patients to continue receiving open-label drug based on additional safety data reviewed during the updated Investigator's Brochure (IB).
Section 1, Synopsis, Duration of Study Participation	An example of zilucoplan access in another qualifying extension study has been added.	To provide flexible means for zilucoplan access for participants with close medical supervision afforded by a clinical study.
Section 1, Synopsis, Inclusion/Exclusion Criteria	Added exclusion criterion 14 (hypersensitivity to study drug).	Consolidation of earlier country-specific (UK) protocol amendment into global protocol.
Section 1, Synopsis, Study Objectives and Endpoints	Revised objectives and endpoints.	Updated to reflect UCB practices for categorization and description of study objectives, estimands, and endpoints.
Section 1, Synopsis, Study Objectives and Endpoints	"Change from Baseline to Week 8 in American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Response Criteria" was updated to "At least minimal response based on ACR/EULAR Response Criteria Scale at Week 8".	Updated for clarity.
Section 1, Synopsis, Study Objectives and Endpoints	"Change in physical examination" has been removed as an other safety endpoint.	Clinically significant abnormal physical examination findings will be categorized as adverse events (AEs).

Section # and Name	Description of Change	Brief Rationale
Section 1, Synopsis, Study Objectives and Endpoints	The UK protocol amendment included a note that the primary and secondary efficacy endpoints evaluated in the Main Portion of the study will continue to be collected during in the Extension Portion of the study to determine the long-term safety, tolerability, and efficacy of zilucoplan in subjects with IMNM. This change has been incorporated into this global protocol amendment by including the Extension Portion objective and endpoints in the Objectives and Endpoints table.	Consolidation of earlier country-specific (UK) protocol amendment into global protocol.
Section 1, Statistical Considerations, Study Populations	Per protocol population description has been corrected.	Typographical error has been corrected.
Section 1, Statistical Considerations, Study Populations	General considerations sentence has been updated to clarify that subject disposition breakdowns will include reasons for discontinuation.	Updated for clarity.
Section 1, Statistical Considerations, Efficacy Analysis	Efficacy analysis has been updated from 2-sided Wilcoxon rank sum test to the 2-sided stratified Wilcoxon rank sum test (Van Elteren test). A sentence has been added to state that the effect of Zilucoplan on ACR/EULAR minimal response will be investigated using a binary logistic regression model with treatment and stratification included as factors.	The Van Elteren version of the Wilcoxon rank sum test has been selected to provides a more specific analysis. Updated for clarity.

Section # and Name	Description of Change	Brief Rationale
Section 2, Schedule of assessments, Table 1: Main portion time and events table	Footnote "a" has been updated to state that if a subject permanently discontinues study drug treatment prior to the Week 8 visit for any reason, he/she will not be eligible for the Extension Portion. For subjects who permanently discontinue treatment with study drug, a Safety Follow-up Visit will be performed at 40 days after the last dose to collect information on any ongoing AEs or new serious AEs (SAEs) since the last study visit.	Clarification of study procedures.
Section 2, Schedule of assessments, Table 1: Main portion time and events table	Adverse event collection added to the screening visit, and footnote "k" has been updated to state that only SAEs should be collected at the screening visit.	Clarification of study procedures.
Section 2, Time and Events Table 1: Main Portion time and events table	Footnote "j" after anti-drug antibody has been corrected to "h."	Correction of error.
Section 2, Time and Events, Table 2: Extension Portion time and events table	A new footnote "b" has been added to the "Visits after Day E117" to state that for France only, the duration of study participation during the Extension Portion will include an open-label, single-arm, 18-month Treatment Period.	Consolidation of earlier country-specific (France) protocol amendment into global protocol. Extending the duration in France of the open-label extension from 4 months to 18 months to allow for enrolled patients to continue receiving open-label drug based on additional safety data reviewed during the updated IB.
Section 5.4.2, Rationale for Blinding and Placebo Control, paragraph 3	The last sentence has been updated to specify Week 8 of the Main Portion of the study.	To clarify that the snapshot will be taken after the Week 8 visit.

Section # and Name	Description of Change	Brief Rationale
Section 6, Study Objectives and Endpoints	Revised objectives and endpoints.	Updated to reflect UCB practices for categorization and description of study objectives, estimands, and endpoints.
Section 6, Study Objectives and Endpoints	"Change from Baseline to Week 8 in ACR/EULAR Response Criteria" was updated to "At least minimal response based on ACR/EULAR Response Criteria Scale at Week 8".	Updated for clarity.
Section 6, Study Objectives and Endpoints	"Change in physical examination" has been removed as an other safety endpoint.	Clinically significant abnormal physical examination findings will be categorized as adverse events.
Section 6, Study Objectives and Endpoints	The UK protocol amendment included a note that the primary and secondary efficacy endpoints evaluated in the Main Portion of the study will continue to be collected during in the Extension Portion of the study to determine the long-term safety, tolerability, and efficacy of zilucoplan in subjects with IMNM. This change has been incorporated into this global protocol amendment by including the Extension Portion objective and endpoints in the Objectives and Endpoints table.	Consolidation of earlier country-specific (UK) protocol amendment into global protocol.
Section 7.1 Overview of Study Design, paragraph 9	The last sentence has been updated to specify Week 8 of the Main Portion of the study.	To clarify that the snapshot will be taken after the Week 8 visit.
Section 7.2 Study Periods, paragraph 3	An example of zilucoplan access in another qualifying extension study has been added.	To provide flexible means for zilucoplan access for participants with close medical supervision afforded by a clinical study.

Section # and Name	Description of Change	Brief Rationale
Section 7.2 Study Periods, paragraph 3	The study duration for the Extension Portion has been amended from the France amendment from 4 months to 18 months.	Consolidation of earlier country-specific (France) protocol amendment into global protocol. Extending the duration in France of the open-label extension from 4 months to 18 months to allow for enrolled patients to continue receiving open-label drug based on additional safety data reviewed during the updated IB.
Section 7.2.2.1 Randomization and Blinding, paragraph 2	Updated the text to specify Week 8 of the Main Portion of the study.	To clarify that the snapshot will be taken after the Week 8 visit.
Section 7.4, Study Conduct During COVID-19	Added new section.	Update to include provisions for the COVID-19 pandemic.
Section 8.2, Exclusion Criteria, Exclusion Criterion 14	Added exclusion criterion 14 (hypersensitivity to study drug).	Consolidation of earlier country-specific (UK) protocol amendment into global protocol.
Section 9.2.1.1, Alternative Study Treatment Supply due to COVID-19 Pandemic	Added a new section.	Update to include provisions for the COVID-19 pandemic.
Section 9.1.3	Sentence updated to clarify that subjects presenting with a body weight outside of these ranges will be accommodated on a case-by-case basis, in consultation with the medical monitor.	Updated for clarity.
Section 10.2.1 Physical Examination	Sentence #2 has been updated to state that any clinically significant abnormalities after Day 1 will be recorded as AEs in the eCRF.	Updated for clarity.
Section 10.2.4.3, Pregnancy Testing and Contraception	Revised information on contraception.	Consolidation of earlier country-specific (UK) protocol amendment into global protocol.

Section # and Name	Description of Change	Brief Rationale
Section 10.3.2.2 Proximal Manual Muscle Testing	Manual muscle testing in 8 muscle groups has been corrected to 7.	Typographical error has been corrected.
Section 11.1.1.1, Occurrence of COVID-19	Added section regarding reporting cases of COVID-19.	Update to include provisions for the COVID-19 pandemic.
Section 11.4.1.1 Adverse Events	Sentence has been updated that AE reporting will end 40 days following the last dose of study drug.	To comply with UCB safety guidance.
Section 11.4.2.1 Safety Monitoring Committee, paragraph 2	Text regarding safety data review has been updated.	Consolidation of earlier country-specific (France) protocol amendment into global protocol.
Section 12.1 Analysis population	A sentence has been added to clarify that further details of additional analysis populations will be described in the SAP, which will be finalized prior to study unblinding.	Updated for clarity.
Section 12.2.1 General Methods, paragraph 3	Updated the text to specify Week 8 of the Main Portion of the study.	To clarify that the snapshot will be taken after the Week 8 visit.
Section 12.2.2 Subject Disposition	Sentence has been updated to clarify that subject disposition breakdowns will include reasons for discontinuation and the disposition for the Main Portion as well as Extension Portion will be provided.	Updated for clarity.
Section 12.2.4.1 Adverse Events	The last sentence has been updated to clarify that SAEs occurring before first dose of study drug will be listed.	To align with the Time and Events Table 1.
Section 12.2.5.1 Primary Efficacy Analysis	Efficacy analysis has been updated from 2-sided Wilcoxon rank sum test to the 2-sided stratified Wilcoxon rank sum test (Van Elteren test). Primary estimands have been included.	The Van Elteren version of the Wilcoxon rank sum test has been selected to provides a more specific analysis. To align with the updated ICH E9 (R1) addendum.

Section # and Name	Description of Change	Brief Rationale
Section 12.2.5.2 Secondary Efficacy Analysis	Definition of the secondary estimands have been included.	To align with the updated ICH E9 (R1) addendum.
Section 12.2.6.1 Pharmacokinetic and Pharmacodynamic Analysis	Details of a potential population pharmacokinetic analysis and reporting have been added.	To conduct, if necessary, additional investigation to support the clinical development of zilucoplan in IMNM.
Section 12.2.7 Interim analysis	Updated the text to specify Week 8 of the Main Portion of the study.	To clarify that the snapshot will be taken after the Week 8 visit.
Sponsor Signature Page	Moved sponsor signature page to end of document.	Alignment with UCB document practices, including the use of electronic sponsor signatures.

1 SYNOPSIS

Protocol Title	A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Efficacy of Zilucoplan in Subjects with Immune-Mediated Necrotizing Myopathy
Protocol Number	RA101495-02.202 (UCB Study IMNM01)
Phase of Clinical Development	Phase 2
Investigational Medicinal Product	Zilucoplan (RA101495) administered by daily subcutaneous (SC) injection (0.3 mg/kg)
Study Population	Immune-Mediated Necrotizing Myopathy (IMNM)
Investigative Sites	Approximately 7 centers are planned worldwide
Planned Number of Subjects	Approximately 24 subjects (12 per treatment arm)

Study Objectives

- To evaluate the safety and tolerability of zilucoplan in subjects with IMNM
- To evaluate the efficacy of zilucoplan in subjects with IMNM

  Please note: The long-term safety, tolerability, and efficacy will be evaluated during the open-label Extension Portion of the trial.

Study Design

This study is a multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and efficacy of zilucoplan in subjects with IMNM who are positive for anti-HMGCR (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase) or anti-SRP (signal recognition particle) autoantibodies.

The planned enrollment is approximately 24 subjects. Subjects will be randomized in a 1:1 ratio to receive daily SC doses of 0.3 mg/kg zilucoplan or matching placebo. Randomization will be stratified based on antibody status (anti-HMGCR+ versus anti-SRP+).

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

Randomized subjects will receive 0.3 mg/kg zilucoplan or matching placebo administered SC at the Day 1 visit. Following in-clinic education and training, all subjects will self-inject daily SC doses of blinded study drug, according to randomized treatment allocation, for the subsequent 8 weeks. Single-use pre-filled syringes in injection devices will be provided for use during the study.

All standard of care (SOC) therapy medications for IMNM should be kept at the same doses throughout the study, including corticosteroids, immunosuppressive drugs, and intravenous immunoglobulin (IVIG).

To reduce the risk of meningococcal infection (*Neisseria meningitidis*), all subjects must be vaccinated against meningococcal infections (with a quadrivalent vaccine and, where available and in accordance with local SOC, serogroup B vaccine) within 3 years prior to, or at the time of, initiating study drug. Subjects who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics (e.g., ciprofloxacin, erythromycin, penicillin V) until at least 2 weeks after initial dose of vaccine(s). Booster vaccinations should be administered in accordance with local SOC.

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

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

At the conclusion of the Treatment Period of the study, all subjects will have the option to receive zilucoplan in the Extension Portion of the study provided they meet the Extension Portion selection criteria. Visits during the first 8 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. The study will remain double-blinded until after the data from Week 8 of the Main Portion of the study have been reviewed, locked, and unblinded.

If a subject permanently discontinues study drug treatment prior to the Week 8 visit for any reason, he/she will not be eligible for the Extension Portion. For subjects who permanently discontinue treatment with study drug, a Safety Follow-up Visit will be performed at 40 days after the last dose to collect information on any ongoing AEs or new SAEs since the last study visit.

Duration of Study Participation

Main Portion: The duration of study participation during the Main Portion will include a Screening Period of up to 4 weeks and an 8-week Treatment Period for a total of approximately 12 weeks.

Extension Portion: The investigational medicinal product (IMP) will continue to be provided by the Sponsor until zilucoplan is approved and available in the territory (e.g. in another qualifying extension study begins) or until the Sponsor terminates development of zilucoplan for IMNM. In countries where zilucoplan is not approved or marketed, but in which sponsored clinical studies have been conducted, subjects may continue to receive zilucoplan through a compassionate use pathway.

For France only: The duration of study participation during the Extension Portion of this study (RA101495-02.202) will include an open-label, single-arm, 18-month Treatment Period.

Inclusion/Exclusion Criteria

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

1. Male or female ≥ 18 years and < 75 years.
2. Able to provide informed consent, including signing and dating the informed consent form (ICF).
3. Clinical diagnosis of IMNM (Immune-Mediated Necrotizing Myopathy).
4. Positive serology for anti-HMGCR or anti-SRP autoantibodies.
5. Clinical evidence of weakness (≤ grade 4 out of 5) on manual muscle testing in at least one proximal limb muscle group.
6. Creatinine kinase (CK) of >1000 U/L at Screening.
7. No change in corticosteroid dose for at least 30 days prior to Baseline or anticipated to occur during the first 8-weeks on study.
8. No changes in immunosuppressive therapy, including dose, for at least 30 days prior to Baseline or anticipated to occur during the first 8-weeks on study.
9. Female subjects of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test within 24 hours prior to the first dose of study drug.
10. Sexually active female subjects of childbearing potential (i.e., women who are not postmenopausal or who have not had a hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) and all male subjects (who have not been surgically sterilized by vasectomy) must agree to use effective

contraception during the study. Postmenopausal women are, for the purposes of this protocol, defined as women who have gone 12 consecutive months without menstruation.

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

1. History of meningococcal disease.
2. Current or recent systemic infection within 2 weeks prior to Screening or infection requiring intravenous (IV) antibiotics within 4 weeks prior to Screening.
3. Pregnant, planning to become pregnant, or nursing female subjects.
4. Recent surgery requiring general anesthesia within 2 weeks prior to Screening or expected to have surgery requiring general anesthesia during the 8-week Treatment Period.
5. Treatment with a complement inhibitor or an experimental drug within 30 days or 5 half-lives of the drug (whichever is longer) prior to Baseline.
6. Statin use within 30 days prior to Baseline or anticipated to occur during study.
7. Rituximab use within 90 days prior to Baseline or anticipated to occur during study.

   NOTE: In subjects who received rituximab more than 90 days but less than 6 months prior to Baseline, prophylactic antibiotics (e.g., ciprofloxacin, erythromycin, penicillin V) should be given upon initiation of study drug until 6 months after the last rituximab dose.
8. Recent initiation of intravenous immunoglobulin (IVIG) (i.e., first cycle administered less than 90 days prior to Baseline).
9. Plasma exchange within 4 weeks prior to Baseline or expected to occur during the 8-week Treatment Period.
10. Active malignancy (except curatively resected squamous or basal cell carcinoma of the skin) requiring surgery, chemotherapy, or radiation within the prior 12 months (subjects with a history of malignancy who have undergone curative resection or otherwise not requiring treatment for at least 12 months prior to Screening with no detectable recurrence are allowed).
11. History of any significant medical, psychiatric disorder, or laboratory abnormality that in the opinion of the investigator would make the subject unsuitable for participation in the study.
12. Participation in another concurrent clinical trial involving an experimental therapeutic intervention (participation in observational studies and/or registry studies is permitted).
13. Unable or unwilling to comply with the requirements of the study.
14. Subjects who have a known hypersensitivity to zilucoplan or any of its excipients.

Study Objectives and Endpoints

Objectives	**Estimands / Endpoints**
Primary	
Primary Objective: to evaluate the safety and efficacy of zilucoplan over placebo in CK levels in participants with IMNM	Primary Efficacy Estimand: • Treatment: Zilucoplan administered by daily SC injection (0.3 mg/kg) vs matching placebo. • Target Population: is defined through the inclusion/exclusion criteria in Section 8.1 and Section 8.2 of the study protocol reflecting the targeted IMNM population. • Endpoint: Percent change from Baseline to Week 8 in CK levels. • Intercurrent event (ICE) handling: regardless of any treatment

	discontinuation for any reason; censoring after prohibited medication. • Population level summary: The difference in ranks of the percentage change from baseline between treatments followed by the Wilcoxon-Mann-Whitney odds (WMWodds) and Hodges–Lehmann estimator followed by the corresponding 95% Confidence Intervals (CI). Primary Safety Endpoint • Incidence of treatment-emergent adverse events.	
Secondary		
Secondary Objective(s): to further evaluate the efficacy and the safety of zilucoplan over placebo in participants with IMNM	Secondary Efficacy Estimands: • Treatment: Zilucoplan administered by daily SC injection (0.3 mg/kg) vs matching placebo. • Target Population: is defined through the inclusion/exclusion criteria in Section 8.1 and Section 8.2 of the study protocol reflecting the targeted IMNM population. • Endpoints: o At least minimal response based on the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Response Criteria Scale at Week 8; o Change from Baseline to Week 8 in Triple Timed Up and Go (3TUG) Test (in ambulatory patients only); o Change from Baseline to Week 8 in Proximal Manual Muscle Testing (MMT); o Change from Baseline to Week 8 in Physician Global Activity Visual Analogue Scale (VAS); o Change from Baseline to Week 8 in Patient Global Activity VAS; o Change from Baseline to Week 8 in Health Assessment Questionnaire (HAQ); o Change from Baseline to Week 8 in myositis disease activity assessment tool (MDAAT) Extramuscular Disease Activity VAS Score; o Change from Baseline to Week 8 in Functional Assessment of Chronic	

	Illness Therapy (FACIT)-Fatigue Scale; • ICE handling: regardless of any treatment discontinuation for any reason; censoring after administration of prohibited medication. • Population level summary: o Odds Ratio of ACR/EULAR ≥ 20 response proportion between treatment conditions; o Difference in continuous endpoint means, between treatment conditions.	
Other		
To further evaluate the safety of zilucoplan over placebo in participants with IMNM	Other safety endpoints • Change in clinical laboratory tests • Change in ECG parameters • Change vital signs parameters, and • Presence of Anti-Drug Antibodies	
Exploratory		
To assess the long term efficacy of zilucoplan	• At least minimal response based on the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Response Criteria Scale at each visit following Week 8; • Change from Baseline of Timed Up and Go (3TUG) Test (in ambulatory patients only) at each visit following Week 8; • Change from Baseline of Proximal Manual Muscle Testing (MMT) at each visit following Week 8; • Change from Baseline of Physician Global Activity Visual Analogue Scale (VAS) at each visit following Week 8; • Change from Baseline of Patient Global Activity Visual Analogue Scale (VAS) at each visit following Week 8; • Change from Baseline of Health Assessment Questionnaire (HAQ) at each visit following Week 8;	

	• Change from Baseline of MDAAT Extramuscular Disease Activity VAS Score at each visit following Week 8; • Change from Baseline of FACIT-Fatigue Scale at each visit following Week 8;
To assess the pharmacokinetics (PK) of zilucoplan	• Plasma concentrations of zilucoplan and its major metabolites
To assess the pharmacodynamics (PD) of zilucoplan	• Sheep red blood cell lysis assay for evaluation of classical complement pathway activation • Complement component 5 levels
To assess the effect of zilucoplan on biomarkers	• Mechanistic biomarkers [e.g., complement fixation, complement function, complement pathway proteins, autoantibody characterization (titer and immunoglobulin class), myocyte markers, and inflammatory markers].
To assess the effect of zilucoplan on pharmacogenomics	• Pharmacogenomic analyses (optional): Genomic studies [e.g., deoxyribonucleic acid (DNA) sequencing, including exploration of whether specific genomic features correlate with response or resistance to study drug] may be performed.

Statistical Considerations

Study Populations:

The following study populations are defined:

- *Intention-to-Treat (ITT) Population:* All subjects randomized.
- *Per Protocol Population*: All subjects in the ITT Population who have completed the 8-week Treatment Period and have no major protocol deviations.
- *Safety Population*: All subjects who have received at least 1 dose of study drug, with subjects to be analyzed based on the actual study treatment received.

General Considerations: A disposition of all consented subjects will be provided and will include a breakdown of subjects who were randomized, were treated, and discontinued treatment (including reasons for discontinuation).

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

Stratification of Randomization:

Subjects will be randomized in a 1:1 ratio to receive daily SC doses of 0.3 mg/kg zilucoplan or matching placebo. Randomization will be stratified based on autoantibody status (anti-HMGCR+ versus anti-SRP+).

Determination of Sample Size:

A sample size of 12 subjects per group yields approximately 95% power to detect a difference in the percent reduction from baseline in creatine kinase between the active and placebo groups using a Wilcoxon rank sum test at the two-sided 0.05 type 1 error rate. The power calculations assume that the percent reduction in creatine kinase in the active dose group is approximately normally distributed with a mean of 80% and a standard deviation of 8%; that 4 of the placebo patients will have a percent reduction similar to the active dose group; and the remaining 8 placebo patients will have a percent reduction that is normally distributed with a mean of 10% and a standard deviation of 8%. The estimation of the creatine kinase baseline levels and treatment effect are based on the data presented in Mammen et Tiniakou, 2015 (Mammen and Tiniakou 2015).

Efficacy Analyses:

The primary efficacy endpoint, percent reduction from baseline in creatine kinase at Week 8, will be compared between the two treatment groups using a 2-sided stratified Wilcoxon rank sum test (Van Elteren test).

Treatment group differences for each of the continuous secondary efficacy change from baseline endpoints will be assessed using a mixed model analysis of covariance (ANCOVA) with treatment and baseline score as fixed effects and subject as a random effect. Additional subgroup analyses, including autoantibody serotype, will be prespecified in the SAP.

The effect of Zilucoplan on ACR/EULAR minimal response will be investigated using a binary logistic regression model with treatment and stratification included as factors.

Safety:

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Incidence rates for treatment-emergent AEs will be summarized overall, by maximum severity, and by relationship to study drug for each treatment group. SAEs will also be summarized by treatment group. Quantitative laboratory endpoints will be summarized by treatment group at each scheduled assessment time point using descriptive statistics. Descriptive statistics for ECG parameters [i.e., heart rate (HR), PR interval, RR interval, QRS interval, and QT interval at each assessment time point will be presented by treatment group. Descriptive statistics for vital signs (HR, body temperature, and blood pressure) will be presented by treatment group. Clinically significant physical examination abnormalities will be reported as AEs, when appropriate.

Pharmacokinetics:

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

Pharmacodynamics:

Pharmacodynamic endpoints will be summarized using descriptive statistics.

2 SCHEDULE OF ASSESSMENTS

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

Table 1: MAIN PORTION Time and Events Table

			Week 1	*Week 2*	*Week 4*	*Week 8*	
Study Procedure	**Screening** Days -28 to -1	**Day 1** ('Baseline')	**Day 8** (± 2 days)	**Day 15** (± 2 days)	**Day 29** (± 2 days)	**End of Main[a] Day 57** (± 7 days)	**Safety Follow-up Visit[a]** (last dose + 40d)
Informed consent[b]	X						
Review eligibility[b]	X						
Randomization		X					
Medical history[c] and demographics	X						
Height[d] and weight	X				X	X	
Prior and concomitant medications[e]	X	X	X	X	X	X	X
Safety							
Physical examination	X	X	X	X	X	X	X
Vital signs[f]	X	X	X	X	X	X	X
12-Lead electrocardiogram	X					X	
Neisseria meningitidis vaccination[g]	X	SOC	SOC	SOC	SOC	SOC	
Prophylactic antibiotics[g] *(if applicable)*		X	X	X			
Hematology/Chemistry/CK[h]	X	X	X	X	X	X	
Coagulation[h,i]	X	X	X	X	X	X	
Urinalysis[h]	X	X	X	X	X	X	
Pregnancy test[j]	X	X	X	X	X	X	X
Adverse events[k]	X	X	X	X	X	X	X[k]
Anti-drug antibody[h]	X		X		X	X	
Efficacy							
3TUG[l,m]	X	X			X	X	
Proximal MMT[l]	X	X			X	X	
Physician Global Activity VAS[l]	X	X			X	X	
Patient Global Activity VAS[l]	X	X			X	X	
HAQ[l]	X	X			X	X	
MDAAT[l]	X	X			X	X	
FACIT-Fatigue[l]	X	X			X	X	
Pharmacokinetic/Pharmacodynamic							
Zilucoplan plasma PK[n]		X	X	X	X	X	
Pharmacodynamic analysis[n]		X	X	X	X	X	
Exploratory							
Autoantibodies testing[o]	X	X			X	X	
Biomarker testing[p]		X	X	X	X	X	
Pharmacogenomic analysis *(optional)*[q]	X						
Study Drug							
Zilucoplan or placebo administration[r]		X	X	X	X	X	

See footnotes on following page.

1-a. If a subject permanently discontinues study drug prior to completion of the Day 57 visit during the Main Portion, the subject should return to clinic for an End of Main Visit. If a subject consents to the Extension Portion, please see Table 2 for Day 57/E1 assessments. If a subject permanently discontinues study drug treatment prior to the Week 8 visit for any reason, he/she will not be eligible for the Extension Portion. For subjects who permanently discontinue treatment with study drug, a Safety Follow-up Visit will be performed at 40 days after the last dose to collect information on any ongoing AEs or new SAEs since the last study visit.

1-b. 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. Eligibility must be established prior to randomization on Day 1.

1-c. Screening includes a detailed history of IMNM diagnosis information and local serology for anti-HMGCR or anti-SRP autoantibodies from a reputable laboratory.

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

1-e. 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 all medication taken for the treatment of IMNM will be collected.

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

1-g. To reduce the risk of meningococcal infection (*Neisseria meningitidis*), all subjects must be vaccinated against meningococcal infections (with a quadrivalent vaccine and, where available and in accordance with local SOC, serogroup B vaccine) within 3 years prior to, or at the time of, initiating study drug. Subjects who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics (e.g., ciprofloxacin, erythromycin, penicillin V) until at least 2 weeks after initial dose of vaccine(s). Booster vaccinations should be administered in accordance with local SOC.

NOTE: In subjects who received rituximab more than 90 days but less than 6 months prior to Baseline, prophylactic antibiotics (e.g., ciprofloxacin, erythromycin, penicillin V) should be given upon initiation of study drug until 6 months after the last rituximab dose.

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

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

1-j. 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-k. 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. Subjects will attend a clinic visit 40 days after their last dose to gather information on ongoing AEs and report any new SAEs since the last study visit. Only SAEs are collected during the screening period.

1-l. The clinical assessments should be performed at approximately the same time of day (preferably in the morning) and should be administered in the same order by the same well-trained evaluator (e.g., neurologist, physical therapist, or other study staff) at each visit throughout the study.

1-m. 3TUG will only be completed in subjects who are ambulatory.

1-n. Blood samples for PK and PD analysis will be obtained prior to administration of study drug (within 1 hour of dosing).

1-o. Confirmatory serology testing for anti-HMGCR or anti-SRP autoantibodies will be done at a central laboratory.

1-p. Blood samples for biomarker testing will be obtained prior to administration of study drug (within 1 hour of dosing).

1-q. The pharmacogenomic sample may be collected at any study visit.

1-r. Dosing on study visit days should be held until clinical assessment and blood collection has been completed.

Table 2: EXTENSION PORTION Time and Events Table

	Month 2			*Month 3*	*Month 4*	*Month 5*	*Month 6*	Visits after Day E117[b]			
Study Procedure	**Day E1[a] (Day 57)**	**Day E8 (± 2 days)**	**Day E15 (± 2 days)**	**Day E29 (± 2 days)**	**Day E57 (± 7 days)**	**Day E87 (± 7 days)**	**Day E117 (± 7 days)**	**Each Month (± 7 days)**	**Every 3 Months (± 7 days)**	**Final Extension Visit[c]**	**Safety Follow-up Visit (last dose + 40d)**
Informed consent	X										
Review eligibility and randomization	X										
Weight	X			X	X		X		X	X	
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Safety											
Physical examination	X	X	X	X	X		X		X	X	X
Vital signs[d]	X	X	X	X	X		X		X	X	X
12-Lead electrocardiogram	X				X				X		
Neisseria meningitidis vaccination[e]	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC		
Hematology/Chemistry/CK[f]	X	X	X	X	X		X		X	X	
Coagulation[f, g]	X	X	X	X	X		X		X	X	
Urinalysis[f]	X	X	X	X	X		X		X	X	
Pregnancy test[h]	X	X	X	X	X	X	X	X	X	X	X
Adverse events[i]	X	X	X	X	X	X	X	X	X	X	X[h]
Anti-drug Antibody[f]	X	X		X	X		X		X	X	
Efficacy											
3TUG[j,k]	X			X	X		X		X	X	
Proximal MMT[j]	X			X	X		X		X	X	
Physician Global Activity VAS[j]	X			X	X		X		X	X	
Patient Global Activity VAS[j]	X			X	X		X		X	X	
HAQ[j]	X			X	X		X		X	X	
MDAAT[j]	X			X	X		X		X	X	
FACIT-Fatigue[j]	X			X	X		X		X	X	
Pharmacokinetic/Pharmacodynamic											
Zilucoplan plasma PK[l]	X	X	X	X	X		X		X	X	
Pharmacodynamic analysis[l]	X	X	X	X	X		X		X	X	
Exploratory											
Autoantibodies testing	X			X	X		X		X	X	
Biomarker testing[m]	X	X	X	X	X		X		X	X	
Study Drug											
Zilucoplan administration[n]	X	X	X	X	X	X	X	X	X	X	

See footnotes on following page.

2-a. For subjects that decide and are eligible to continue in the Extension Portion of the study, the Day 57 visit from the Main Portion will serve as the Day E1 visit and will also include review of eligibility to continue (see Section 8.3) and signing of an informed consent for the Extension Portion.

2-b. For France only: The duration of study participation during the Extension Portion of this study (RA101495-02-202) will include an open-label, single-arm, 18-month Treatment Period.

2-c. If a subject discontinues study drug treatment at any time during the Extension Portion, the subject should return to clinic for a Final Extension 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 of the study, 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 after clinical assessments and prior to administration of study drug at applicable visits.

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. Subjects will attend a clinic visit 40 days after their last dose to gather information on ongoing AEs and report any new SAEs since the last study visit.

2-j. The clinical assessments should be performed at approximately the same time of day (preferably in the morning) and should be administered in the same order by the same well-trained evaluator (e.g., neurologist, physical therapist, or other study staff) at each visit throughout the study.

2-k. 3TUG will only be completed in subjects that are ambulatory.

2-l. Blood samples for PK and PD analysis will be obtained prior to administration of study drug (within 1 hour of dosing).

2-m. Blood samples for the exploratory tests will be obtained prior to administration of study drug (within 1 hour of dosing).

2-n. Dosing on study visit days should be held until clinical assessment and blood collection has been completed.

3 TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

4 LIST OF ABBREVIATIONS AND DEFINITIONS

3TUG	Triple Timed Up and Go Test
ADA	anti-drug antibody
AChR	acetylcholine receptor
ACR	American College of Rheumatology
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP	alternative pathway of the complement cascade
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BUN	blood urea nitrogen
C5	complement component 5
C6	complement component 6
CFB	change from baseline
CK	creatine kinase
CI	confidence interval
COVID-19	coronavirus disease 2019
CP	classical pathway of the complement cascade
CRO	Clinical Research Organization
CRP	C-reactive protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DAP	data analysis plan
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EMG	electromyography
ENMC	European Neuromuscular Center
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue Scale
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
gMG	generalized myasthenia gravis
HAQ	Health Assessment Questionnaire
HCG	human chorionic gonadotropin
HMGCR	3-hydroxy-3-methyl-glutaryl-coenzyme A reductase
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IMNM	immune-mediated necrotizing myopathy
INR	international normalized ratio
IRB	Institutional Review Board
ITT	Intention-to-Treat Population
IV	intravenous
IVIG	intravenous immunoglobulin
IXRS	interactive voice/web response system
LDH	lactate dehydrogenase
LOCF	last observation carried forward
LS	least squares
LSLV	last subject last visit
MAC	membrane attack complex (C5b-9)
MBL	Mannose-binding Lectin pathway of the complement cascade
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MD	multiple dose
MDAAT	myositis disease activity assessment tool
MedDRA	Medical Dictionary for Regulatory Activities
MG-ADL	MG-Activities of Daily Living Scale
MGC	MG Composite Scale
MG-QOL15r	MG-Quality of Life 15 (revised)
MITAX	myositis intention to treat activity index
MMRM	mixed model with repeated measures
MMT	manual muscle testing
MRI	magnetic resonance imaging
MYOACT	myositis disease activity assessment visual analogue scales
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
PT	prothrombin time
PTT	partial thromboplastin time
QMG	Quantitative Myasthenia Gravis Scale
RBC	red blood cell
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SC	subcutaneous
SD	standard deviation
se	standard error
SMC	Safety Monitoring Committee
SOC	standard of care
SOP	standard operating procedure
sRBC	sheep red blood cell
SRP	signal recognition particle
TEAE	treatment-emergent adverse event
TMF	trial master file
ULN	upper limit of normal
VAS	visual analogue scale
WBC	white blood cell

5 INTRODUCTION

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

Please refer to the IB for additional information on the chemistry, toxicology, pharmacology, and safety of zilucoplan.

5.1 OVERVIEW OF IMMUNE-MEDIATED NECROTIZING MYOPATHY

Immune-mediated necrotizing myopathy (IMNM) is a rare, severe, inflammatory myopathy characterized by proximal limb weakness; markedly elevated serum creatine kinase (CK) levels; the presence of anti-SRP or anti-HMGCR auto-antibodies in serum; and paucicellular necrosis with prominent terminal complement deposition on muscle biopsy. IMNM is a relatively newly defined inflammatory myopathy, a group of diseases that also includes polymyositis, dermatomyositis, inclusion body myositis, and other, less well-defined myopathies. Previously, all patients who presented with proximal limb weakness and elevated CK, in the absence of skin involvement were classified as having polymyositis. However, many patients with the diagnostic label of 'polymyositis' were subsequently found to have distinctive findings on muscle biopsy as described above (Amato and Griggs 2003), leading to their separate classification as 'necrotizing myopathy'. Subsequently, autoantibodies against HMGCR, a key enzyme in cholesterol biosynthesis, and SRP, a ubiquitous ribonucleoprotein involved in delivery of newly synthesized proteins to the endoplasmic reticulum, were found to be associated with this new entity which led to its designation as IMNM (see Pinal Fernandez 2018 for review).

The prevalence of IMNM is estimated at approximately 16,000 patients in the US, Europe and Japan (Pinal-Fernandez 2018, Smoyer-Tomic 2012, Anquetil 2019). The disease is more common in women than in men. It does not show any clear racial predominance amongst Caucasians, Black or Asian populations, except for the association of anti-HMGCR positive IMNM with statin use, which is higher in non-Asian populations. The mean age at presentation is approximately 40 to 55 years old (Pinal-Fernandez 2018).

Clinically, IMNM presents with prominent proximal limb weakness due to the myopathy and can progress rapidly to disabling muscle atrophy. Although the clinicopathological presentation is generally similar among patients with anti-SRP and anti-HMGCR antibodies, there are subtle differences that have emerged since reliable and validated assays for these pathogenic autoantibodies have become more widely available. Patients with anti-SRP antibodies usually experience more severe weakness; more frequent neck weakness, dysphagia and respiratory insufficiency; and more prominent muscle atrophy. Moreover, clinically manifest cardiac involvement occurs in approximately 15% of patients with anti-SRP autoantibodies. In contrast, extra-muscular manifestations are rare in patients with anti-HMGCR autoantibodies (Pinal-Fernandez 2018).

Muscle biopsy, muscle MRI and EMG are often used for narrowing of the differential diagnosis and further characterization of patients with IMNM. However, based on criteria set forth by the 224th European Neuromuscular Center (ENMC) International Workshop

which included experts from Europe, the US, and Japan, these additional investigations are not required to confirm the diagnosis of IMNM in patients with the characteristic clinical picture of high CK levels and positive anti-SRP or anti-HMGCR autoantibodies (Y. e. Allenbach 2018). If a muscle biopsy is performed, findings typically include myofiber necrosis and, in contrast to other inflammatory myopathies, only small numbers of infiltrating inflammatory cells. Moreover, with specific staining, prominent complement activation and diffuse deposition of the C5b-9 membrane attack complex (MAC) are observed, the pattern of which is distinct from other inflammatory myopathies (Cong 2014). MRI may demonstrate fatty replacement of muscle tissue which begins early after onset of IMNM (Pinal-Fernandez 2018), and EMG may confirm the presence of a myopathic pattern, and rules out other causes of muscle weakness.

IMNM patients invariably exhibit the greatest elevation of serum CK levels seen among all forms of myositis, and serum CK levels correlate well with disease activity. Unlike in myopathies with less prominent tissue destruction, plasma CK levels in IMNM directly reflect the degree of myocyte necrosis due to ongoing release of this enzyme from injured skeletal muscle cells. Therefore, CK can be used for routine clinical follow-up and to evaluate treatment response in patients with IMNM, in addition to clinical measures such as standardized muscle strength testing. Specifically, CK levels may increase prior to manifestation or deterioration of clinical weakness, and a decline in CK levels is often the first sign of treatment response after treatment initiation while muscle regeneration and recovery of muscle strength may follow weeks to months later (Pinal-Fernandez 2018).

Given the rapidly progressing symptoms and muscle pathology in IMNM, timely diagnosis and initiation of treatment are critical to help reduce long-term disability and improve prognosis. While most immune mediated myopathies, to varying degrees, are responsive to non-specific immunosuppressive therapy, there are currently no FDA approved treatments for IMNM, and no randomized trials have been performed. The ENMC treatment recommendations identify corticosteroids as first line therapy in combination with, or rapidly followed by, an immunosuppressive agent such as methotrexate depending on disease severity. Intravenous immunoglobulin (IvIg) and rituximab are also increasingly used as first line therapy (Allenbach and Benveniste 2018).

Despite the treatments outlined above, disabling relapses and progressive muscle damage often continue, with particularly poor prognosis and permanent disability observed in younger patients and those with anti-SRP autoantibodies (Allenbach and Benveniste 2018). Therefore, a high unmet medical need exists for additional treatment options for patients with IMNM.

5.2 MECHANISM OF ACTION OF ZILUCOPLAN

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

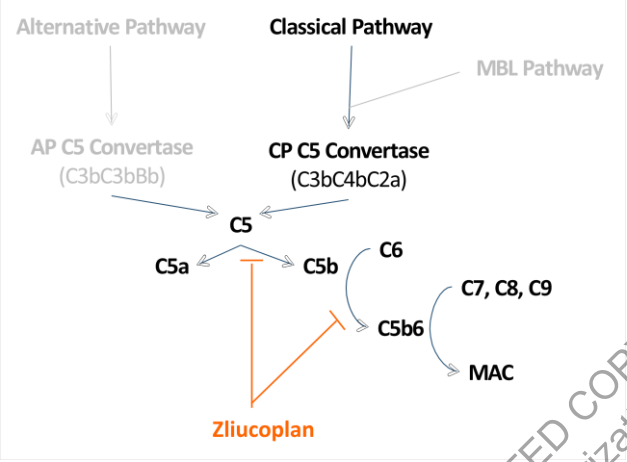
Using surface plasmon resonance and analysis of a high-resolution co-crystal structure, zilucoplan has been shown to bind to a specific site on C5 and to exhibit a strong and

rapid association with C5, coupled with a slow dissociation rate. Zilucoplan binds to the portion of C5 which corresponds to C5b. In binding to this region of C5, should any C5b be formed, it will be blocked from binding to C6 by zilucoplan, which further prevents the subsequent assembly of the MAC (C5b-9).

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

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

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



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

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

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

5.3 CLINICAL TRIAL EXPERIENCE WITH ZILUCOPLAN

Zilucoplan is currently in advanced clinical development by Ra Pharmaceuticals, Inc. for the treatment of patients with generalized myasthenia gravis (gMG) and paroxysmal nocturnal hemoglobinuria (PNH).

5.3.1 ZILUCOPLAN PHASE 1 EXPERIENCE

RA101495-1001 was a randomized, double-blind, placebo-controlled, single-ascending dose (SAD) and multiple-dose (MD) study in healthy volunteers. The study was

conducted to evaluate the safety, tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) of single-ascending doses of zilucoplan at dose levels of 0.05, 0.10, 0.20, and 0.40 mg/kg administered by SC injection, and multiple-doses of 0.20 mg/kg administered SC once daily for 7 days. Zilucoplan displayed a dose-proportional and predictable pharmacokinetic profile that was tightly correlated with the intended pharmacodynamic effect, suppression of the terminal complement pathway.

Study RA101495-03.101 was an open-label, single dose Phase 1 pharmacokinetic study of zilucoplan in subjects with severe renal impairment (as defined by a creatinine clearance < 30 ml/min) and healthy controls who received a single dose of 0.3 mg/kg zilucoplan SC. A total of 16 subjects were enrolled into this study: 8 subjects with severe renal impairment and 8 healthy controls. Based on the data from this study, there is no significant impact of reduced creatinine clearance on the elimination of zilucoplan, and therefore no dose adjustment is needed for the use of zilucoplan in patients with renal impairment.

Study RA101495-01.102 was a double-blind, single- and multiple-dose Phase 1 study evaluating safety and tolerability of zilucoplan in healthy Japanese subjects in comparison to healthy Caucasian subjects. A total of 36 subjects were enrolled into this study: 18 Japanese subjects and 18 Caucasian subjects. Based on the data from this study, there is no significant difference between Caucasian and Japanese subjects with respect to the pharmacokinetic, pharmacodynamic, and safety profiles of zilucoplan.

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

5.3.2 ZILUCOPLAN PHASE 2 EXPERIENCE

5.3.2.1 COMPLETED PHASE 2 STUDY IN gMG

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

The following clinical assessments were performed in Study RA101495-02.201 to evaluate efficacy: The Quantitative Myasthenia Gravis (QMG) scale was the primary outcome measure, and the secondary outcome measures included the MG-ADL (MG-Activities of Daily Living), the MGC (MG Composite), and the MG-QOL15r [MG-Quality of Life 15 (revised)]. The study met its primary endpoint, showing a rapid, statistically significant, and clinically meaningful difference on the QMG between the 0.3 mg/kg zilucoplan and placebo groups, favoring zilucoplan. Additional analyses supported the primary analysis and showed a consistent clinical benefit of zilucoplan over placebo. The results for the primary and secondary analyses are presented in Table 3.

Table 3: Clinical Efficacy Outcomes in Study RA101495-02.201 at Week 12 (ANCOVA)

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

* p-values are one-sided based on an ANCOVA model with baseline values as a covariate and using LOCF for subjects who received rescue therapy

Abbreviations: ANCOVA = analysis of covariance; CFB = change from baseline; LOCF = last observation carried forward; LS = least squares; MG-ADL = MG-Activities of Daily Living; MG-QOL15r = MG-Quality of Life 15 (revised); MGC = MG Composite; QMG = quantitative myasthenia gravis; se=standard error

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

5.3.2.2 COMPLETED PHASE 2 STUDIES IN PNH PATIENTS

The global, dose-finding Phase 2 PNH program consisted of studies RA101495-01.201 and RA101495-01.203 as well as a long-term extension protocol RA101495-01.202. A total of 32 subjects were screened in the zilucoplan Phase 2 PNH program, of which 29 subjects were enrolled, 2 subjects did not meet eligibility criteria, and 1 subject declined to participate. Studies RA101495-01.201 and RA101495-01.203 included an 8-week screening period and a 12-week Treatment Period. During the Treatment Period, subjects returned to the clinic weekly for the first 4 weeks followed by visits every 2 weeks. At the conclusion of the Treatment Period, subjects who completed the study and were demonstrating benefit had the option to enroll in the long-term extension protocol (RA101495-01.202).

In treatment-naïve patients, zilucoplan achieved rapid, complete, and sustained inhibition of complement activity in the sheep red blood cell (sRBC) and MAC ELISA assays. Study RA101495-01.201 (Cohort A, n=10) met the pre-specified primary endpoint for LDH reduction from baseline (1174 U/L) to the mean of Week 6 to 12 (479 U/L) in treatment-naïve subjects, (p=0.002). The effects of zilucoplan on LDH, transfusion-requirements, and quality of life measures in treatment-naïve patients were all similar to those observed with eculizumab in the pivotal TRIUMPH study (Hillmen P 2006).

In patients switching from eculizumab to zilucoplan (Study RA101495-01.201 Cohort B and Study RA101495-01.203) near-complete, sustained, and uninterrupted inhibition of complement activity was observed in the sRBC and MAC ELISA assays during and after eculizumab washout. The level of complement inhibition achieved on zilucoplan exceeded the level of inhibition present at eculizumab trough. However, a divergent LDH response after switching from eculizumab to zilucoplan was observed. In switch patients with no evidence of pre-existing extravascular hemolysis on eculizumab (i.e., transfusion-independent and reticulocytes < 2 × ULN), switching was successful in all

cases with sustained LDH control after eculizumab washout. In switch patients with pre-existing extravascular hemolysis on eculizumab (i.e., transfusion-dependent or reticulocytes > 2 × ULN), there was a high incidence of breakthrough intravascular hemolysis resulting in early withdrawal from the study.

Please refer to the zilucoplan IB for additional information regarding the results from studies RA101495-01.201 and RA101495-01.203 as well as the long-term extension protocol (RA101495-01.202).

5.4 RATIONALE FOR THE CURRENT STUDY

There is substantial pre-clinical and clinical evidence supporting a role for the terminal complement cascade in the pathogenesis of IMNM (Cong 2014) (Y. e. Allenbach 2018). 80% of anti-SRP and 100% of anti-HMGCR autoantibodies are of the IgG1 immunoglobulin subclass which efficiently activates the classical pathway of complement (Anquetil 2019). These autoantibodies bind to skeletal muscle and the immune complex formed by the autoantibody-antigen interaction is recognized by the initiating component of the classical complement pathway, the C1 complex. Binding of the C1 complex leads to a series of enzymatic cleavage steps culminating in the cleavage of C5 into C5a and C5b and deposition of MAC onto the sarcolemma, a characteristic finding in IMNM muscle biopsies (Y. e. Allenbach 2018).

This uncontrolled and inappropriate activation of the classical complement cascade in muscle tissue is thought to lead to the characteristic histopathological findings and ultimately clinical weakness in patients with IMNM. Inhibition of the terminal complement pathway by zilucoplan is expected to prevent MAC deposition; to attenuate cell injury; reduce muscle cell derived creatine kinase in plasma; and potentially attenuate or even reverse clinical manifestations of IMNM.

The compelling treatment effect observed with zilucoplan in patients with anti-AChR positive gMG (Section 5.3.2.1), a similar disease which shares with IMNM autoantibody-driven hyperactivation of the classical complement pathway in skeletal muscle, supports the evaluation of zilucoplan as a potential therapy for IMNM in the present study.

5.4.1 RATIONALE FOR PRIMARY ENDPOINT

IMNM patients invariably exhibit the greatest elevation of serum CK levels seen among all forms of myositis, and serum CK levels correlate well with disease activity. Unlike in myopathies with less prominent tissue destruction, plasma CK levels in IMNM directly reflect the degree of myocyte necrosis due to ongoing release of this enzyme from injured skeletal muscle cells. Therefore, CK can be used for routine clinical follow-up and to evaluate treatment response in patients with IMNM, in addition to clinical measures such as standardized muscle strength testing. Specifically, CK levels may increase prior to manifestation or deterioration of clinical weakness, and a decline in CK levels is often the first sign of treatment response after treatment initiation while muscle regeneration and recovery of muscle strength may follow weeks to months later (Pinal-Fernandez 2018). Given the reliable relationship between CK levels, disease activity and treatment response in IMNM, and the faster response and greater higher sensitivity of CK to

effective treatment interventions compared with clinical measures, CK was chosen as the primary endpoint for this phase 2 clinical trial.

5.4.2 RATIONALE FOR BLINDING AND PLACEBO CONTROL

The secondary objective of this study is the evaluation of efficacy based on functional outcomes including 3TUG and components of the ACR/EULAR scale. Such clinical assessments are prone to placebo effects and may be influenced by knowledge of treatment assignment by the clinical evaluator and/or subject. Moreover, the evaluation of potential adverse effects may also be influenced by knowledge of treatment assignment. To enable rigorous efficacy and safety evaluation without the potential bias caused by knowledge of treatment assignment, this study was designed as a double-blind, placebo-controlled study.

Subjects entering the study will have stable disease and will be allowed to continue all of their pre-existing SOC therapies. Therefore, subjects receiving placebo will not be subject to increased risk due to withholding of medically necessary interventions. In addition, the placebo study drug contains substances that are known to be well-tolerated ([redacted]) and are delivered in a small volume < 1 mL; therefore, placebo administration by daily SC injection over the 8-week study period is expected to be well-tolerated. Consequently, administration of a placebo in Study RA101495-02.202 is not anticipated to cause undue burden or risk for study subjects.

Following the completion of the 8-week Treatment Period in the Main Portion of the study, all subjects will have the option to receive zilucoplan in the Extension Portion of the study. Therefore, subjects originally randomized to placebo will eventually have the opportunity to receive active study drug. The study will remain double-blinded until after the data from Week 8 of the Main Portion of the study have been reviewed, locked, and unblinded.

5.4.3 DOSE SELECTION AND PRESENTATION

The dose of 0.3 mg/kg was selected for this study based on its superior efficacy, greater inhibition of the terminal complement pathway, and similar safety profile as compared with the 0.1 mg/kg and placebo arms in the completed Phase 2 studies in patients with myasthenia gravis and PNH.

In the Phase 2 Study in gMG patients (RA101495-02.201), the magnitude and speed of improvement on the primary (QMG) and key secondary (MG-ADL) endpoints were greater with the 0.3 mg/kg dose than the 0.1 mg/kg dose, and both active doses were superior to placebo (see Investigator's Brochure for additional details).

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

There was no apparent difference with respect to the pattern and distribution of adverse events or tolerability between the zilucoplan treated and the placebo groups. No dose response in the safety profile was seen between the 0.1 mg/kg and 0.3 mg/kg zilucoplan groups.

Similarly, in the Phase 2 studies in patients with PNH (RA101495-01.201, RA101495-01.202, and RA101495-01.203), the starting dose of 0.1 mg/kg daily tested did not consistently achieve complete inhibition of complement activity in the sRBC lysis assay. The 0.3 mg/kg daily dose, by contrast, consistently achieved complete inhibition in the sRBC lysis assay (≥95% inhibition at trough) and reduced LDH to levels similar to those observed in patients receiving eculizumab. It is expected that the same pharmacodynamic response to zilucoplan as seen in patients with MG and PNH, i.e. complete complement inhibition, will drive the therapeutic response in patients with IMNM. Therefore, the well-understood and extensively-tested dosing regimen for PNH and MG, i.e. 0.3 mg/kg daily dosing with three weight brackets, has again been selected for use in this study.

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 zilucoplan based on their weight, and each fixed amount will cover a range of subject weights). This weight-bracketed dosing strategy will result in the potential for a range of doses to be received at each dose level (see Section 9.1.3).

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 OBJECTIVES

Objectives	Estimands / Endpoints
Primary	
Primary Objective: to evaluate the safety and efficacy of zilucoplan over placebo in CK levels in participants with IMNM	Primary Efficacy Estimand: • Treatment: Zilucoplan administered by daily SC injection (0.3 mg/kg) vs matching placebo. • Target Population: is defined through the inclusion/exclusion criteria in Section 8.1 and Section 8.2 reflecting the targeted IMNM population. • Endpoint: Percent change from Baseline to Week 8 in CK levels. • Intercurrent event (ICE) handling: regardless of any treatment discontinuation for any reason; censoring after prohibited medication. • Population level summary: The difference in ranks of the percentage change from baseline between treatments followed by the Wilcoxon-Mann-Whitney odds (WMWodds)

	and Hodges–Lehmann estimator followed by the corresponding 95% CIs. Primary Safety Endpoint • Incidence of treatment-emergent adverse events.
Secondary	
Secondary Objective(s): to further evaluate the efficacy and the safety of zilucoplan over placebo in participants with IMNM	Secondary Efficacy Estimands: • Treatment: Zilucoplan administered by daily SC injection (0.3 mg/kg) vs matching placebo. • Target Population: is defined through the inclusion/exclusion criteria at Sections 8.1 and 8.2 of the study protocol reflecting the targeted IMNM population. • Endpoints: o At least minimal response based on the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Response Criteria Scale at Week 8; o Change from Baseline to Week 8 in 3TUG Test (in ambulatory patients only); o Change from Baseline to Week 8 in Proximal Manual Muscle Testing (MMT); o Change from Baseline to Week 8 in Physician Global Activity Visual Analogue Scale (VAS); o Change from Baseline to Week 8 in Patient Global Activity VAS; o Change from Baseline to Week 8 in Health Assessment Questionnaire (HAQ); o Change from Baseline to Week 8 in myositis disease activity assessment tool (MDAAT) Extramuscular Disease Activity VAS Score; o Change from Baseline to Week 8 in Functional Assessment of

	Chronic Illness Therapy (FACIT)-Fatigue Scale. • ICE handling: regardless of any treatment discontinuation for any reason; censoring after administration of prohibited medication. • Population level summary: o Odds Ratio of ACR/EULAR ≥ 20 response proportion between treatment conditions; o Difference in continuous endpoint means, between treatment conditions.
Other	
To further evaluate the safety of zilucoplan over placebo in participants with IMNM	Other safety endpoints • Change in clinical laboratory tests • Change in ECG parameters • Change vital signs parameters, and • Presence of Anti-Drug Antibodies
Exploratory	
To assess the long term efficacy of zilucoplan	• At least minimal response based on the ACR/EULAR Response Criteria Scale at each visit following Week 8; • Change from Baseline of 3TUG Test (in ambulatory patients only) at each visit following Week 8; • Change from Baseline of Proximal MMT at each visit following Week 8; • Change from Baseline of Physician Global Activity VAS at each visit following Week 8; • Change from Baseline of Patient Global Activity VAS at each visit following Week 8; • Change from Baseline of HAQ at each visit following Week 8; • Change from Baseline of MDAAT Extramuscular Disease Activity VAS Score at each visit following Week 8;

	• Change from Baseline of FACIT-Fatigue Scale at each visit following Week 8;
To assess the PK of zilucoplan	• Plasma concentrations of zilucoplan and its major metabolites
To assess the PD of zilucoplan	• Sheep red blood cell lysis assay for evaluation of classical complement pathway activation • Complement component 5 levels
To assess the effect of zilucoplan on biomarkers	• Mechanistic biomarkers [e.g., complement fixation, complement function, complement pathway proteins, autoantibody characterization (titer and immunoglobulin class), myocyte markers, and inflammatory markers].
To assess the effect of zilucoplan on pharmacogenomics	• Pharmacogenomic analyses (optional): Genomic studies [e.g., deoxyribonucleic acid (DNA) sequencing, including exploration of whether specific genomic features correlate with response or resistance to study drug] may be performed.

7 STUDY DESIGN

7.1 OVERVIEW OF STUDY DESIGN

RA101495-02.202 is a multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and efficacy of zilucoplan in subjects with IMNM who are positive for anti-HMGCR (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase) or anti-SRP (signal recognition particle) autoantibodies.

The planned enrollment is approximately 24 subjects. Subjects will be randomized in a 1:1 ratio to receive daily SC doses of 0.3 mg/kg zilucoplan or matching placebo. Randomization will be stratified based on antibody status (anti-HMGCR+ versus anti-SRP+).

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

Randomized subjects will receive 0.3 mg/kg zilucoplan or matching placebo administered SC at the Day 1 visit. Following in-clinic education and training, all subjects will self-inject daily SC doses of blinded study drug, according to randomized treatment allocation, for the subsequent 8 weeks. Single use pre-filled syringes in injection devices will be provided for use during the study.

All SOC therapy medications for IMNM should be kept at the same doses throughout the study, including corticosteroids, immunosuppressive drugs, and IVIG.

To reduce the risk of meningococcal infection (*Neisseria meningitidis*), all subjects must be vaccinated against meningococcal infections (with a quadrivalent vaccine and, where available and in accordance with local SOC, serogroup B vaccine) within 3 years prior to, or at the time of, initiating study drug. Subjects who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics (e.g., ciprofloxacin, erythromycin, penicillin V) until at least 2 weeks after initial dose of vaccine(s). Booster vaccinations should be administered in accordance with local SOC. (see Section 11.2).

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

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

At the conclusion of the Treatment Period of the study, all subjects will have the option to receive zilucoplan in the Extension Portion of the study provided they meet the Extension Portion selection criteria. Visits during the first 8 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. The study will remain double-blinded until after the data from Week 8 of the Main Portion of the study have been reviewed, locked, and unblinded.

If a subject permanently discontinues study drug treatment prior to the Week 8 visit for any reason, he/she will not be eligible for the Extension Portion. For subjects who permanently discontinue treatment with study drug, a Safety Follow-up Visit will be performed at 40 days after the last dose to collect information on any ongoing AEs or new SAEs since the last study visit.

7.2 STUDY PERIODS

During the Main Portion of the study, the total duration of study participation for all subjects will be up to approximately 12 weeks, including a Screening Period of up to 4 weeks and an 8-week Treatment Period.

During the Extension Portion of the study, the investigational medicinal product (IMP) will continue to be provided by the sponsor until zilucoplan is approved and available in the territory (e.g., in another qualifying extension study) or until the sponsor terminates development of zilucoplan for IMNM. In countries where zilucoplan is not approved or

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

For France only: The duration of study participation during the Extension Portion of this study (RA101495-02.202) will include an open-label, single-arm, 18-month Treatment Period .

7.2.1 SCREENING PERIOD

The Screening visit(s) will occur no more than 28 days (4 weeks) prior to the first dose of study drug on Day 1.

Subjects that do not meet the entry criteria for the study may rescreen after 56 days (8 weeks). Subjects may be rescreened no more than 2 times.

7.2.1.1 SCREENING AND ENROLLMENT

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

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

- Informed consent
- Review of eligibility criteria
- Review of medical history and demographics, including collection of a detailed history of IMNM diagnosis information, as well as local serology for anti-HMGCR or anti-SRP autoantibodies.
- Review and documentation of prior and concomitant medications
  Note: A complete history of medications taken for the treatment of IMNM will be collected. All medications taken during 30 days prior to Screening will be recorded.
- Completion of the following efficacy assessments:
  - 3TUG (in ambulatory subjects only)
  - Proximal MMT
  - Physician Global VAS
  - Patient Global VAS
  - HAQ
  - MDAAT
  - FACIT-Fatigue
- Measurement of height and weight
- Full physical examination
- Vital signs [heart rate (HR), body temperature, blood pressure in the sitting position]
- 12-lead ECG
- *Neisseria meningitidis* vaccination and, if applicable, prophylactic antibiotics (see Section 11.2)
- Collection of blood samples for laboratory testing: hematology, chemistry, CK, and coagulation (if applicable)
- Collection of urine sample for urinalysis
- Serum pregnancy testing for females of childbearing potential only
- Collection of blood sample for anti-drug antibody (ADA) testing

- Collection of blood samples for central testing of disease specific antibody testing (anti-HMGCR or anti-SRP autoantibodies)
- Collection of blood sample for pharmacogenomic analysis (optional)
  NOTE: If the pharmacogenomic analysis sample is not collected at the Screening visit, it may also be collected on any other visit during the study.
- Enrollment and randomization

7.2.2 TREATMENT PERIOD (MAIN AND EXTENSION PORTIONS)

Subjects will receive treatment with 0.3 mg/kg zilucoplan or placebo, according to randomization, from Day 1 to Day 57 during the Treatment Period of the Main Portion of the study. Subjects who complete the Week 8 (Day 57) visit (including those randomized to the placebo arm) will have the option to continue treatment with zilucoplan in the Extension Portion of the study. If a subject chooses not to participate in the Extension Portion, the subject will receive SOC treatment off-study, as recommended by the treating physician.

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

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

7.2.2.1 RANDOMIZATION AND BLINDING

Subjects who meet all entry criteria will be randomized in a 1:1 ratio to receive daily SC doses of 0.3 mg/kg zilucoplan or placebo. Subjects will be assigned to study arms in a blinded fashion using a computerized randomization algorithm. Randomization will be stratified based on antibody status (anti-HMGCR+ versus anti-SRP+).

This is a double-blind study. Subjects and study staff will remain blinded to treatment assignments until after the data from Week 8 of the Main Portion of the study have been reviewed, locked, and unblinded.

Instructions for emergency unblinding, if warranted, for safety reasons are provided in Section 11.4.2.3.

7.2.2.2 DISCONTINUATION OF INVESTIGATIONAL MEDICINAL PRODUCT

During the Main Portion, if a subject permanently discontinues study drug at any time prior to completion of Day 57 (see Section 8.4.2), the subject should return to clinic for an End of Main Visit. During the Extension Portion, if a subject permanently discontinues study drug at any time (see Section 8.4.2), the subject should return to clinic for a Final Extension Visit. If a subject discontinues study drug at any time, a 40 day follow up visit is required.

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

- Completion of the following efficacy assessments:
  - 3TUG (in ambulatory subjects only)
  - Proximal MMT
  - Physician Global VAS
  - Patient Global VAS
  - HAQ
  - MDAAT
  - FACIT-Fatigue
- Measurement of weight
- Review and documentation of concomitant medications
- Physical examination
- Vital signs (HR, body temperature, blood pressure in the sitting position)
- 12-lead ECG
- Collection of blood samples for laboratory testing: hematology, chemistry, and coagulation (if applicable)
- Collection of urine sample for urinalysis
- Urine pregnancy testing for females of childbearing potential only
- Record AEs
- Collection of blood samples for the following assessments:
  - ADA sampling
  - PK analysis
  - PD analyses
  - Autoantibody testing
  - Biomarker analysis
- Return of all used and unused study drug syringes to site

All subjects who discontinue study treatment will have a Safety Follow-up Visit 40 days after the last dose of study drug, to collect the following information:

- Review and documentation of concomitant medications
- Physical examination
- Vital signs (HR, body temperature, blood pressure in the sitting position)
- Urine pregnancy testing for females of childbearing potential only
- Record information on ongoing AEs or new SAEs since the last study visit.

7.3 EARLY STUDY TERMINATION

The end of study, or study termination, is defined as the time at which the last subject has performed their last visit (LSLV). Following LSLV, all remaining data will be collected

in the appropriate case report forms (see Section 14.3) and the study results will be summarized in the clinical study report (CSR) (see Section 14.5).

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

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

7.4 STUDY CONDUCT DURING COVID-19

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

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

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

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

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

If a subject visits another facility for a medical issue, the investigator should request contact with the physician providing care to provide a detailed explanation of the subject's condition and his/her participation in the clinical study. Subjects or caregivers shall be reminded to completely collect and keep records of this visit.

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

8 SELECTION OF STUDY POPULATION

8.1 INCLUSION CRITERIA

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

1. Male or female ≥ 18 years and < 75 years.
2. Able to provide informed consent, including signing and dating the informed consent form (ICF).
3. Clinical diagnosis of IMNM (Immune-Mediated Necrotizing Myopathy).
4. Positive serology for anti-HMGCR or anti-SRP autoantibodies.
5. Clinical evidence of weakness (≤ grade 4 out of 5) on manual muscle testing in at least one proximal limb muscle group.
6. CK (creatine kinase) of >1000 U/L at Screening.
7. No change in corticosteroid dose for at least 30 days prior to Baseline or anticipated to occur during the first 8-weeks on study.
8. No changes in immunosuppressive therapy, including dose, for at least 30 days prior to Baseline or anticipated to occur during the first 8-weeks on study.
9. Female subjects of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test within 24 hours prior to the first dose of study drug.
10. Sexually active female subjects of childbearing potential (i.e., women who are not postmenopausal or who have not had a hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) and all male subjects (who have not been surgically sterilized by vasectomy) must agree to use effective contraception during the study. Postmenopausal women are, for the purposes of this protocol, defined as women who have gone 12 consecutive months without menstruation.

8.2 EXCLUSION CRITERIA

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

1. History of meningococcal disease.

2. Current or recent systemic infection within 2 weeks prior to Screening or infection requiring intravenous (IV) antibiotics within 4 weeks prior to Screening.
3. Pregnant, planning to become pregnant, or nursing female subjects.
4. Recent surgery requiring general anesthesia within 2 weeks prior to Screening or expected to have surgery requiring general anesthesia during the 8-week Treatment Period.
5. Treatment with a complement inhibitor or an experimental drug within 30 days or 5 half-lives of the drug (whichever is longer) prior to Baseline.
6. Statin use within 30 days prior to Baseline or anticipated to occur during study.
7. Rituximab use within 90 days prior to Baseline or anticipated to occur during study.

   NOTE: In subjects who received rituximab more than 90 days but less than 6 months prior to Baseline, prophylactic antibiotics (e.g., ciprofloxacin, erythromycin, penicillin V) should be given upon initiation of study drug until 6 months after the last rituximab dose
8. Recent initiation of intravenous immunoglobulin (IVIG) (i.e., first cycle administered less than 90 days prior to Baseline).
9. Plasma exchange within 4 weeks prior to Baseline or expected to occur during the 8-week Treatment Period.
10. Active malignancy (except curatively resected squamous or basal cell carcinoma of the skin) requiring surgery, chemotherapy, or radiation within the prior 12 months (subjects with a history of malignancy who have undergone curative resection or otherwise not requiring treatment for at least 12 months prior to Screening with no detectable recurrence are allowed).
11. History of any significant medical, psychiatric disorder, or laboratory abnormality that in the opinion of the investigator would make the subject unsuitable for participation in the study.
12. Participation in another concurrent clinical trial involving an experimental therapeutic intervention (participation in observational studies and/or registry studies is permitted).
13. Unable or unwilling to comply with the requirements of the study.
14. Subjects who have a known hypersensitivity to zilucoplan or any of its excipients.

8.3 SELECTION CRITERIA FOR THE EXTENSION PORTION

1. Completion of the Main Portion of the study.
2. Continues to meet inclusion criteria 2, 11, and 12 from the Main Portion of the study.

   2. Able to provide informed consent, including signing and dating the ICF.

   11. Female subjects of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test within 24 hours prior to the first dose of study drug.

   12. Sexually active female subjects of childbearing potential (i.e., women who are not postmenopausal or who have not had a hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) and all male subjects (who have not been surgically sterilized by vasectomy) must agree to use effective contraception during the study. Postmenopausal women are, for the purposes of this protocol, defined as women who have gone 12 consecutive months without menstruation.

3. Did not start any disallowed medication per the exclusion criteria from the Main Portion of the study or alter the dose of any other concomitant medication, unless medically indicated.
4. Is able and willing to comply with the requirements of the study.
5. Does not have any new medical condition (since entry into the Main Portion) or any other reason that, in the opinion of the investigator or Sponsor, would disqualify the subject from participation in the Extension Portion of the study.

8.4 REMOVAL OF SUBJECTS IN THE STUDY

8.4.1 WITHDRAWAL OF CONSENT

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

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

8.4.2 PREMATURE DISCONTINUATION

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

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

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

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

Subjects may be withdrawn from study treatment due to unacceptable or intolerable AEs.

All subjects who permanently discontinue study treatment in the Main Portion of the study (i.e., prior to Day 57 visit) for any reason will not be eligible to participate in the Extension Portion of the study.

8.4.3 REPLACEMENT OF SUBJECTS

In order to obtain an adequate number of subjects that complete the study (see Section 12.3), additional subjects may be enrolled into the study, at the discretion of the Sponsor.

9 INVESTIGATIONAL MEDICINAL PRODUCT

9.1 STUDY TREATMENT ADMINISTRATION

9.1.1 INVESTIGATIONAL MEDICINAL PRODUCT AND MATCHING PLACEBO

The IMP, zilucoplan, and the placebo will be supplied as a sterile, preservative-free, aqueous solution prefilled into 1 mL glass syringes with a 29-gauge, ½-inch, staked needle placed within a self-administration device. Subjects will be instructed to self-administer SC doses daily. Three dosage strengths of zilucoplan will be supplied as shown in Table 4.

9.1.2 DOSING SCHEDULE

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

Dosing on study visit days should be held until efficacy assessments (i.e., Physician Global Activity VAS, Patient Global Activity VAS, Proximal MMT, HAQ, 3TUG, MDAAT, and FACIT-Fatigue) and PK/PD sample collection have been completed. Patients should be supervised while injecting to ensure adequate injection technique and re-instructed if and as needed.

9.1.3 DOSE PRESENTATION

Investigational drug product will be provided in prefilled syringes for self-injection using weight bracketed dosing (i.e., subjects will be provided prefilled syringes based on their weight containing fixed amounts of zilucoplan, and each fixed amount will cover a range of subject weights). As shown in Table 4, this weight bracketed dosing strategy will result in the potential for a range of doses to be received, from a minimum of 0.22 mg/kg daily (nominal dose) to a maximum dose of 0.42 mg/kg daily.

Matching placebo for the 0.3 mg/kg dose will be provided in 1 presentation of 0.574 mL.

Table 4: Zilucoplan Dose Presentations by Weight Brackets

Minimum (Nominal) Target Dose (mg/kg)	Actual Dose (mg)	Weight Range (kg)	Dose Range (mg/kg)
0.3	16.6	≥43 to <56	0.30 to 0.39
0.3	23.0	≥56 to <77	0.30 to 0.41
0.3	32.4	≥77 to 150	0.22 to 0.42

Subjects who present with a body weight outside of these ranges will be accommodated on a case-by-case basis, in consultation with the medical monitor.

9.1.3.1 MISSED DOSES

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

9.2 STUDY TREATMENT MANAGEMENT

9.2.1 PREPARATION AND DISPENSING

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

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

9.2.1.1 ALTERNATIVE STUDY TREATMENT SUPPLY DUE TO COVID-19 PANDEMIC

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

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

9.2.2 STUDY DRUG SUPPLY, STORAGE, AND HANDLING

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

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

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

9.2.3 DISPOSAL, RETURN, OR RETENTION OF UNUSED DRUG

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

All unused study drug syringes and disposal containers containing used syringes must be returned to the site at the last study visit for each Treatment Period (i.e., Day 57/End of Main Visit or the Final Extension Visit).

9.2.4 DRUG ACCOUNTABILITY

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

10 STUDY ASSESSMENTS

Please refer to Table 1 and Table 2 for the timing of study assessments.

10.1 SUBJECT AND BASELINE DISEASE CHARACTERISTICS

10.1.1 MEDICAL HISTORY AND DEMOGRAPHICS

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

The screening assessment will also include disease history with documentation of the diagnosis of IMNM, disease course and any IMNM-specific treatments. Muscle biopsy findings (including presence or absence of C5b-9 staining) and other diagnostic tests (e.g., MRI, serology, and electromyography) will also be recorded.

10.1.2 HEIGHT AND WEIGHT

Height (cm) will be collected at the Screening visit only. Weight (kg) will be measured at the study visits indicated in Table 1 and Table 2.

10.1.3 PRIOR AND CONCOMITANT MEDICATIONS

Subjects are prohibited from receiving another complement inhibitor, rituximab, statins, or any investigational medicinal product while on study. All other medications are permitted while on study.

Subjects are expected to remain on stable doses of permitted SOC therapy for IMNM throughout the Main Portion of the study and through the Week 8 visit of the Extension Portion, including corticosteroids, immunosuppressive drugs, and IVIG. The medical monitor should be contacted prior to any changes throughout the duration of the study in IMNM specific therapy.

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 IMNM will be collected.

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

Medications, including over-the-counter therapeutics, natural products, and vitamins, should not be changed during the Screening or Treatment Periods, unless medically

necessary. All concomitant medications necessary for the health and well-being of a subject will be permitted.

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

10.2 SAFETY ASSESSMENTS

10.2.1 PHYSICAL EXAMINATION

A physical examination will be performed on all subjects at the visits listed in the Time and Events tables (Table 1 and Table 2) and will include the following assessments:

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

Any clinically significant abnormalities after Day 1 found will be recorded as AEs in the eCRF.

Physical examinations should also include an examination of the injection site(s). If an injections site reaction is observed, it should be recorded as an adverse event in the eCRF.

10.2.2 VITAL SIGNS

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

10.2.3 ELECTROCARDIOGRAM

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

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

10.2.4 LABORATORY SAFETY ASSESSMENTS

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

10.2.4.1 HEMATOLOGY, CHEMISTRY, AND COAGULATION

Hematology, chemistry, and coagulation analytes that will be assessed during the study are identified in Table 5 and should be performed as specified in the Time and Events Tables (Table 1 and Table 2).

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

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

Table 5: Chemistry, Hematology, and Coagulation Analytes

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

* The results from these labs will be blinded to site personnel in order to avoid inadvertent biasing of functional assessments.

10.2.4.2 URINALYSIS

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

10.2.4.3 PREGNANCY TESTING AND CONTRACEPTION

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

A urine dipstick pregnancy test (HCG) will be performed on female subjects of childbearing potential at all other study visits as specified in the Time and Events Tables (Table 1 and Table 2).

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

Sexually active female subjects of childbearing potential (i.e., women who are not postmenopausal or who have not had a hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) and all male subjects (who have not been surgically sterilized by vasectomy) must agree to use effective contraception during the study, including the 40-day safety follow-up visit. Postmenopausal women are, for the purposes of this protocol, defined as women who have gone 12 consecutive months without menstruation. Effective contraception is defined as:

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

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

10.2.5 ADVERSE EVENT RECORDING

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

10.2.6 IMMUNOGENICITY

Blood samples for ADA assessment will be collected as specified in the Time and Events Tables (Table 1 and Table 2) in all enrolled subjects. These samples will be banked and used to investigate and characterize any ADA response over time in the general study population.

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

10.3 EFFICACY ASSESSMENTS

10.3.1 PRIMARY EFFICACY ASSESSMENT

The primary efficacy endpoint is percent change from Baseline to Week 8 in CK levels.

CK levels will be measured by a central laboratory in accordance with the Time and Events Tables (Table 1 and Table 2).

10.3.2 SECONDARY EFFICACY ASSESSMENTS

10.3.2.1 TRIPLE TIMED UP AND GO TEST

The 3TUG is a non-invasive and reproducible measure, which measures clinically important muscle weakness that impairs subject's ability to walk, climb stairs, and stand up from a chair. The test will only be performed in subjects who are ambulatory.

The 3TUG test involves the subject getting up from a seated position in a chair, walking at their normal pace for 3 meters, turning around, walking back to the chair, and sitting down. This sequence is repeated 3 times without rest, and the 3TUG time is the average of the 3 lap times (Sanders, et al. 2018).

3TUG evaluators must be adequately trained prior to conducting any 3TUG test. The 3TUG test will be performed at Screening and at each study visit according to the Time and Events Tables (Table 1 and Table 2). The 3TUG test must be performed at approximately the same time of day (preferably in the morning) and administered by the same well-trained evaluator (e.g., neurologist, physical therapist, or other study staff experienced in clinical assessments) at each visit throughout the study.

Detailed instructions regarding the administration of the 3TUG test will be provided to sites.

10.3.2.2 PROXIMAL MANUAL MUSCLE TESTING

The proximal MMT assesses muscle strength using manual muscle testing in 7 muscle groups. A zero to 10-point scale based on standard MMT grades will be used (Kendall

and al. 1993) of 7 proximal, distal, and axial muscles performs similarly to a total of 24 muscle groups (Rider, Koziol, et al. 2010).

Proximal MMT evaluators must be adequately trained prior to conducting any MMT grading. MMT grading will be performed at Screening and at each study visit according to the Time and Events Tables (Table 1 and Table 2). MMT grading must be performed at approximately the same time of day (preferably in the morning) and administered by the same well-trained evaluator (e.g., neurologist, physical therapist, or other study staff experienced in clinical assessments) at each visit throughout the study.

Detailed instructions regarding the administration of the proximal MMT will be provided to sites.

10.3.2.3 PHYSICIAN GLOBAL ACTIVITY VISUAL ANALOGUE SCALE

The Physician Global Activity VAS score measures the global evaluation by the treating physician of the overall disease activity of the patient at the time of assessment using a 10 cm visual analogue scale and a 5-point Likert scale (Rider, Werth, et al. 2011).

Detailed instructions regarding the administration of the Physician Global Activity VAS will be provided to sites.

10.3.2.4 PATIENT GLOBAL ACTIVITY VISUAL ANALOGUE SCALE

The Patient Global Activity VAS score measures the global evaluation by the patient of the patient's overall disease activity at the time of assessment using a 10 cm visual analogue scale (Rider, Werth, et al. 2011).

Detailed instructions regarding the administration of the Patient Global Activity VAS will be provided to sites.

10.3.2.5 HEALTH ASSESSMENT QUESTIONNAIRE

The HAQ Score is a patient related outcome measure that assesses physical function. There are 8 sections: dressing, arising, eating, walking, hygiene, reach, grip, and activities. There are 2 or 3 questions for each section. Scoring within each section is from 0 (without any difficulty) to 3 (unable to do) (Rider, Werth, et al. 2011).

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

10.3.2.6 MYOSITIS DISEASE ACTIVITY ASSESSMENT TOOL

The MDAAT measures the degree of disease activity of extra-muscular organ systems and muscle. This is a combined tool that includes the myositis disease activity assessment visual analogue scales (MYOACT), which is a series of physician's assessments of disease activity of various organ systems modified from the Vasculitis Activity Index (Whiting-O'Keefe, Stone and Hellmann 1999), and the Myositis Intention to Treat Activity Index (MITAX). The MITAX is scored on a 0 - 4 scale, based on worsening or improvement in specific clinical features and their correlation with the intention to treat.

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

10.3.2.7 ACR/EULAR RESPONSE CRITERIA

The ACR/EULAR scale was created to develop a response criterion for patients with myopathy. The scale utilizes a conjoint analysis-based continuous model using absolute percent change in core set measures (physician, patient, and MDAAT; muscle strength; Health Assessment Questionnaire; and muscle enzyme levels). A total improvement score (range 0-100) is determined by summing scores for each core set measure and comparing improvement in each respective core set measure. Thresholds for minimal, moderate, and major improvement are ≥20, ≥40, and ≥60 points in the total improvement score (Aggarwal, et al. 2017). The total improvement score will be calculated based on the core set measures as recorded in the eCRF and from central laboratory results.

10.3.2.8 FACIT-FATIGUE SCALE

The FACIT-Fatigue Scale is a 13-item, easy to administer tool that measures an individual's level of fatigue during their usual daily activities over the past week. The level of fatigue is measured on a four-point Likert scale (4 = not at all fatigued, to 0 = very much fatigued) (Webster, Cella and Yost 2003). All subjects will be asked to complete the FACIT-Fatigue Scale in accordance with the Time and Events Tables (Table 1 and Table 2).

10.4 PHARMACOKINETIC/ PHARMACODYNAMIC ASSESSMENTS

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

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

Blood samples for PK and PD analysis will be obtained prior to administration of study drug (within 1 hour of dosing) at the study visits according to Table 1 and Table 2.

All samples will be sent to an accredited laboratory for analysis. Detailed instructions regarding PK/PD sample collection, processing, and shipping will be provided to sites.

10.5 EXPLORATORY ASSESSMENTS

10.5.1 BIOMARKERS

Blood samples for biomarker testing will be obtained prior to administration of study drug (within 1 hour of dosing) at study visits according to Table 1 and Table 2.

The analysis of biomarkers pertaining to the pathophysiology of IMNM [e.g., complement fixation, complement function, complement pathway proteins, autoantibody characterization (titer and immunoglobulin class), myocyte markers, and inflammatory markers] may provide further insight into the clinical efficacy and safety of zilucoplan in subjects with IMNM. Complement protein levels and complement activity will be tested to evaluate response to zilucoplan and to understand subject characteristics related to

variations in response to drug. Markers of inflammation may be tested to assess correlation with complement function and clinical response to zilucoplan. A list of analytes will be created through review of the literature, ongoing clinical studies, and ongoing exploratory work and may be finalized after completion of the study.

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

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

10.5.2 PHARMACOGENOMIC ASSESSMENTS

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

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

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

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

11 SAFETY REPORTING

11.1 DEFINITIONS

11.1.1 ADVERSE EVENTS

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

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

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

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

11.1.1.1 OCCURRENCE OF COVID-19

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

11.1.2 SERIOUS ADVERSE EVENTS

An SAE is any AE that:

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

An SAE may also be any other important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events include intensive treatment in an emergency room or at home for bronchospasm, hyperkalemia, or convulsions that do not result in a formal hospitalization.

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

11.2 MONITORING OF INFECTION

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

To reduce the risk of meningococcal infection (*Neisseria meningitidis*), all subjects must be vaccinated against meningococcal infections (with a quadrivalent vaccine and, where available and in accordance with local SOC, serogroup B vaccine) within 3 years prior to, or at the time of, initiating study drug. Subjects who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics (e.g., ciprofloxacin, erythromycin, penicillin V) until at least 2 weeks after initial dose of vaccine(s). Booster vaccinations should be administered in accordance with local SOC. In subjects who have received rituximab less than 6 months prior to Day 1, prophylactic antibiotics should be given until at least 6 months after the last rituximab dose (e.g., ciprofloxacin, erythromycin, penicillin V).

NOTE: In subjects who received rituximab more than 90 days but less than 6 months prior to Baseline, prophylactic antibiotics (e.g., ciprofloxacin, erythromycin, penicillin V) should be given upon initiation of study drug until 6 months after the last rituximab dose.

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

seek immediate medical attention if any such symptoms occur, will be provided to each subject. Should a subject lose/misplace their safety instruction card they will be provided a new card.

11.3 EVALUATION AND CLASSIFICATIONS

11.3.1 SEVERITY

The investigator should determine the severity of the reported AE by using the CTCAE (Version 5.0 or higher).

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

Adverse Event Severity	
Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s).
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

11.3.2 CAUSALITY

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

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

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

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

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

11.4 RECORDING, REPORTING, AND MONITORING

11.4.1 RECORDING AND REPORTING

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

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

- The fulfilled criteria for seriousness as presented in Section 0
- The severity of the event as defined in Section 11.3.1
- The relationship of the event to study treatment as defined in Section 11.3.2

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

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

11.4.1.1 ADVERSE EVENTS

Pre-existing conditions that are detected prior to administration of the first dose of study drug will be recorded as part of the medical history. For all subjects, the AE reporting period will start with the first administration of study drug on Day 1 (for SAE reporting period, see Section 11.4.1.2) and will end 40 days following the last dose of study drug (i.e., the End of Main Visit, Day 57 Visit, or Final Extension Visit), after which no new non-serious AEs are to be reported. The subjects will be monitored throughout the study for any AEs, including clinically significant findings at vital signs measurements, spontaneous reports by study subjects, and observations by the study personnel.

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

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

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA; Version 20.0 or higher) after the eCRFs have been monitored and signed by the investigator.

11.4.1.2 SERIOUS ADVERSE EVENTS

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

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

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

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

The Sponsor, or designee, will prepare any required safety reports for Competent Regulatory Authorities and all active investigators. These reports will be provided as addenda to the IB, and the investigator will place these with the IB. All Competent Regulatory Authorities will be informed as per applicable legislation.

11.4.1.3 DEATH

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

11.4.1.4 ABNORMAL LABORATORY VALUES

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

11.4.2 SAFETY MONITORING

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

11.4.2.1 SAFETY MONITORING COMMITTEE

The safety of study subjects will be monitored throughout the study on an ongoing basis. Given the double blind, placebo-controlled design of Study RA101495-02.202, this standard safety data review will be performed while blinded to treatment assignment.

If an additional data review should become necessary to ensure subject safety, a separate supervisory committee (i.e., an SMC) will convene and evaluate study data as appropriate. To ensure the scientific integrity of the study, members of the SMC will not be directly involved in management of the study.

11.4.2.2 POST-STUDY EVENTS

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

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

11.4.2.3 EMERGENCY UNBLINDING

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

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

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

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

Following emergency unblinding, the subject's further participation in the study should be discussed with the medical monitor.

11.5 SPECIAL CIRCUMSTANCES

11.5.1 PREGNANCY

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

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

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

11.5.2 OTHER

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

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

Special situations should be reported whether they result in an AE/SAE or not.

12 STATISTICAL AND ANALYTICAL PLANS

12.1 ANALYSIS POPULATIONS

Further details of additional analysis populations will be described in the SAP, which will be finalized prior to study unblinding.

12.1.1 INTENTION-TO TREAT (ITT) POPULATION

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

12.1.2 PER PROTOCOL POPULATION

The Per Protocol Population will include all subjects in the ITT Population who have completed the 8-week Treatment Period and have no major protocol deviations.

12.1.3 SAFETY POPULATION

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

12.2 ANALYSIS METHODS

12.2.1 GENERAL METHODS

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

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

Once all patients have completed Week 8 of the Main Portion of the study, the study database will be locked, unblinded, and efficacy analyses for the Main Portion will be performed.

12.2.2 SUBJECT DISPOSITION

A disposition of all consented subjects will be provided and will include a breakdown of subjects who were randomized, were treated, and discontinued treatment (including reasons for discontinuation) at the Main Portion. A disposition of all consented subjects entered the Extension Portion will be also provided. Additionally, a summary of subjects included in the analysis populations defined in Section 12.1 will be provided.

12.2.3 DEMOGRAPHY AND BASELINE DISEASE CHARACTERISTICS

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

12.2.4 SAFETY ANALYSIS

Safety analyses will be performed on the Safety Population.

12.2.4.1 ADVERSE EVENTS

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; Version 20.0 or higher). Incidence rates for treatment-emergent AEs will be summarized overall, by maximum severity, and by relationship to study drug for each treatment group. SAEs will also be summarized by treatment group.

Incidence rates for TEAEs and SAEs will be summarized overall, by maximum severity, and by relationship to study drug. A TEAE is defined as:

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

The SAEs occurring before the first dose of study drug will be listed.

12.2.4.1.1 INFECTION

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

12.2.4.2 CLINICAL LABORATORY EVALUATION

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

12.2.4.3 ELECTROCARDIOGRAMS

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

12.2.4.4 VITAL SIGNS

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

12.2.4.5 PHYSICAL EXAMINATION

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

12.2.5 EFFICACY ANALYSIS

Details of analyses beyond what is specified in this protocol will be discussed in detail in the SAP.

12.2.5.1 PRIMARY EFFICACY ANALYSES

The primary efficacy endpoint, percent reduction from baseline in creatine kinase at Week 8, will be compared between the two treatment groups using a 2-sided stratified Wilcoxon rank sum test (Van Elteren test). Magnitude of treatment effect will be shown by the WMWOdds and the Hodges-Lehman estimator followed by the corresponding 95% Confidence Intervals (CIs).

Definition of primary estimand:

- Treatment: zilucoplan administered by daily SC injection (0.3 mg/kg) vs matching placebo.
- Target Population: is defined through the inclusion/exclusion criteria at Sections 8.1 and 8.2 of the study protocol reflecting the targeted IMNM population.
- Endpoint: percentage change from Baseline to Week 8 in CK levels while on non-prohibited medication.
- Intercurrent event: regardless of any treatment discontinuation for any reason; censoring after prohibited medication
- Population level summary: difference in ranks of the percentage change from baseline between treatments followed by the WMWodds and Hodges–Lehmann estimator followed by the corresponding 95% CIs.

12.2.5.2 SECONDARY EFFICACY ANALYSES

Secondary Estimands are defined below:

- Treatment: Zilucoplan administered by daily subcutaneous (SC) injection (0.3 mg/kg) vs matching placebo.
- Target Population: is defined through the inclusion/exclusion criteria at Sections 8.1 and 8.2 of the current document, reflecting the targeted IMNM population.
- Endpoints:
    - At least minimal response based on the ACR/EULAR minimal Response Criteria at Week 8
    - Change from Baseline to Week 8 in 3TUG Test (in ambulatory patients only);
    - from Baseline to Week 8 in Proximal MMT;
    - Change from Baseline to Week 8 in Physician Global Activity VAS;
    - Change from Baseline to Week 8 in Patient Global Activity VAS;
    - Change from Baseline to Week 8 in HAQ;
    - Change from Baseline to Week 8 in MDAAT Extramuscular Disease Activity VAS Score;
    - Change from Baseline to Week 8 in FACIT-Fatigue Scale;
    - ICE handling: regardless of any treatment discontinuation for any reason; censoring after administration of prohibited medication;
    - Population level summary:
        - Odds ratio of ACR/EULAR of ACR/EULAR ≥ 20 response proportion between treatment conditions;
        - Difference in the continuous endpoint means between treatment conditions;

The analysis to determine the odds ratio and the corresponding 95%CI for the ACR/EULAR response will be performed via logistic regression. Treatment group differences for each of the continuous secondary efficacy change from baseline endpoints will be assessed using a linear mixed effects model using the change from baseline to Week 8 as response variable; treatment, and baseline score (i.e., the baseline score for the secondary efficacy endpoint being analyzed) will be fitted as fixed effects and subject as a random effect.

Secondary efficacy endpoint analyses will be performed on the ITT Population.

12.2.6 CLINICAL PHARMACOLOGY ANALYSIS

12.2.6.1 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

For the PK analysis, concentrations of zilucoplan and metabolites were presented in listings and summarized using descriptive statistics.

Plasma concentration data of zilucoplan may be subjected to population PK analysis to derive population estimates of PK parameters and test the effect of various covariates such as anti-drug antibodies, age, weight, and gender. Details of the analysis will be described in a separate Data Analysis Plan (DAP). This analysis may be performed by

combining the data from the current study with data from other zilucoplan studies if deemed appropriate. The results of the population PK analysis will not be reported in the CSR but in a separate modeling report.

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

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

12.2.7 INTERIM ANALYSIS

No interim analysis is planned for the Main Portion of the study.

Interim analyses of the Extension Portion of the study, after Week 8 of the Main Portion of the study has been locked and unblinded, may be performed.

12.3 SAMPLE SIZE DETERMINATION

A sample size of 12 subjects per group yields approximately 95% power to detect a difference in the percent reduction from baseline in creatine kinase between the active and placebo groups using a Wilcoxon rank sum test at the two-sided 0.05 type 1 error rate. The power calculations assume that the percent reduction in creatine kinase in the active dose group is approximately normally distributed with a mean of 80% and a standard deviation of 8%; that 4 of the placebo patients will have a percent reduction similar to the active dose group; and the remaining 8 placebo patients will have a percent reduction that is normally distributed with a mean of 10% and a standard deviation of 8% (Mammen and Tiniakou 2015).

13 ETHICAL CONSIDERATIONS

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

13.1 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE COMMUNICATIONS

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

13.1.1 PROGRESS REPORTS

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

13.1.2 FINAL INVESTIGATOR REPORT

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

13.2 INFORMED CONSENT OF STUDY SUBJECTS

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

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

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

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

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

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

13.3 PROTOCOL COMPLIANCE

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

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

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

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

13.4 PROTECTION OF CONFIDENTIALITY

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

In addition, prior to study participation, the subject must be informed that the records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available; if the results of the study are published, the subject's identity will remain confidential.

13.5 DISCLOSURE OF STUDY RESULTS

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

14 REGULATORY AND ADMINISTRATIVE CONSIDERATIONS

14.1 QUALITY ASSURANCE

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

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

14.1.1 MONITORING

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

14.1.2 AUDIT

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

14.2 CLINICAL RESEARCH ORGANIZATIONS

A Clinical Research Organization (CRO) will be utilized to assist in the conduct of this study. Accredited central laboratories will be used for the analysis of all clinical samples.

14.3 DATA MANAGEMENT

14.3.1 CASE REPORT FORMS

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

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel. All data entered into the eCRF will be supported by source documentation.

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

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

14.3.2 SOURCE DOCUMENTS

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

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

14.4 PREMATURE TERMINATION OR SUSPENSION OF THE STUDY

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

14.5 CLINICAL STUDY REPORT

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

14.6 PUBLICATION POLICY

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

15 REFERENCES

Aggarwal, R, LG Rider, N Ruperto, N Bayat, B Erman, BM Feldman, CV Oddis, et al. 2017. "2016 American College of Rheumatology/European League Against Rheumatism Criteria for Minimal, Moderate, and Major Clinical Response in Adult Dermatomyositis and Polymyositis." *Arthritis & Rheumatology* 898-910.

Allenbach, Y et. al. 2018. "224th ENMC International Workshop:: Clinico-sero-pathological classification of immune-mediated necrotizing myopathies Zandvoort, The Netherlands, 14-16 October 2016." *Neuromuscul Disord* 28 (1): 87-99.

Allenbach, Y, and O Benveniste. 2018. "Peculiar clinicopathological features of immune-mediated necrotizing myopathies." *Curr Opin Rheumatol* 30 (6): 655-663.

Amato, AA, and RC Griggs. 2003. "Unicorns, dragons, polymyositis, and other mythological beasts." *Neurology* 288-289.

Anquetil, C et. al. 2019. "Myositis-specific autoantibodies, a cornerstone in immune-mediated necrotizing myopathy." *Autoimmun Rev* 18 (3): 223-230.

Cong, J et. al. 2014. "Complement membrane attack complex is related with immune-mediated necrotizing myopathy." *Int J Clin Exp Pathol* 7 (7): 4143-4149.

Hay, EM, PA Bacon, C Gordon, DA Isenberg, P Maddison, ML Snaith, DP Symmons, N Viner, and A Zoma. 1993. "The BILAG index: a reliable and valid instrument for measuring clinical disease activity in systemic lupus erythematosus." *Q J Med* 447-458.

Hillmen P, Young NS, Schubert J, et al. 2006. "The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria." *N Engl J Med* 355 (12): 1233-43.

Kendall, FP, and et. al. 1993. *Muscles, testing and function: With Posture and pain.*

Mammen, AL, and E Tiniakou. 2015. "Intravenous Immune Globulin for Statin-Triggered Autoimmune Myopathy." *N Engl J Med* 1680-1682.

Nishimura J, Yamamoto M, Hayashi S, et al. 2014. "Genetic variants in C5 and poor response to eculizumab." *N Engl J Med* 370: 632-639.

Pinal-Fernandez, I et. al. 2018. "Immune-Mediated Necrotizing Myopathy." *Current Rheumatology Reports* 20: 21.

Rider, LG, D Koziol, Giannini EH, MS Jain, MR Smith, K Whitney-Mahoney, BM Feldman, et al. 2010. "Validation of manual muscle testing and a subset of eight muscles for adult and juvenile idiopathic inflammatory myopathies." *Arthritis Care Res* 465-472.

Rider, LG, VP Werth, AM Huber, H Alexanderson, AP Rao, N Ruperto, L Herbelin, R Barohn, D Isenberg, and FW Miller. 2011. "Measures of adult and juvenile

dermatomyositis, polymyositis, and inclusion body myositis: Physician and Patient/Parent Global Activity, Manual Muscle Testing (MMT), Health Assessment Questionnaire (HAQ)/Childhood Health Assessment Questionnaire (C-HAQ), ." *Arthritis Care Res* 118-57.

Sanders, DB, JT Guptill, KL Ales, LD Hobson-Webb, DP Jacobus, R Mahmood, JM Massey, et al. 2018. "Reliability of the triple timed-up-and-go (3TUG) test." *Muscle Nerve* 136-139.

Smoyer-Tomic, KE et. al. 2012. "Incidence and prevalence of idiopathic inflammatory myopathies among commercially insured, Medicare supplemental insured, and Medicaid enrolled populations: an administrative claims analysis." *BMC Musculoskeletal Disorders* 13.

Webster, K, D Cella, and K Yost. 2003. "The functional assessment of chronic illness therapy (FACIT) measurement system: properties, applications, and interpretation." *Health Qual Life Outcomes* (1): 79-85.

Whiting-O'Keefe, QE, JH Stone, and DB Hellmann. 1999. "Validity of a vasculitis activity index for systemic necrotizing vasculitis." *Arthritis Rheum* 2365-71.

SPONSOR SIGNATURE PAGE

Protocol Number: RA101495-02.202

Protocol Title: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Efficacy of Zilucoplan in Subjects with Immune-Mediated Necrotizing Myopathy

Protocol Version: Version 2.0/16 February 2021

Approval Signatures

Name: imnm01-protocol-amend-v2.0

Version: 1.0

Document Number: CLIN-000168746

Title: IMNM01 (RA101495-02.202) Study Protocol v2.0

Approved Date: 17 Feb 2021

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 16-Feb-2021 16:05:26 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 16-Feb-2021 18:08:29 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 17-Feb-2021 12:14:44 GMT+0000