HEALEY ALS Platform Trial - Regimen A Zilucoplan

NCT04436497

Document Date: 15 Jul 2021

REGIMEN-SPECIFIC APPENDIX A

FOR ZILUCOPLAN

Regimen-Specific Appendix Date: 15 July 2021

Version Number: *5.0*

TABLE OF CONTENTS

List of Figures and Tables

SIGNATURE PAGE

I have read the attached Regimen-Specific Appendix (RSA) entitled, "Regimen A: Zilucoplan," dated July 15, 2021 (Version 5.0) and agree to abide by all described RSA procedures. I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice, applicable FDA regulations and guidelines identified in 21 CFR Parts 11, 50, 54, and 312, central Institutional Review Board (IRB) guidelines and policies, and the Health Insurance Portability and Accountability Act (HIPAA).

By signing the RSA, I agree to keep all information provided in strict confidence and to request the same from my staff. Study documents will be stored appropriately to ensure their confidentiality. I will not disclose such information to others without authorization, except to the extent necessary to conduct the study.

Site Name: _____

Site Investigator: _____

Signed: _____ Date: _____

LIST OF ABBREVIATIONS

ALS	Amyotrophic Lateral Sclerosis
ALSAQ-40	Amyotrophic Lateral Sclerosis Assessment Questionnaire-40
C5	Complement component 5
CNS-BFS	Center for Neurologic Study Bulbar Function Scale
Covid-19	Coronavirus Disease 2019
FVC	Forced Vital Capacity
gMG	Generalized Myasthenia Gravis
IMNM	Immune-mediated Necrotizing Myopathy
IP	Investigational product
ITT	Intent-to-Treat
IV	Intravenous
OLE	Open Label Extension
PD	Pharmacodynamic
PK	Pharmacokinetic
RBC	Red blood cells
RSA	Regimen-Specific Appendix
SOC	Standard of care
SVC	Slow Vital Capacity
VC	Vital Capacity

REGIMEN-SPECIFIC APPENDIX SUMMARY

Regimen-Specific Appendix A
For 0.3mg/kg SC zilucoplan administered once daily and placebo

Allocation to Treatment Regimens
Participants must first be screened under the Master Protocol and before they are randomized to an RSA.

As soon as pre-defined criteria for futility for the RSA are met, or the target number of randomized participants has been reached, enrollment will stop in the RSA.

Number of Planned Participants and Treatment Groups
The number of planned participants for this regimen is approximately 160.

There are 2 treatment groups for this regimen, active and placebo. Participants will be randomized in a 3:1 ratio to active treatment or placebo (i.e., 120 active: 40 placebo).

Planned Number of Sites
Research participants will be enrolled from approximately 60 centers in the US.

Treatment Duration
The maximum duration of the placebo-controlled portion is 24 weeks.

Follow-up Duration
At the conclusion of the 24-week placebo-controlled period of the study, all participants will either schedule a 40-day follow up safety phone call and end their participation in the regimen or have the option to receive zilucoplan in the Open Label Extension phase of the study.

In the Open Label Extension, zilucoplan will be provided by Ra Pharmaceuticals, Inc. until zilucoplan is approved and available in the United States, or Ra Pharmaceuticals, Inc. terminates development of zilucoplan for ALS.

Total Planned Trial Duration
For participants completing the placebo-controlled treatment period of the study, the planned amount of time in the trial is up to 36 weeks, or about 9 months. This duration assumes a 6-week screening window, a 24-week placebo-controlled treatment period, and a 40-day safety follow-up period for those participants who do not enter the Open Label Extension.

If participants opt into the subsequent Open Label Extension, their participation in the trial will have no set endpoint. The Open Label Extension will continue until zilucoplan is approved and available in the territory, or Ra Pharmaceuticals, Inc. terminates development of zilucoplan for ALS. For participants continuing into the OLE, their total planned participation in the trial will include the 6-week screening window, 24-week placebo-controlled period, and the open-ended Open Label Extension.

SCHEDULE OF ACTIVITIES

As per the Schedule of Activities (SOA) below, visits must occur every 4 weeks and will be alternatively clinic-, phone-, or telemedicine-based, as applicable. There is a maximum 24-week duration of placebo-controlled treatment for a Regimen.

		Screening											Open Label Extension (Optional)							
Activity (page 1 of 3) (Master Protocol or Regimen-Specific)		**Master Protocol Screening[1]**	**Regimen Specific Screening[1]**	**Baseline**	**Week 2**	**Week 4[23]**	**Week 8[22, 23]**	**Week 12**	**Week 16[22, 23]**	**Week 20**	**Week 24 or Early Term. Visit[16, 22]**	**Follow-Up Safety Call[15, 16]**	**Week 2**	**Week 4[23]**	**Week 8[23]**	**Week 12**	**Week 16[22, 23]**	**Week 20**	**Week 24**	**Week 28 and Q12 Wks[22, 23]**
		Clinic	Clinic	Clinic	Phone	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone	Phone	Clinic	Clinic	Phone	Clinic	Phone	Phone	Clinic
		-42 to -1 Days	-41 to -14 Days	Day 0	Day 14 ±3	Day 28 ±7	Day 56 ±7	Day 84 ±3	Day 112 ±7	Day 140 ±3	Day 168 ±7	40d ±3 after last dose	Day 14 ±3	Day 28 ±7	Day 56 ±7	Day 84 ±3	Day 112 ±7	Day 140 ±3	Day 168 ±3	q12w ±14d
Written Informed Consent - Placebo-Controlled Period[2]	**Master**	X	X[25]																	
Written Informed Consent -OLE	**Regimen**								X											
Inclusion/ Exclusion Review	**Master**	X	X[3]																	
ALS & Medical History	**Master**	X																		
Demographics	**Master**	X																		
Physical Examination	**Master**	X																		
Neurological Exam	**Master**	X																		
Vital Signs[4]	**Master**	X		X		X	X		X		X			X	X		X			X
Slow Vital Capacity	**Master**	X[24]		X			X		X		X			X	X		X			X
Home Spirometry	**Regimen**	X[24]		X			X		X		X			X	X		X			X
Muscle Strength Assessment	**Master**			X			X		X		X									
ALSFRS-R	**Master**	X		X		X	X	X	X	X	X			X	X	X	X	X	X	X
ALSAQ-40	**Regimen**			X							X									X[20]
CNS Bulbar Function Scale	**Regimen**			X			X		X		X				X		X			X[21]

Activity (page 1 of 3) (Master Protocol or Regimen-Specific)		Screening											Open Label Extension (Optional)							
		Master Protocol Screening[1]	**Regimen Specific Screening**[1]	**Baseline**	**Week 2**	**Week 4**[23]	**Week 8**[22, 23]	**Week 12**	**Week 16**[22, 23]	**Week 20**	**Week 24 or Early Term. Visit**[16, 22]	**Follow-Up Safety Call**[15, 16]	**Week 2**	**Week 4**[23]	**Week 8**[23]	**Week 12**	**Week 16**[22, 23]	**Week 20**	**Week 24**	**Week 28 and Q12 Wks**[22, 23]
		Clinic	Clinic	Clinic	Phone	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone	Phone	Clinic	Clinic	Phone	Clinic	Phone	Phone	Clinic
		-42 to -1 Days	-41 to -14 Days	Day 0	Day 14 ±3	Day 28 ±7	Day 56 ±7	Day 84 ±3	Day 112 ±7	Day 140 ±3	Day 168 ±7	40d ±3 after last dose	Day 14 ±3	Day 28 ±7	Day 56 ±7	Day 84 ±3	Day 112 ±7	Day 140 ±3	Day 168 ±3	q12w ±14d
12-Lead ECG	**Master**	X									X									
Clinical Safety Labs[5]	**Master**	X		X		X	X		X		X			X	X		X			X
Anti-drug Antibody Sampling	**Regimen**			X			X		X		X						X			X[18]
Zilucoplan PK Analysis[11]	**Regimen**			X			X		X		X						X			X[18]
Zilucoplan PD Analysis[12]	**Regimen**			X			X		X		X						X			X[18]
Zilucoplan Biomarker Samples[13]	**Regimen**			X			X		X		X						X			X[18]
Biomarker Blood Collection[13]	**Master**			X			X		X		X						X			X[18]
Biomarker Urine Collection[13]	**Master**			X			X		X		X						X			X[18]
DNA Collection[7] (optional)	**Master**			X																
CSF Collection (optional)	**Master**			X					X[19]											
Concomitant Medication Review	**Master**	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Adverse Event Review[6]	**Master**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale	**Master**			X		X	X		X		X			X	X		X			X
Install Smartphone App[26]	**Regimen**			X																
Voice Recording[8]	**Regimen**			X		X	X		X		X									

Activity (page 1 of 3) (Master Protocol or Regimen-Specific)		Screening											Open Label Extension (Optional)							
		Master Protocol Screening[1]	**Regimen Specific Screening**[1]	**Baseline**	**Week 2**	**Week 4**[23]	**Week 8**[22, 23]	**Week 12**	**Week 16**[22, 23]	**Week 20**	**Week 24 or Early Term. Visit**[16, 22]	**Follow-Up Safety Call**[15, 16]	**Week 2**	**Week 4**[23]	**Week 8**[23]	**Week 12**	**Week 16**[22, 23]	**Week 20**	**Week 24**	**Week 28 and Q12 Wks**[22, 23]
		Clinic	Clinic	Clinic	Phone	Clinic	Clinic	Phone	Clinic	Phone	Clinic	Phone	Phone	Clinic	Clinic	Phone	Clinic	Phone	Phone	Clinic
		-42 to -1 Days	-41 to -14 Days	Day 0	Day 14 ±3	Day 28 ±7	Day 56 ±7	Day 84 ±3	Day 112 ±7	Day 140 ±3	Day 168 ±7	40d ±3 after last dose	Day 14 ±3	Day 28 ±7	Day 56 ±7	Day 84 ±3	Day 112 ±7	Day 140 ±3	Day 168 ±3	q12w ±14d
Uninstall Smartphone App	**Regimen**										X									
Assignment to the Regimen	**Master**	X																		
Randomization within the Regimen	**Master**			X																
Administer/ Dispense Investigational Product (IP)	**Regimen**			X[9]		X	X		X		X[14]			X	X		X			X[27]
IP Accountability/ Compliance	**Master**				X[28]	X	X	X[28]	X	X[28]	X		X[28]	X	X	X[28]	X	X[28]	X[28]	X
Exit Questionnaire	**Master**										X									
N. meningitidis Vaccination[10]	**Regimen**		X			X	X										X[10]			
Vital Status Determination[17]	**Master**										X[17]									

1. Master Protocol Screening procedures must be completed within 42 days to 1 day prior to Baseline Visit.
2. During the Master Protocol Screening Visit, participants will be consented via the Master Protocol informed consent form (ICF). After a participant is randomized to a regimen, participants will be consented a second time via the regimen-specific ICF.
3. At the Regimen Specific Screening Visit, participants will have regimen-specific inclusion and exclusion criteria assessed.
4. Vital signs include weight, systolic and diastolic pressure, respiratory rate, heart rate and temperature. Height measured at Master Protocol Screening Visit only.
5. Clinical safety labs include hematology (CBC with differential), complete chemistry panel, thyroid function and urinalysis. Serum pregnancy testing will occur in women of child-bearing potential at the Master Protocol Screening Visit and as necessary during the study. Pregnancy testing is only repeated as applicable if there is a concern for pregnancy.
6. Adverse events that occur after signing master protocol consent form will be recorded.

7. The DNA sample can be collected after Baseline Visit if a baseline sample is not obtained or the sample is not usable.
8. In addition to study visits outlined in the SOA, participants will be asked to complete twice weekly voice recordings at home. During weeks when a participant is doing a voice recording in-clinic, he or she would only do one other voice recording at home that week.
9. Administer first dose of investigational product (IP) only after Baseline Visit procedures are completed
10. To reduce the risk of meningococcal infection (*Neisseria meningitidis*), all participants must be vaccinated against meningococcal infections (with a quadrivalent vaccine and serogroup B vaccine) prior to initiating study drug. Booster vaccinations should be administered in accordance with the vaccination and booster guidance document for this regimen and may occur at different study visits in the OLE based on the vaccine brand. To mitigate the risk of infection, participants 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 participant.
11. Blood samples for PK analysis (zilucoplan and metabolites) should be obtained prior to administration of study drug at each clinic visit (i.e., pre-dose).
12. Blood samples for PD analysis (sheep RBC hemolysis assay, Wieslab alternative pathway assay, C5 levels) should be obtained prior to administration of study drug at each clinic visit (i.e., pre-dose).
13. Blood samples for biomarker analysis should be obtained prior to administration of study drug at each clinic visit (i.e., pre-dose).
14. Drug will only be dispensed at this visit if the participant continues in the OLE.
15. Participants will only have a Follow-Up Safety Call at this time if they *do not* continue into the OLE.
16. Participants who continue into the OLE and then early terminate will be asked to complete an Early Termination Visit and Follow-Up Safety Call as described in the body of this RSA.
17. Vital status, defined as a determination of date of death or death equivalent or date last known alive, will be determined for each randomized participant at the end of the placebo-controlled portion of their follow-up (generally the Week 24 Visit, as indicated). If at that time the participant is alive, his or her vital status should be determined again at the time of the last participant's last visit (LPLV) of the placebo-controlled portion of a given regimen. We may also ascertain vital status at later time points by using publicly available data sources as described in section 8.15 of the Master Protocol.
18. During the OLE, Master Biomarker Blood Collection, Master Biomarker Urine Collection, and all regimen-specific samples will occur at OLE Weeks 16, 28, and 52 only.
19. If the CSF collection is unable to be performed for logistical reasons, such as scheduling, at the Week 16 Visit, it may be performed at the Week 24 Visit
20. The ALSAQ-40 is done only at Week 28 and Week 52 during OLE
21. The CNS Bulbar Function Scale is done only at Weeks 8, 16, 28, 40 and 52 during OLE.
22. Participants should be instructed to hold the morning dose of study drug on the day of the study visit. Study drug should not be taken until after study visit procedures are complete.
23. Visit may be conducted via phone or telemedicine with remote services instead of in-person if this is needed to protect the safety of the participant due to a pandemic, or other reason. During the OLE, the Week 4, 8, 16, 28, and 40 Visits may be done remotely. The Week 52 Visit should still be done in clinic.
24. If required due to pandemic-related restrictions, Forced Vital Capacity (FVC) performed by a Pulmonary Function Laboratory evaluator or with a study-approved home spirometer, or sustained phonation using a study approved method may be used for eligibility (Master Protocol Screening ONLY).
25. If a participant chooses to obtain the vaccination from their local provider, Regimen A informed consent may be completed remotely to allow a participant to consent to the regimen prior to obtaining the vaccination so that the participant does not need to attend an in-person screening visit to obtain the vaccination. The process for obtaining remote consent is detailed in section 6.1.1.
26. Two smartphone apps should be installed on the participant's phone, once to collect the voice recordings and one to collect home spirometry.
27. Investigational product is not administered at the participant's final in-clinic visit at the completion of the OLE.
28. Drug accountability will not be done at phone visits. A drug compliance check-in should be held during phone visits to ensure participant is taking drug per dose regimen and to note any report of missed doses.

1 INTRODUCTION

Regimen 1: Zilucoplan

1.1 Zilucoplan Background Information

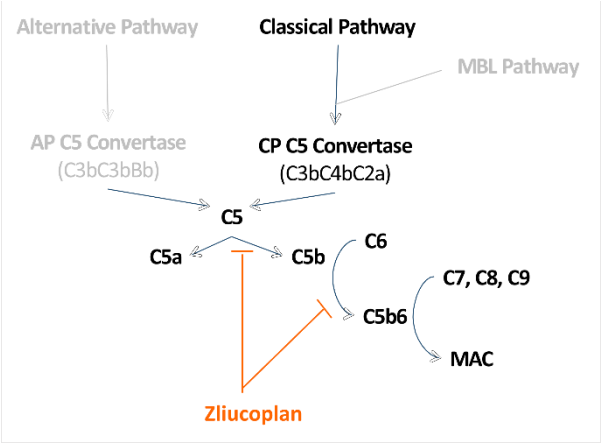
Zilucoplan targets C5, a component of the terminal complement activation pathway. Zilucoplan binds to C5 with high affinity and prevents its cleavage by C5 convertases into the cleavage products C5a and C5b. Inhibition of C5 cleavage prevents the downstream assembly and cytolytic activity of the MAC.

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

Thus, zilucoplan inhibits MAC formation by a dual mechanism (4):

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

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



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

The binding site of zilucoplan on the C5 protein is distinct from that of the complement C5 inhibitory monoclonal antibody eculizumab. Nishimura and colleagues have described 11 patients in Japan (≈3.2% of the PNH population) who carry mutations in the C5 gene that prevent the binding of eculizumab to C5 and who are resistant to treatment with the antibody

(Nishimura et al. 2014). Zilucoplan has been shown to effectively bind to C5 from blood samples from patients with this mutation, and to inhibit complement activation in vitro. Pharmacologically, zilucoplan has demonstrated dose-dependent inhibition of C5a and C5b formation following activation of classical or alternative complement pathways, as well as inhibition of red blood cell (RBC) lysis in the serum/plasma from various species. Zilucoplan is a potent complement inhibitor in humans and primates and a poor inhibitor in most other laboratory animal species.

1.1.1 Clinical Trial Experience with Zilucoplan

The experience in clinical trials with zilucoplan can be referenced in the most current version of the Investigator's Brochure (IB).

1.2 Zilucoplan- US FDA IND Background

Zilucoplan has ongoing clinical trials to assess the safety and efficacy for the treatment of patients with PNH (Paroxysmal Nocturnal Hemoglobinuria), gMG (generalized Myasthenia Gravis), and IMNM (Immune Mediated Necrotizing Myopathy), Coronavirus Disease 2019 (COVID-19)-associated respiratory syndrome, amyotrophic lateral sclerosis (ALS), and potentially for other complement-mediated diseases. Clinical trials in the US are being conducted under the US FDA IND oversight process. To support clinical studies in multiple diseases, zilucoplan has undergone extensive preclinical characterization to understand the pharmacology, pharmacokinetics, safety pharmacology, and toxicology of the drug. The preclinical data package has been extensively reviewed by the FDA's Division of Neurology Products, Office of Hematology and Oncology Product, as well as the FDA DPARP (Division of Pulmonary, Allergy, Rheumatology Products). Additionally, clinical safety data generated from completed clinical trials has been reviewed by the FDA as part of the IND review process. The FDA has determined the benefit/risk to be suitable for clinical investigations of zilucoplan for the treatment of multiple neurodegenerative diseases.

The Regimen A protocol was designed with input from the US FDA as well as designed to be consistent with FDA's Guidance for Industry for ALS. This includes overall study design, appropriate ALS clinical study endpoints, as well as long-term safety follow-up.

2 OBJECTIVES

2.1 Study Objectives and Endpoints

Primary Efficacy Objective:
To evaluate the efficacy of zilucoplan as compared to placebo on ALS disease progression.

Secondary Efficacy Objective:

- To evaluate the effect of zilucoplan on selected secondary measures of disease progression, including survival.

Safety Objective:

- To evaluate the safety of zilucoplan for ALS.

Exploratory Efficacy Objective:

- To evaluate the effect of zilucoplan on selected biomarkers and endpoints.

Primary Efficacy Endpoint:
Change in disease severity as measured by the ALS Functional Rating Scale-Revised (ALSFRS-R) total score using a Bayesian repeated measures model that accounts for loss to follow-up due to mortality.

Secondary Efficacy Endpoints:

- Change in respiratory function as assessed by slow vital capacity (SVC).
- Change in muscle strength as measured isometrically using hand-held dynamometry (HHD) and grip strength.
- Survival.

Safety Endpoints:

- Treatment-emergent adverse and serious adverse events.
- Changes in laboratory values and treatment-emergent and clinically significant laboratory abnormalities.
- Changes in ECG parameters and treatment-emergent and clinically significant ECG abnormalities.
- Treatment-emergent suicidal ideation and suicidal behavior.

Exploratory Efficacy Endpoints:

- Changes in quantitative voice characteristics.
- Changes in biofluid biomarkers of neurodegeneration.
- Changes in patient reported outcomes.
- Change in respiratory function as assessed by home spirometry.

- Change in circulating complement pathway biomarker levels (e.g. sC5b-9)
- Optional CSF sampling for complement pathway biomarkers in CNS (e.g. sC5b-9)
- Optional CSF sampling for pharmacokinetics of zilucoplan in CNS
- Optional CSF sampling for pharmacodynamics of zilucoplan in CNS

3. RSA DESIGN

3.1 Scientific Rationale for RSA Design

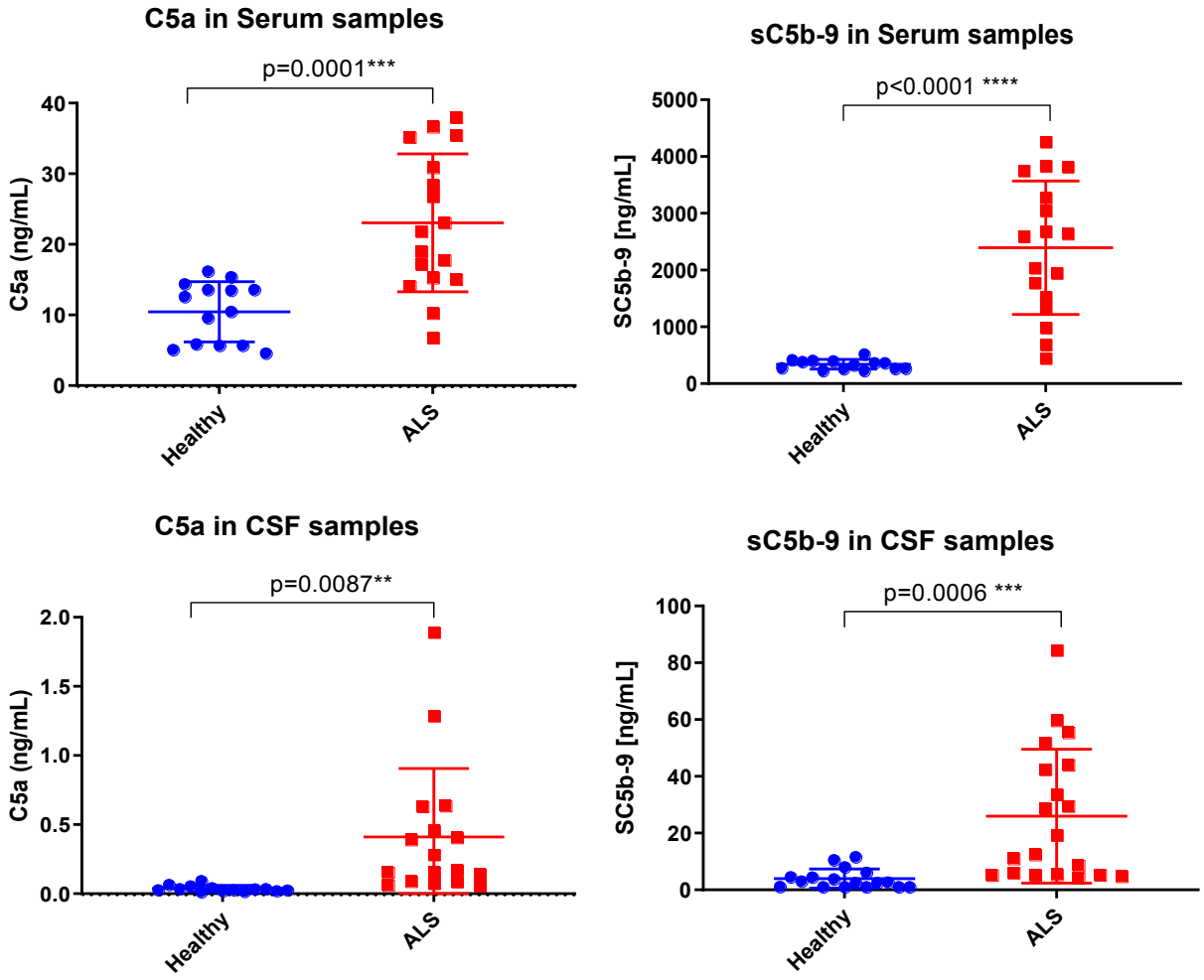
This RSA is designed to correspond with the design of the Master Protocol and the goals of the Platform Trial.

Rationale for Complement Inhibition in ALS

The complement cascade is one of the most potent effector mechanisms in the immune system which, through the formation of the terminal membrane attack complex (C5b-9 or MAC) and the recruitment of inflammatory cells via the potent anaphylatoxin C5a, has great potential to cause tissue injury. All components of the complement cascade can be locally synthesized in the CNS, specifically by neurons, astrocytes, oligodendrocytes and microglia (Barnum, 1995; Gasque et al., 1997; O'Barr et al., 2001). Hyperactivation of the complement system has been shown to participate in several neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, Huntington's disease and ALS (Kjaeldgaard et al., 2018; Loeffler et al., 2006; Morgan, 2018; Singhrao et al., 1999). At the time of study design, no complement inhibitor had been investigated in a clinical trial of ALS, although substantial preclinical and clinical data provide rationale to do so.

The predominant pathway involved in ALS pathophysiology is the classical complement pathway. This is primarily activated by the recognition molecule C1q, which binds to antigen antibody complexes and endogenous pattern recognition molecules. Elevations in biomarkers of classical pathway activation such as C1q and C4 have been shown to be associated with ALS in serum, cerebrospinal fluid, CNS parenchyma (motor cortex and spinal cord) and skeletal muscle tissue (Bahia El Idrissi et al., 2016a; Sta et al., 2011; Trbojevic- Cepe et al., 1998). In house data has also identified marked elevations in serum and cerebrospinal fluid markers of terminal complement pathway activation (C5a and C5b-9) in patients with ALS as compared with healthy controls (Figure).

Figure 2: Terminal complement activation products in the serum and CSF of healthy controls versus ALS patients. Data represents individual patients with mean ± standard deviation. Data on record at Ra Pharma.



Peripheral nervous involvement of the classical complement pathway has also been documented, suggesting that pharmacological inhibition of the complement cascade outside the CNS may also deliver therapeutic benefit in ALS. In a study by Bahia El Idrissi et al., 2016 on post-mortem intercostal muscle from ALS patients and control donors, increased levels of C1q on the axons innervating the motor end plates of ALS patients were identified but C1q was undetectable in control (p=0.001). Additionally, C1q was deposited on innervated motor endplates prior to denervation, suggesting that classical pathway activation may play an early role in the degradation of the neuromuscular junction, the so-called "dying-back" mechanism (Chou and Norris 1993), suggesting that effective complement inhibition at the neuromuscular junction (as achieved by zilucoplan in Ra Pharma's gMG Phase 2 trial: RA101495-02.201) could salvage early motor junction deterioration in ALS and prevent further loss.

With regard to investigation into the role of complement C5 in animal models of ALS this has been limited. The contribution of C5a and C5b have been investigated separately and support the concept that broader inhibition of complement C5 could be effective in ALS. SOD1G93A rats and mice were treated with the specific C5aR1 antagonist, PMX205. Chronic administration of PMX205 in SOD1G93A rats markedly delayed the onset of motor symptoms and increased survival (Woodruff et al., 2008). PMX205 treatment in SOD1G93A mice also extended survival, improved motor function (i.e. hind-limb grip strength) and slowed disease progression (Lee et al., 2017). Furthermore, deletion of the C5a receptor 1 (CD88) in SOD1G93A mice resulted in a significant extension in survival compared to control SOD1G93A mice in both sexes, also supporting a pathogenic role for C5a in this model of ALS (Woodruff et al., 2014). With respect to the MAC forming C5b product this has been implicated by antisense inhibition of C6 (another MAC pore-forming protein) which also resulted in delayed disease progression and extended survival in SOD1G93A mice (Bahia El-Idrissi et al., 2016b).

These data have been supported by broader description of classical complement pathway activation in several animal models of ALS at the transcript level. In SOD1G93A mice, up-regulation of C1qA and C1qB mRNA transcripts was observed in the spinal cord at later stages of disease (Olsen et al., 2001) and was subsequently confirmed by RT-PCR in isolated lumbar motor neurons from other SOD1 models: SOD1G93A, SOD1G37R and SOD1G85R mice (Ferraiuolo et al., 2007; Lobsiger et al., 2007; Perrin et al., 2005). Similarly, in non-SOD1 models increases in C1qB and C4 mRNA levels in the lumbar spinal cord of TDP43Q331K transgenic mice have also been identified (Lee et al., 2018). Downstream of C1q an upregulation of C3 mRNA and protein expression is observed in SOD1G93A and TDP43Q331K rodents' spinal cord (Heurich et al., 2011; Lee et al., 2013, 2018; Woodruff et al., 2008). C3b, the activated fragment of C3, is found localized with activated glia and dying motor neurons, consistent with its role as an opsonin.

Analysis of peripheral changes in classical complement proteins using SOD1G93A and TDP43Q331K mice has demonstrated upregulated mRNA expression of C1qB and C4 in the tibialis anterior at the mid-stage and end stages of disease (Lee et al., 2018; Wang et al., 2017) and at the motor end-plates of SOD1G93A mice, (Bahia El Idrissi et al., 2016a; Heurich et al., 2011). Increases in downstream markers such as C3, C5, C5b9 (MAC) deposition at the motor end plates and nerve terminals, starting at the pre-symptomatic stage, have been observed in SOD1G93A mice, as well as TDP43 models.

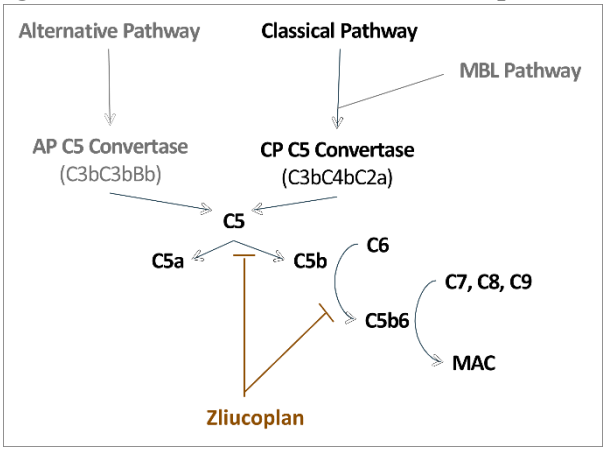
In summary, there are numerous studies documenting activation of the complement cascade in both the peripheral and central pathophysiology of ALS. In the periphery, studies suggest that activation of complement may temporally precede motor end plate degeneration and therefore complement inhibition could be disease modifying. In the CNS, complement activation is closely associated with the ongoing neuroinflammatory process. More broadly, complement activation has been documented in association with a diverse set of other neurodegenerative disorders including trauma, MS, Alzheimer's disease, Parkinson's disease and Huntington's disease. In all cases, the presence of terminal complement components C5a and C5b, potent inflammatory and membrane attack moieties, respectively, suggests that inhibition of C5 activation could contribute to the treatment of ALS and other neurodegenerative diseases.

Zilucoplan and the Complement Cascade

Zilucoplan has undergone extensive preclinical characterization to understand the pharmacology, pharmacokinetics, safety pharmacology and toxicology of the drug. The preclinical data package has been reviewed by all major regulatory agencies including the FDA's Division of Neurology Products.

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

Figure 3: 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.

Zilucoplan shows species selectivity for non-human primate and human complement C5 only. The primary pharmacology of zilucoplan was established in vitro using direct binding and functional inhibition of complement assays, as well as enzyme-linked immunosorbent assays (ELISAs). 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, as well as a slow dissociation rate. The binding site is distinct from that of the complement C5 inhibitor monoclonal antibody eculizumab and therefore is not affected by mutations in complement C5 known to prevent binding of eculizumab in patients of Asian and Han-Chinese descent (Nishimura et al. 2014). Target (C5) binding was confirmed using a competitive ELISA employing biotinylated zilucoplan to capture C5. Additionally, zilucoplan demonstrated dose-dependent inhibition of C5a and C5b formation following activation of classical or alternative pathways, as well as inhibition of RBC lysis in serum/plasma. Zilucoplan is a potent complement inhibitor in primates and humans and a weak/poor inhibitor in all other animal species tested (see below).

Species	IC_{50} (nM)
Human	6.6
Non-human primate	
Baboon	5.2
Chimpanzee	11.7
Cynomolgus	3.5
Rhesus	17.6
Dog	> 4,700
Rabbit	> 67,000
Porcine	
Mini-pig	51.9
Pig	118.6
Rodents	
Mouse	> 36,000
Rat	591.2
Guinea Pig	> 100,000

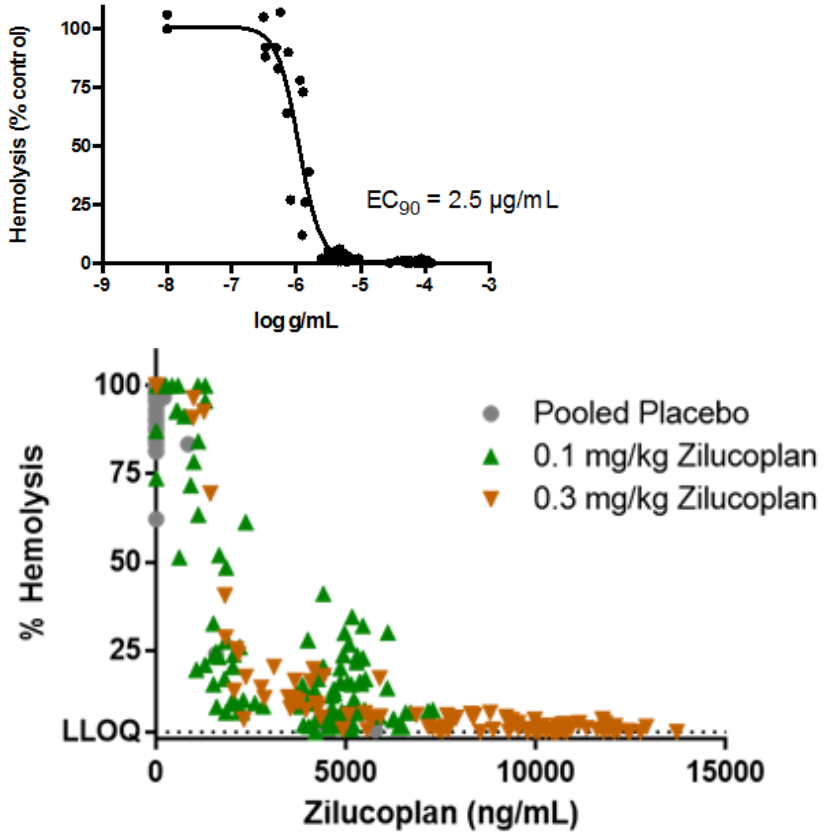
Table 1: Pharmacological potency of zilucoplan (IC50) in species tested

Zilucoplan is slowly absorbed in preclinical species after single SC administration, with mean T_{max} ranging from approximately 5 to 8 hours post-dose. The mean elimination half-life in plasma is 7 days in monkeys and humans. The slow elimination kinetics are largely driven by high affinity interaction with the target protein C5 and a much lower affinity interaction with albumin and other plasma proteins. Metabolism of zilucoplan is well-characterized and studies have identified two primary metabolites that occur in similar ratios in both monkeys and humans. Excretion of parent and major metabolites is predominantly hepatobiliary.

The PK/PD relationship of zilucoplan has been extensively investigated in cynomolgus monkeys. An EC_{90} of 2500 ng/mL was determined in monkeys which translated nearly precisely to the clinical experience in generalized myasthenia gravis trials (Figure).

Figure 4: PK/PD Relationship for Zilucoplan in Cynomolgus Monkeys and Translation to the Clinic

A) Zilucoplan PK/PD in Cynomolgus Monkeys **B) Zilucoplan PK/PD in Phase 2 gMG trial**



Quantitative whole-body autoradiography studies in rats have been conducted using [^{14}C]-zilucoplan to determine the in vivo biodistribution of zilucoplan. Importantly, zilucoplan biodistribution to ALS disease compartments such as muscle, spinal cord and brain are enhanced when compared to literature data of therapeutic monoclonal antibodies (see below). Furthermore, as this rodent study was carried out in "normal" animals, the blood brain barrier would be intact, potentially analogous to current understanding of ALS blood brain barrier integrity. Ra Pharma believes that this biodistribution advantage is conferred by smaller molecular size of a macrocyclic peptide (3.5 kDa) versus a monoclonal antibody (approx. 140 kDa). Therefore, zilucoplan may be ideally suited to test the hypothesis of both peripheral and CNS involvement of complement in ALS.

	Antibody Biodistribution[1] (%)	Zilucoplan Biodistribution[2] (%)
Lung	14.9	37.5
Heart	10.2	22.9
Muscle	3.97	7.0
Skin	15.7	Not analyzed
Small Intestine	5.22	10.9
Large Intestine	5.03	21.7
Spleen	12.8	15.5
Liver	12.1	27.1
Bone	7.27	15.3
Stomach	4.98	8.5
Lymph nodes	8.46	12.8
Fat	4.78	16.2
Brain	0.35	0.9
Pancreas	6.4	15.8
Testes	5.88	15.5
Thyroid	67.5	14.9
Thymus	6.62	7.8

Table 2: Rodent Quantitative Whole-Body Radiography of [14C]-zilucoplan**:**
Improved biodistribution into tissue vs. literature values of typical mAb taken from Shah DK, Betts AM (2013). Ra data represent tissue AUC0-24 as a percentage of plasma.

In summary, preclinical studies have extensively characterized the pharmacokinetics, pharmacology, safety, and toxicology of zilucoplan. The biodistribution advantages of zilucoplan when compared to monoclonal antibodies particularly with respect to access to the muscle and brain/spinal cord compartments may be an important determinant of success in treating ALS. Literature data support a strong activation of complement in the peripheral and central nervous system in both patients and animal models of ALS.

3.2 End of Participation Definition

A participant is considered to have ended his or her participation in the placebo-controlled period of the Regimen if they:

- Complete planned placebo-controlled period visits, as described in the SOA, including participants on or off study drug
- Early terminate from the study and complete the Early Termination Visit and Follow-Up Phone call as described in *Section 6.1.11*

- Withdraw consent to continue participation in the study, or are lost to follow up

If a participant initiates open-label study drug in the OLE period, he or she is considered to have completed his or her participation in the OLE period of the Regimen if they choose to withdraw or all planned OLE period visits, including the last visit or the last scheduled procedure shown in the SOA, have been completed.

3.3 End of Regimen Definition

The end of the placebo-controlled period in a Regimen occurs when all randomized participants have completed their participation in the placebo-controlled period as defined in section 3.2.

The end of the OLE period in a Regimen occurs when all participants who initiated open-label study drug in the OLE period have completed their participation in the OLE period as defined in *Section 3.2*.

4. RSA ENROLLMENT

4.1 Number of Study Participants

Approximately 160 participants will be randomized for this Regimen.

4.2 Inclusion and Exclusion Criteria

To be randomized to an RSA, participants must meet the Master Protocol eligibility criteria. In addition, participants meeting all the following inclusion and exclusion criteria will be allowed to enroll in this Regimen:

4.2.1 RSA Inclusion Criteria

1. Vaccination with a quadrivalent meningococcal vaccine and meningococcal serotype B vaccine at least 14 days prior to the first dose of study drug at the Baseline (Day 0) visit. Meningococcal vaccines (including boosters) should be administered in accordance with the study's vaccination worksheet.

4.2.2 RSA Exclusion Criteria

1. History of meningococcal disease.
2. Prior treatment with a complement inhibitor.

5 INVESTIGATIONAL PRODUCT

5.1 Investigational Product Manufacturer

Zilucoplan injection is manufactured in accordance with current Good Manufacturing Practices.

Drug Substance
RA101495 sodium drug substance is comprised of all L-α-amino acids. There are 15 L-α-amino acids in the main chain and an additional L-glutamic acid in the side-chain group on lysine^{15}. This side-chain group on lysine^{15} contains a palmitic acid, a γ-linked L-glutamic acid, and then an amino-ethylene-glycol-acid spacer (EG_{24}) attached to the ε-group of lysine^{15}. Using IUPAC naming convention for peptides and writing the EG_{24} as a polyoxygenated long-chain fatty acid, the name of RA101495 sodium is:

> Acetyl-[L-lysyl^{1}-L-valyl^{2}-L-glutamyl^{3}-L-arginyl^{4}-L-phenylalanyl^{5}-L-aspartyl^{6}] -N-methyl-L-aspartyl^{7}-L-tert-leucyl^{8}-L-tyrosyl^{9}-L-7-azatryptophyl^{10}-L-glutamyl^{11}-L-tyrosyl^{12}-L-prolyl^{13}-L-cyclohexylglycyl^{14}-[L-lysyl^{15}, N$^{\varepsilon}$-palmitoyl-γ-L-glutamyl-(1-amino-3,6,9,12,15,18,21,24,27,30,33,36,39,42,45,48,51,54, 57,60,63,66,69,72-tetracosaoxapentaheptacontan-75-oyl)], cyclic (Lactam 1-6), tetra sodium

Excipients
The excipients used in the manufacture of zilucoplan injection are commonly used excipients in the pharmaceutical industry for parenteral dosage forms. All excipients comply with the requirements of the relevant monographs in the United States Pharmacopeia (USP)/National Formulary (NF), European Pharmacopoeia (Ph. Eur.), the British Pharmacopoeia (BP) and the Japanese Pharmacopoeia (JP). The purpose of the formulation components are as follows: phosphate buffer to maintain product pH (6.5 to 7.5) and saline to maintain an isotonic product (270 to 330 mOsm/kg).

The excipients used in the manufacture of zilucoplan placebo drug product for injection are the same as those used to produce 40 mg/mL zilucoplan drug product, however the molar quantities of the formulation ingredients differ in order to account for absence of active zilucoplan drug substance and to produce an isotonic solution within specified pH range. All excipients comply with the requirements of their respective monographs in the USP/NF and Pharm. Eur., as well as the Japanese Pharmacopoeia (JP), as applicable.

Drug Product / Investigational Product (IP)
Zilucoplan for injection is packaged into a Beckton Dickinson (BD) 1 mL long glass syringe with a 29-gauge ½" long staked in needle. The glass syringe is closed with a West 4423/50

Bromobutyl rubber B2/40 coated, Teflon-faced stopper. The zilucoplan injection syringes are then placed into the secondary packaging BD UltraSafe Plus. The Becton Dickinson UltraSafe Plus device is a non-sterile, non-measuring, single use needle safety shield system. The device does not perform, interfere with or in any way impact the delivery of the drug, which is accomplished by the prefilled syringe.

Drug product will be provided in prefilled syringes for self-injection using weight bracketed dosing (i.e., participants will be provided prefilled syringes based on their weight containing fixed amounts of zilucoplan, and each fixed amount will cover a range of participant weights). As shown in Table 3, 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 to a maximum dose of 0.42 mg/kg daily.

Placebo will be provided in 1 presentation of 0.574 mL.

Nominal Target Dose (mg/kg)	Actual Dose (mg)	Injection Volume (mL)	Weight Range (kg)	Dose Range (mg/kg)
0.3	16.6	0.416	≥43 to <56	0.30 to 0.39
0.3	23.0	0.574	≥56 to <77	0.30 to 0.41
0.3	32.4	0.810	≥77 to 150	0.22 to 0.42

Table 3: Zilucoplan Dose Presentations by Weight Brackets

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

5.2 Acquisition, Storage, and Preparation

Zilucoplan and placebo should be stored at 2°C to 8°C at the study site. Once dispensed to participants, zilucoplan and placebo may be stored at room temperature. Storage of zilucoplan and placebo outside of room temperatures should be avoided, eg, it should not be refrigerated once it has been removed to room temperature. Please refer to the Regimen specific pharmacy manual for additional details.

Participants will receive secure containers to dispose of used syringes while at home. At each visit, the participant should return the disposal container containing all used syringes to the site. The participant should also bring any unused study drug (i.e., unused syringes) back to the site at each in-person study visit.

All unused study drug syringes and disposal containers containing used syringes must be returned to the site at the end of the participant's participation in the Regimen. For participants not continuing on in the OLE, this would be the Week 24 Visit or earlier if study participation is terminated early. Participants who enter the OLE and end their participation in the OLE early should also return all unused study drug syringes and disposal containers containing used syringes to the site once their participation in the OLE ends.

5.3 Study Medication/Intervention, Administration, Escalation, and Duration

The drug product, 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. Participants will be instructed to self-administer SC doses daily; when necessary the SC injections may be administered by a caregiver. Three dosage strengths of zilucoplan will be supplied as shown in 6.

All eligible participants will be randomized 3:1 to receive 0.3 mg/kg zilucoplan or placebo administered SC at the Baseline (Day 0) visit, which will be performed by the site staff at the study visit. Following in-clinic education and training, all participants and/or caregivers will inject daily SC doses of study drug at approximately the same time each day for the remainder of the 24-week Treatment Period.

Dosing on study visit days as outlined in the SOA should be held until all assessments have been completed. At each clinic study visit, dosing should be supervised to ensure the correct injection technique is being followed by participants and/or caregivers.

Participants and caregivers will be instructed to inject SC doses daily at approximately the same time each day. The participant/caregiver will subcutaneously inject study drug into the abdomen only.

All participants 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.

5.4 Drug Returns and Destruction

At each in person visit the steps outlined in the Manual of Procedures must be followed for study drug accountability and compliance, as well as study drug return and destruction.

Prior to study drug destruction, all partial and empty kits require a second accountability verification to be completed by a different study team member, and both verifications should be documented on the study destruction logs. No study drug may be destroyed on-site until written

approval is provided by the study monitoring team. Sites should comply with their local drug destruction policies.

5.5 Justification for Dosage

The dosage of 0.3 mg/kg daily is selected for this study based on its well-understood safety and efficacy profile from prior clinical trial experience in neurology. In Ra Pharma's Phase 2 gMG study (RA101495-02.201), the 0.3mg/kg dose demonstrated superior efficacy, greater inhibition of the terminal complement pathway, with a similar safety and tolerability profile as compared with the 0.1 mg/kg and placebo arms. The magnitude and speed of improvement on the primary (Quantitative Myasthenia Gravis Score, QMG) and key secondary (MG Activities of Daily Living, MG-ADL) endpoints were greater with the 0.3 mg/kg dose than the 0.1 mg/kg dose, and both active doses were superior to placebo. The superior efficacy of the 0.3 mg/kg dose was further demonstrated by participants' complete freedom from the need for rescue therapy with IVIG or PLEX in the 0.3mg/kg arm, as compared with a 7% rescue rate in the 0.1mg/kg arm, and a 20% rescue rate in the placebo arm. A higher proportion of participants achieved minimal symptom expression (Vissing 2018), defined as an MG-ADL of 0 or 1, in the 0.3mg/kg arm (35.7%) as compared with the 0.1mg/kg arm (26.7%) and placebo (13.3%).

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

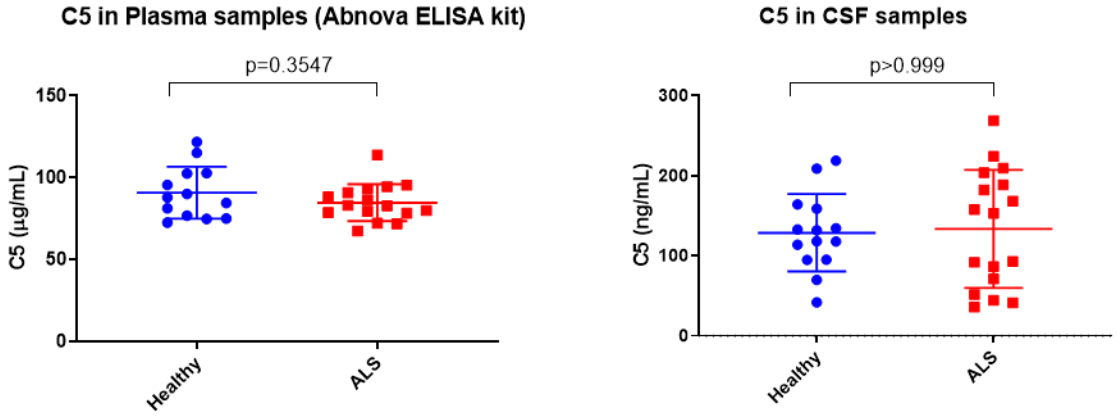
The once daily dosing interval used in study RA101495-02.201 will be retained in this study because pharmacokinetic simulations indicate that longer dosing intervals cannot achieve adequate exposures and fail to maintain the depth of complement inhibition needed for maximum therapeutic benefit. For example, once every other day dosing is estimated to reduce the zilucoplan trough concentration by approximately 50%, resulting in inadequate pharmacodynamic effect.

The same weight brackets as used in study RA101495-02.201 have been selected for use in this study. Study drug will be provided in prefilled syringes for self-injection using weight bracketed dosing (i.e., participants will be provided prefilled syringes containing fixed amounts of zilucoplan based on their weight, and each fixed amount will cover a range of participant weights).

5.5.1 Additional Scientific Justification for Dose Selection

Although activation of the complement system has been shown to participate in several neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, Huntington's disease and ALS (Kjaeldgaard et al., 2018; Loeffler et al., 2006; Morgan, 2018; Singhrao et al., 1999), basal levels of unactivated complement C5 are unchanged in ALS when compared to healthy controls. It is therefore apparent that ALS pathophysiology is driven, in part, by hyperactivation of complement system rather than over expression / elevated levels of the individual fluid phase proteins. This is exemplified by the below figure (**Error! Reference source not found.**) whereby complement C5 levels in plasma and CSF in ALS patients remain in the physiological range and comparable to healthy volunteer samples.

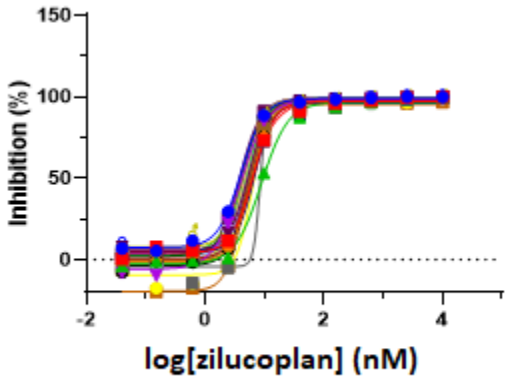
Figure 5: Complement C5 concentrations in healthy donors (n=14), age range 40–77yrs and ALS patients (n=17 of which n=15 sporadic ALS and n=2 familial ALS), age range 40-81yrs.



**Statistical difference assessed using unpaired, non-parametric, 2-tailed Mann-Whitney test in Prism (also called Wilcoxon rank sum test. Data is shown as mean ± Standard Deviation)*

With respect to dose selection for this trial, as drug levels (complement C5) are within the normal range and comparable with healthy volunteers (see above) and myasthenia gravis patients (not shown) no special dose adjustment for the ALS population is necessary. Furthermore, the sponsor assessed the apparent functional potency of zilucoplan in ALS plasma using a bioassay of pharmacodynamic activity (**Error! Reference source not found.**). The potency of zilucoplan to inhibit complement activation is unchanged relative to potency observed in healthy volunteer plasma samples.

Figure 6: Functional potency of zilucoplan in healthy donors (n=13) and ALS patients (n=16) plasma.

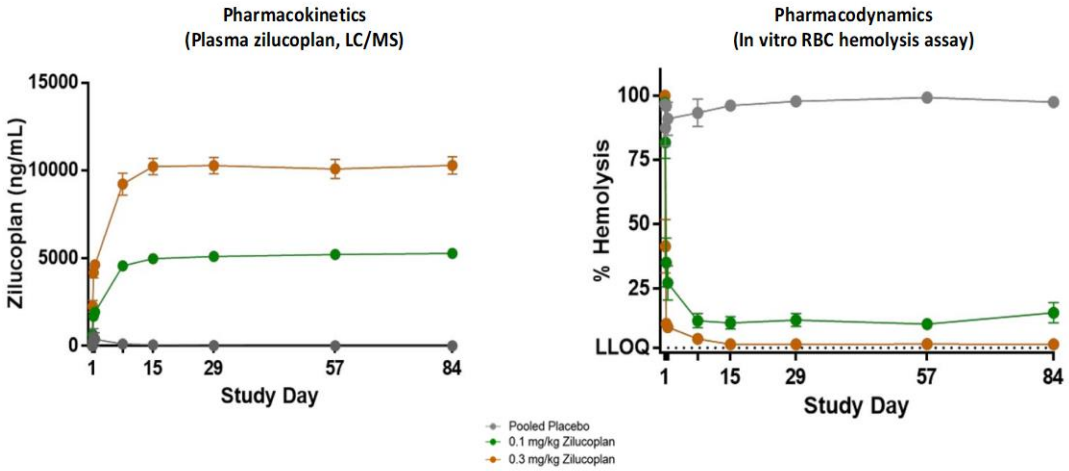


Samples	IC_{50} (nM) Mean ± SD	IC_{90} (nM) Mean ± SD
Healthy (n=13)	5.7 ± 1.3	13.4 ± 3.5
ALS (n=16)	5.4 ± 1.3	12.4 ± 2.5

Donor plasma (1% v/v) was incubated with antibody sensitized sheep erythrocytes. Hemolysis was assessed using OD412nm absorbance of the supernatant. A 10-pt dose-response curve with zilucoplan was generated for each sample to assess the IC50 and IC90 values. Samples are from the same patients and healthy volunteers as described in **Error! Reference source not found.**.

Based on similar target:drug stoichiometry across patient populations studied in the clinical development program of zilucoplan and unchanged functional potency of zilucoplan in ALS biomatrices, a daily dose of 0.3mg/kg/day will provide complete inhibition of complement C5 activity. The PK/PD relationship for zilucoplan in the phase 2, dose ranging study in a comparable neuromuscular disorder generalized myasthenia gravis is shown in **Error! Reference source not found.**.

Figure 7: Pharmacokinetic / Pharmacodynamic relationship of zilucoplan in Phase 2, dose ranging study in generalized myasthenia gravis (IND 134340).



Finally, data supports the blood-brain barrier permeability of zilucoplan in preclinical species (rats and non-human primates). Quantitative whole-body autoradiography studies in rats have been conducted using [^{14}C]-zilucoplan to determine the in vivo biodistribution of zilucoplan). In rats with a fully intact blood brain barrier approximately 1% (AUC0-24 as a percentage of plasma) of dosed compound was detected in the CNS compartment. Microdialysis studies in non-human primates also with an intact blood brain barrier have also been conducted and support these findings.

In summary 0.3mg/kg/day in the current study, should provide complete inhibition of circulating complement C5 in ALS patients. Furthermore, irrespective of blood brain barrier status (compromised vs intact) zilucoplan is expected to enter the CNS and engage complement C5. Pharmacodynamic biomarkers and pharmacokinetic analysis will be employed in this trial in both peripheral and CNS compartments to support interpretation of clinical data.

5.6 Dosage Changes

Not applicable.

5.7 Participant Compliance

Study personnel will assess study drug compliance at every in-person visit to record whether any doses were missed. During phone visits, drug compliance check-in will be discussed to ensure participant is taking drug per dose regimen and to note any report of missed doses. If a participant 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 participant misses 2 or more doses, he/she must notify the investigator immediately and the medical monitor should be consulted.

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

5.8 Overdose

Certain safety events that occur in association with study drug may require reporting. These safety events include, but are not limited to, the following:

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

These safety events should be reported to the Coordination Center whether they result in an AE/SAE or not. Safety events associated with an AE/SAE should also be reported in the EDC.

In the event of overdose, study staff should monitor the participant and provide supportive care as needed. The SI should also contact the Medical Monitor within 24 hours of the SI's awareness.

5.9 Prohibited Medications

Participants are prohibited from receiving another complement inhibitor and/or any other investigational products while on study. All other medications are permitted while on study.

Participants are expected to remain on stable doses of permitted SOC therapy for ALS throughout the Treatment Period of the study.

5.10 Zilucoplan Known Potential Risks and Benefits

5.10.1 Known Potential Risks

There are potential benefits and risks with the administration of any new investigational medicine as the effects are not fully known. To date, zilucoplan has shown good tolerability and a favorable safety profile across studies as described in the current version of the IB.

It is well established that inhibition of C5 and the terminal complement pathway increases the susceptibility to infection with encapsulated bacteria, in particular *N. meningitidis*. This risk is also described in the prescribing information for eculizumab (Soliris® USPI 2017). Given the increased risk for *N. meningitidis* with C5 inhibition or deficit, patients who participate in zilucoplan clinical trials will be required to have documentation of *N. meningitidis* vaccination (and booster if appropriate) prior to study entry. In addition, while on treatment with zilucoplan, participants will be monitored closely for signs and symptoms of *N. meningitidis* infection. More information on the safety profile of zilucoplan can be found in the IB.

5.10.2 Known Potential Benefits

The potential benefits of zilucoplan comprise improved control of complement-mediated disease processes (e.g., such effects have already demonstrated on muscle weakness due to impaired neuromuscular signaling in patients with gMG). In ALS we hypothesize that zilucoplan can inhibit complement-mediated tissue damage in the CNS and the neuromuscular junction, and that this may translate into improved neurological function as assessed by ALSFRS-R.

5.11 Treatment Assignment Procedures

Each participant who meets all eligibility criteria for the RSA will be randomized to receive either 0.3 mg/kg zilucoplan daily or placebo for approximately 24 weeks of placebo-controlled treatment (with the option of an Open Label Extension).

6 REGIMEN SCHEDULE

6.1 Placebo-Controlled Period

In addition to procedures in the Master protocol, the following regimen specific procedures will be conducted during the study:

- Home Spirometry
    - Note: Home spirometry should be collected within the visit window but will occur while the participant is not in the clinic (at home or other remote location).
- ALSAQ-40
- CNS Bulbar Function Scale
- Smartphone installation and removal
- Voice recording
- Dispense investigational product to participant
- Neisseria Meningitidis Vaccination
    - **Note: Booster vaccinations should be administered in accordance with SOC. Please refer to SOC and vaccination worksheet for details about timing.**
- Anti-drug Antibody Sampling
- Zilucoplan Plasma PK Analysis
- Zilucoplan Pharmacodynamic Analysis
- Zilucoplan Peripheral Blood Biomarker Samples

Participants may be required to reconsent to the regimen if new procedures or information is added in the future. Should a participant need to reconsent, this should occur during the participant's next in-person visit. If the participant's next in-clinic visit is conducted remotely, reconsent may also be completed remotely using the following procedures:

1. The site staff sends a copy of the informed consent form to the participant.
2. The participant reads through the consent form but does not sign.
3. The Site Investigator, or other study staff member approved and delegated to obtain informed consent, contacts the participant and reviews the informed consent form with the participant.
4. The participant signs the informed consent form and returns the original signed consent form back to the site.
5. Once received at the site, the individual who consented the participant signs the informed consent form.

Modifications to Regimen Schedule

Designated visits in the Schedule of Activities (i.e., Week 4, Week 8, and Week 16) may be conducted via telemedicine (or phone if telemedicine is not available) with remote services instead of in-person if needed to protect the safety of the participant due to a pandemic or other reason. If a planned in-clinic visit is conducted via telemedicine (or phone if telemedicine is not available) with remote services, only selected procedures will be performed. Instructions on how to document missed procedures are included in the MOP.

In addition to the procedures in the Master Protocol that should be conducted during the phone or telemedicine and remote visits, the following regimen-specific procedures should be completed:

- Home Spirometry (Week 8 and 16 only)
- Voice Recording
- CNS Bulbar Function Scale (Week 8 and 16 only)
- Neisseria Meningitidis Vaccination booster shots

Details on collection of the CNS Bulbar Function Scale, dispensing IP during remote visits, and documenting participants' willingness to participate in OLE are described in the MOP.
Blood samples for anti-drug antibody sampling, PK and PD analyses, and peripheral blood biomarker samples are not collected during the remote visits by the home health agency and this should be recorded as such in the applicable source documentation and EDC.

6.1.1 Regimen-Specific Screening Visit

This visit will take place in-person after the Master Protocol randomization to a regimen. **The visit must occur at least 14 days prior to the Baseline Visit. This is because the meningococcal vaccine needs 14 days to take effect. Participants must not start study drug until the 14-day period has elapsed.** The following procedures will be performed:

- *Neisseria Meningitidis* Vaccination

The regimen-specific screening may occur remotely if the participant would like to obtain the vaccination from their local provider, rather than traveling to the study site to obtain the vaccination during the screening visit. If the regimen-specific screening visit occurs remotely, then informed consent must be obtained remotely. The site should follow the steps below for obtaining remote consent from the participant prior to when the participant receives the vaccination:

- The site staff sends the informed consent form to the participant.
- The participant reads through the consent form but does not sign.
- The Site Investigator, or other study staff member approved and delegated to obtain informed consent, contacts the participant and reviews the informed consent form with the participant.
- The participant signs the informed consent form and returns the original signed consent form back to the site.
- Once received at the site, the individual who consented the participant signs the informed consent form.

6.1.2 Baseline Visit

This visit will take place in-person at least 14 days after the Regimen-Specific Screening Visit. The following procedures will be performed:

- ALSAQ-40
- CNS Bulbar Function Scale
- Install Smartphone Apps
- Home Spirometry
- Voice Recording
- Anti-drug Antibody Sampling
- Zilucoplan Plasma PK Analysis
- Zilucoplan Pharmacodynamic Analysis
- Zilucoplan Peripheral Blood Biomarker Samples
- Dispense investigational product to participant
- Administer investigational product to participant once all other Baseline procedures are complete
- Remind participant to bring investigational product to the next visit

6.1.3 Week 2 Telephone Visit

This visit will take place 14 ± 3 days after the Baseline Visit via telephone. No regimen-specific procedures will be performed at this visit.

6.1.4 Week 4 Visit

This visit will take place in-person 28 ± 7 days after the Baseline Visit The following procedures will be performed:

- Voice Recording
- Dispense investigational product to participant
- Remind participant to bring investigational product to the next visit

6.1.5 Week 8 Visit

Participants should be instructed to hold study drug on the day of the study visit. Study drug should not be taken until after study visit procedures are complete.

This visit will take place in-person 56 ± 7 days after the Baseline Visit. The following procedures will be performed:

- Home Spirometry
- CNS Bulbar Function Scale
- Voice Recording
- Anti-drug Antibody Sampling
- Zilucoplan Plasma PK Analysis
- Zilucoplan Pharmacodynamic Analysis
- Zilucoplan Peripheral Blood Biomarker Samples
- Dispense investigational product to participant
- Remind participant to bring investigational product to the next visit

6.1.6 Week 12 Telephone Visit

This visit will take place 84 ± 3 days after the Baseline Visit via telephone. No regimen-specific procedures will be performed at this visit.

6.1.7 Week 16 Visit

Participants should be instructed to hold study drug on the day of the study visit. Study drug should not be taken until after study visit procedures are complete.

This visit will take place in-person 112 ± 7 days after the Baseline Visit. The following procedures will be performed:

- Home Spirometry
- CNS Bulbar Function Scale

- Voice Recording
- Anti-drug Antibody Sampling
- Zilucoplan Plasma PK Analysis
- Zilucoplan Pharmacodynamic Analysis
- Zilucoplan Peripheral Blood Biomarker Samples
- Document participant's willingness to participate in the OLE
    - If OLE consent is not obtained at Week 16, it may be obtained at Week 24.
- Dispense investigational product to participant
- Remind participant to bring investigational product to the next visit

6.1.8 Week 20 Telephone Visit

This visit will take place 140 ± 3 days after the Baseline Visit via telephone. No regimen-specific procedures will be performed at this visit.

6.1.9 Week 24 Visit or Early Termination Visit

Participants should be instructed to hold study drug on the day of the study visit. Study drug should not be taken until after study visit procedures are complete.

The Week 24 Visit will take place in-person 168 ± 7 days after the Baseline Visit. The following procedures will be performed at either the Week 24 Visit or the Early Termination Visit:

- Home Spirometry
- ALSAQ-40
- CNS Bulbar Function Scale
- Voice Recording
- Uninstall Smartphone App
- Anti-drug Antibody Sampling
- Zilucoplan Plasma PK Analysis
- Zilucoplan Pharmacodynamic Analysis
- Zilucoplan Peripheral Blood Biomarker Samples
- Dispense investigational product to participant **[See note below.]**
- Remind participant to bring investigational product to the next visit (only if continuing in OLE)

Note: Drug is only dispensed at this visit if the participant is continuing in the Open Label Extension. Participants should be instructed to continue using effective contraception for at least 40 days after their last dose of study drug.

6.1.10 Follow-Up Safety Call

Participants will have a Follow-Up Safety Call about 40 days after their last dose of study drug. Only those participants NOT continuing on in the Open Label Extension will have the Follow-Up Safety Call following the end of their participation in the placebo-controlled portion of the trial. The following procedures will be performed:

- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)

6.1.11 Process for Early Terminations

Participants who early terminate from the study and do not complete the protocol will be asked to be seen for an in-person Early Termination Visit and complete a Follow-Up Safety Call. If a participant is not able to be seen in-person, safety assessments and others that can be conducted remotely should be performed.

The in-person Early Termination Visit should be scheduled as soon as possible after a participant early terminates. If the participant early terminates during the placebo-controlled portion of the Regimen, all assessments that are collected at the Week 24 in-clinic visit should be conducted. If the participant early terminates during the OLE phase, all assessments that are collected at the OLE Week 52 in-clinic visit should be conducted. The Follow-Up Safety Call should be completed approximately 40 days after the last dose of study drug.

If the Early Termination Visit occurs approximately 40±3 days after the last dose of study drug, the information from the Follow-Up Safety Call can be collected during the Early Termination Visit, and a separate Follow-Up Safety Call does not need to be completed. If the in-person Early Termination Visit does not occur within 40±3 days of the last dose of study drug, the Follow-Up Safety Call should occur approximately 40±3 days after the last dose of study drug and the Early Termination Visit will be completed after the Follow-Up Safety Call.

Note: Participants should be instructed to continue using effective contraception for at least 40 days after their last dose of study drug.

6.2 Open Label Extension

Participants who have completed the placebo-controlled portion of the trial on drug, will be eligible to continue on in the Open Label Extension. The Open Label Extension of the study will continue until zilucoplan is approved and available in the territory, or the Sponsor terminates development of zilucoplan for ALS.

Modifications to OLE Schedule

Designated visits in the Schedule of Activities for the OLE (i.e. Week 4, Week 8, Week 16, Week 28, and Week 40) may be conducted via telemedicine (or phone if telemedicine is not available) with remote services instead of in-person if needed to protect the safety of the participant due to a pandemic or other reason. If a planned in-clinic visit is conducted via telemedicine (or phone if telemedicine is not available) with remote services, only selected procedures will be performed. Instructions on how to document missed procedures are included in the MOP.

In addition to the procedures in the Master Protocol that should be conducted during the phone or telemedicine and remote visits, the following regimen-specific procedures should be completed:

- Home Spirometry
- CNS Bulbar Function Scale (Not done at OLE Week 4).
- Neisseria Meningitidis Vaccination booster shot

Blood samples for anti-drug antibody sampling, PK and PD analyses, and peripheral blood biomarker samples are not collected during the remote visits by the home health agency and this should be recorded as such in the applicable source documentation and EDC.

6.2.1 Week 2 OLE Telephone Visit

This visit will take place via telephone 14 ± 3 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Compliance Check-In
- Remind participant to bring investigational product to the next visit

6.2.2 Week 4 OLE Visit

This visit will take place in-person 28 ± 7 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Collect vital signs including weight
- Perform SVC
- Collect Home Spirometry
- Administer ALSFRS-R questionnaire
- Collect blood samples for Clinical Safety Labs and, for WOCBP, for pregnancy test if applicable
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Administer the C-SSRS Since Last Visit questionnaire
- Perform investigational product compliance
- Dispense investigational product to participant
- Remind participant to bring investigational product to the next visit

6.2.3 Week 8 OLE Visit

This visit will take place in-person at 56 ± 7 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Collect vital signs including weight
- Perform SVC
- Collect Home Spirometry
- Administer ALSFRS-R questionnaire
- CNS Bulbar Function Scale
- Collect blood samples for Clinical Safety Labs and, for WOCBP, for pregnancy test if applicable
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Administer the C-SSRS Since Last Visit questionnaire
- Perform investigational product compliance
- Dispense investigational product to participant
- Remind participant to bring investigational product to the next visit

6.2.4 Week 12 OLE Telephone Visit

This visit will take place via telephone at 84 ± 3 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Administer ALSFRS-R questionnaire
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Compliance Check-In
- Remind participant to bring investigational product to the next visit

6.2.5 Week 16 OLE Visit

Participants should be instructed to hold study drug on the day of the study visit. Study drug should not be taken until after study visit procedures are complete.

This visit will take place in-person at 112 ± 7 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Collect vital signs including weight
- Perform SVC
- Collect Home Spirometry
- Administer ALSFRS-R questionnaire
- CNS Bulbar Function Scale
- Collect blood samples for Clinical Safety Labs and, for WOCBP, for pregnancy test if applicable
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Administer the C-SSRS Since Last Visit questionnaire
- Perform investigational product compliance
- Collect urine sample biomarker analyses
- Collect blood sample for biomarker analyses
- Anti-drug Antibody Sampling
- Zilucoplan Plasma PK Analysis
- Zilucoplan Pharmacodynamic Analysis
- Zilucoplan Peripheral Blood Biomarker Samples
- Dispense investigational product to participant
- Remind participant to bring investigational product to the next visit

6.2.6 Week 20 OLE Telephone Visit

This visit will take place via telephone at 140 ± 3 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Administer ALSFRS-R questionnaire

- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Compliance Check-In
- Remind participant to bring investigational product to the next visit

6.2.7 Week 24 OLE Telephone Visit

This visit will take place via telephone at 168 ± 3 days after the Week 24 Visit of the placebo-controlled portion of the trial. The following procedures will be performed:

- Administer ALSFRS-R questionnaire
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Compliance Check-In
- Remind participant to bring investigational product to the next visit

6.2.8 Week 28 and Q12 Weeks OLE Visits

Participants should be instructed to hold study drug on the day of the study visit. Study drug should not be taken until after study visit procedures are complete.
The Week 28 OLE Visit will take place in-person 196 ± 14 days after the Week 24 Visit of the placebo-controlled portion of the trial. Following the Week 28 OLE Visit, visits will occur every 12 weeks ± 14 days. The following procedures will be performed:

- Collect vital signs including weight
- Perform SVC
- Collect Home Spirometry
- Administer ALSFRS-R questionnaire
- ALSAQ-40 [Only done at OLE Weeks 28 and 52 Visits]
- CNS Bulbar Function Scale [Only done at OLE Weeks 28, 40, and 52 Visits]
- Collect blood samples for Clinical Safety Labs and, for WOCBP, for pregnancy test if applicable
- Review concomitant medications
- Assess and document AEs, including Key Study Events (*see section 10.3 of Master Protocol*)
- Administer the C-SSRS Since Last Visit questionnaire
- Perform investigational product compliance
- Collect urine sample biomarker analyses [Only done at OLE Weeks 16, 28, and 52 Visits]
- Collect blood sample for biomarker analyses [Only done at OLE Weeks 16, 28, and 52 Visits]

- Anti-drug Antibody Sampling [Only done at OLE Weeks 16, 28, and 52 Visits]
- Zilucoplan Plasma PK Analysis [Only done at OLE Weeks 16, 28, and 52 Visits]
- Zilucoplan Pharmacodynamic Analysis [Only done at OLE Weeks 16, 28, and 52 Visits]
- Zilucoplan Peripheral Blood Biomarker Samples [Only done at OLE Weeks 16, 28, and 52 Visits]
- Dispense investigational product to participant
- Remind participant to bring in investigational product to the next visit

7. CLINICAL ASSESSMENTS AND OUTCOME MEASURES

For all assessments listed below, please refer to the Manual of Procedures for detailed instructions.

7.1 Voice Analysis

Voice samples will be collected twice per week, using an app installed on either an android or iOS based smartphone. The app characterizes ambient noise, then asks patients to perform a set of speaking tasks: reading sentences -- 5 fixed and 5 chosen at random from a large sentence bank-- repeating a consonant-vowel sequence, producing a sustained phonation, and counting on a single breath. Voice signals are uploaded to a HIPAA-compliant web server, where an AI-based analysis identifies relevant vocal attributes. Quality control (QC) of individual samples will occur by evaluation of voice records by trained personnel.

The voice analysis app is only available in English, therefore participants who do not speak English should not complete the voice recording. Caregivers cannot provide language assistance when the participant is completing the voice recording.

7.2 ALSAQ-40

The Amyotrophic Lateral Sclerosis Assessment Questionnaire-40 (ALSAQ-40) is a patient self-report health status patient-reported outcome. The ALSAQ-40 consists of forty questions that are specifically used to measure the subjective well-being of patients with ALS and motor neuron disease.

Participants will be handed the questionnaire and asked to write their answers themselves. Caregivers can also help, if needed.

7.3 Center for Neurologic Study Bulbar Function Scale

The Center for Neurologic Study Bulbar Function Scale (CNS-BFS) is a patient self-report scale that has been developed for use as an endpoint in clinical trials and as a clinical measure for evaluating and following ALS patients. The CNS-BFS consists of three domains (swallowing, speech, and salivation), which are assessed with a 21-question, self-report questionnaire.

Participants will be handed the questionnaire and asked to write their answers themselves. Caregivers can also help, if needed.

Instructions on administering the questionnaire during a phone or telemedicine visit will be included in the MOP.

7.4 Home Spirometry

Home-based forced vital capacity will be conducted via telemedicine (or phone if telemedicine is not available) and will be measured with the MIR Spirobank Smart spirometer. Instructions for use will be provided to the participant. The participant will perform the vital capacity maneuver with real time video coaching (or phone coaching, if video is not available) by the evaluator. Three to five vital capacity maneuvers will be performed, consistent with the manner vital capacity is obtained in clinic.

8. BIOFLUID COLLECTION

8.1 Anti-drug Antibody Sampling

All participants will provide blood samples for anti-drug antibody sampling.

8.2 Zilucoplan Plasma PK Analysis

All participants will provide blood samples for PK analysis (zilucoplan and metabolites). These blood samples should be obtained prior to administration of study drug at each clinic visit (i.e., pre-dose).

8.3 Zilucoplan Pharmacodynamic Analysis

All participants will provide blood samples for pharmacodynamic analysis (e.g., sheep RBC hemolysis assay, Wieslab alternative pathway assay, C5 levels). Blood samples should be obtained prior to administration of study drug at each clinic visit (i.e., pre-dose).

8.4 Zilucoplan Peripheral Blood Biomarker Samples

All participants will provide blood samples for biomarker analysis. Blood samples should be obtained prior to administration of study drug at each clinic visit (i.e., pre-dose).

9. REGIMEN-SPECIFIC STATISTICAL CONSIDERATIONS

9.1 Deviations from the Default Master Protocol Trial Design

The statistical design for this regimen will be in accordance with the default statistical design described in Appendix I of the Master Protocol with only one deviation. This regimen will not include interim analyses for early success.

9.2 Regimen Specific Operating Characteristics

Clinical trial simulation is used to quantify operating characteristics for this regimen (refer to the regimen SAP for further details).

9.3 Sharing of Controls from other Regimens

The primary analysis of this regimen will include sharing of all controls from the other regimens. This is justified by the minor differences in inclusion/exclusion criteria of the RSA, such that there are no expected systematic differences in the primary endpoint between the controls across regimens.

APPENDIX I: THE ALSAQ-40

ALSAQ-40

Please complete this questionnaire as soon as possible. If you have any difficulties filling in this questionnaire by yourself, please have someone help you. However it is **your** responses that we are interested in.

The questionnaire consists of a number of statements about difficulties that you may have experienced **during the last 2 weeks.** There are no right or wrong answers: your first response is likely to be the most accurate for you. **Please check the box that best describes your own experiences or feelings.**

Please answer every question even though some may seem very similar to others, or may not seem relevant to you.

All the information you provide is **confidential.**

The following statements all refer to difficulties that you may have had **during the last 2 weeks**.
Please indicate, by checking the appropriate box, how often the following statements have been true for you.

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

If you cannot walk at all
please check **Always/cannot walk at all.**

How often during the last 2 weeks have the following been true?

*Please check **one box** for each question.*

	Never	Rarely	Some-times	Often	Always or cannot walk at all
1. I have found it difficult to walk short distances, e.g. around the house.	☐	☐	☐	☐	☐
2. I have fallen over while walking.	☐	☐	☐	☐	☐
3. I have stumbled or tripped while walking.	☐	☐	☐	☐	☐
4. I have lost my balance while walking.	☐	☐	☐	☐	☐
5. I have had to concentrate while walking.	☐	☐	☐	☐	☐

*Please make sure that you have checked **one box for each question** before going on to the next page.*

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

If you are not able to perform the activity at all please check **Always/cannot at all**

How often during the last 2 weeks have the following been true?

Please check ***one box*** *for each question*

	Never	Rarely	Some-times	Often	Always or cannot do at all
6. Walking had worn me out.	☐	☐	☐	☐	☐
7. I have had pains in my legs while walking.	☐	☐	☐	☐	☐
8. I have found it difficult to go up and down the stairs.	☐	☐	☐	☐	☐
9. I have found it difficult to stand up.	☐	☐	☐	☐	☐
10. I have found it difficult to move from sitting in a chair to standing upright.	☐	☐	☐	☐	☐

Please make sure that you have checked ***one box for each question*** *before going on to the next page.*

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

If you cannot do the activity at all
please check **Always/cannot do at all.**

How often during the last 2 weeks have the following been true?

Please check ***one box*** *for each question*

	Never	Rarely	Some-times	Often	Always or cannot do at all
11. I have had difficulty using my arms and hands.	☐	☐	☐	☐	☐
12. I have found turning and moving in bed difficult.	☐	☐	☐	☐	☐
13. I have had difficulty picking things up.	☐	☐	☐	☐	☐
14. I have had difficulty holding books or newspapers, or turning pages.	☐	☐	☐	☐	☐
15. I have had difficulty writing clearly.	☐	☐	☐	☐	☐

Please make sure that you have checked ***one box for each question*** *before going on to the next page.*

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

If you cannot do the activity at all
please check **Always/cannot do at all.**

How often during the last 2 weeks have the following been true?

Please check ***one box*** *for each question*

	Never	Rarely	Some-times	Often	Always or cannot do at all
16. I have found it difficult to do jobs around the house.	☐	☐	☐	☐	☐
17. I have found it difficult to feed myself.	☐	☐	☐	☐	☐
18. I have had difficulty combing my hair or brushing and/or flossing my teeth.	☐	☐	☐	☐	☐
19. I have had difficulty getting dressed.	☐	☐	☐	☐	☐
20. I have had difficulty washing at the bathroom sink.	☐	☐	☐	☐	☐

Please make sure that you have checked ***one box for each question*** *before going on to the next page.*

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

If you cannot do the activity at all
please check **Always/cannot do at all.**

How often during the last 2 weeks have the following been true?

Please check ***one box*** *for each question*

	Never	Rarely	Some-times	Often	Always or cannot do at all
21. I have had difficulty swallowing.	☐	☐	☐	☐	☐
22. I have had difficulty eating solid food.	☐	☐	☐	☐	☐
23. I have had difficulty drinking liquids.	☐	☐	☐	☐	☐
24. I have had difficulty participating in conversations.	☐	☐	☐	☐	☐
25. I have felt that my speech has not been easy to understand.	☐	☐	☐	☐	☐

Please make sure that you have checked ***one box for each question*** *before going on to the next page.*

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

If you cannot do the activity at all
please check **Always/cannot do at all.**

How often during the last 2 weeks have the following been true?

Please check ***one box*** *for each question*

	Never	Rarely	Some-times	Often	Always or cannot do at all
26. I have stuttered or slurred my speech.	☐	☐	☐	☐	☐
27. I have had to talk very slowly.	☐	☐	☐	☐	☐
28. I have talked less than I used to do.	☐	☐	☐	☐	☐
29. I have been frustrated with my speech.	☐	☐	☐	☐	☐
30. I have felt self-conscious about my speech.	☐	☐	☐	☐	☐

Please make sure that you have checked ***one box for each question*** *before going on to the next page.*

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

How often during the last 2 weeks have the following been true?

*Please check **one box** for each question*

	Never	Rarely	Some-times	Often	Always
31. I have felt lonely.	☐	☐	☐	☐	☐
32. I have been bored.	☐	☐	☐	☐	☐
33. I have felt embarrassed in social situations.	☐	☐	☐	☐	☐
34. I have felt hopeless about the future.	☐	☐	☐	☐	☐
35. I have worried that I am a burden to other people.	☐	☐	☐	☐	☐

*Please make sure that you have checked **one box for each question** before going on to the next page.*

The following statements all refer to certain difficulties that you may have had during the last 2 weeks. Please indicate, by checking the appropriate box, how often the following statements have been true for you.

How often during the last 2 weeks have the following been true?

*Please check **one box** for each question*

	Never	Rarely	Some-times	Often	Always
36. I have wondered why I keep going.	☐	☐	☐	☐	☐
37. I have felt angry because of the disease.	☐	☐	☐	☐	☐
38. I have felt depressed.	☐	☐	☐	☐	☐
39. I have worried about how the disease will affect me in the future.	☐	☐	☐	☐	☐
40. I have felt as if I have lost my independence	☐	☐	☐	☐	☐

*Please make sure that you have checked one **box for each question.***

Thank you for completing this questionnaire.

APPENDIX II: THE BULBAR FUNCTION SCALE (CNS-BFS)

BULBAR FUNCTION SCALE (CNS-BFS)						
SIALORRHEA	**Does Not Apply (1)**	**Applies Rarely (2)**	**Applies Occasionally (3)**	**Applies Frequently (4)**	**Applies Most of the Time (5)**	
1. Excessive saliva is a concern to me.	❍	❍	❍	❍	❍	
2. I take medication to control drooling.	❍	❍	❍	❍	❍	
3. Saliva causes me to gag or choke.	❍	❍	❍	❍	❍	
4. Drooling causes me to be frustrated or embarrassed.	❍	❍	❍	❍	❍	
5. In the morning I notice saliva on my pillow.	❍	❍	❍	❍	❍	
6. My mouth needs to be dabbed to prevent drooling.	❍	❍	❍	❍	❍	
7. My secretions are not manageable.	❍	❍	❍	❍	❍	
				TOTAL Sialorrhea Score: _____		
SPEECH	**Does Not Apply (1)**	**Applies Rarely (2)**	**Applies Occasionally (3)**	**Applies Frequently (4)**	**Applies Most of the Time (5)**	**Unable to Communicate by Speaking (6)**
1. My speech is difficult to understand.	❍	❍	❍	❍	❍	❍
2. To be understood I repeat myself.	❍	❍	❍	❍	❍	❍
3. People who understand me tell other people what I said.	❍	❍	❍	❍	❍	❍
4. To communicate I write things down or use devices such as a computer.	❍	❍	❍	❍	❍	❍
5. I am talking less because it takes so much effort to speak.	❍	❍	❍	❍	❍	❍

6. My speech is slower than usual.	❍	❍	❍	❍	❍	❍
7. It is hard for people to hear me.	❍	❍	❍	❍	❍	❍
				TOTAL Speech Score: _____		
SWALLOWING	**Does Not Apply (1)**	**Applies Rarely (2)**	**Applies Occasionally (3)**	**Applies Frequently (4)**	**Applies Most of the Time (5)**	
☐ Feeding tube is in place						
1. Swallowing is a problem.	❍	❍	❍	❍	❍	
2. Cutting my food makes it easier to chew and swallow.	❍	❍	❍	❍	❍	
3. To get food down I have switched to a soft diet.	❍	❍	❍	❍	❍	
4. After swallowing I gag or choke.	❍	❍	❍	❍	❍	
5. It takes longer to eat.	❍	❍	❍	❍	❍	
6. My weight is dropping because I can't eat normally.	❍	❍	❍	❍	❍	
7. Food gets stuck in my throat.	❍	❍	❍	❍	❍	
				TOTAL Swallowing Score: _____		
				OVERALL SCORE: _____		

REFERENCES

Bahia El Idrissi, N., et al., 2016a. Complement activation at the motor end-plates in amyotrophic lateral sclerosis. J. Neuroinflammation 13, 72.

Bahia El Idrissi, N., et al., 2016b. Complement component C6 inhibition decreases neurological disability in female transgenic SOD1G93A mouse model of amyotrophic lateral sclerosis. Ann Neurodegener Dis. 1, 1015.

Barnum, S.R., 1995. Complement biosynthesis in the central nervous system. Crit. Rev. Oral Biol. Med. 6, 132–146.

Chou SM, Norris FH, 1993. Amyotrophic lateral sclerosis: lower motor neuron disease spreading to upper motor neurons. Muscle & Nerve;16:864–9.

Ferraiuolo, L., et al., 2007. Microarray analysis of the cellular pathways involved in the adaptation to and progression of motor neuron injury in the SOD1 G93A mouse model of familial ALS. J. Neurosci. 27, 9201–9219.

Gasque, P., et al., 1997. Expression of the receptor for complement C5a (CD88) is upregulated on reactive astrocytes, microglia, and endothelial cells in the inflamed human central nervous system. Am. J. Pathol. 150, 31–41.

Heurich, B., et al., 2011. Complement upregulation and activation on motor neurons and neuromuscular junction in the SOD1 G93A mouse model of familial amyotrophic lateral sclerosis. J. Neuroimmunol. 235, 104–109.

Kjaeldgaard, A.L., et al., 2018. Amyotrophic lateral sclerosis: the complement and inflammatory hypothesis. Mol. Immunol. 102, 14–25.

Lee, J.D., et al., 2013. Dysregulation of the complement cascade in the hSOD1G93A transgenic mouse model of amyotrophic lateral sclerosis. J. Neuroinflammation 10,119.

Lee, J.D., et al., 2017. Pharmacological inhibition of complement C5a-C5a1 receptor signalling ameliorates disease pathology in the hSOD1G93A mouse model of amyotrophic lateral sclerosis. Br. J. Pharmacol. 174, 689–699.

Lee, J.D., et al., 2018. Complement components are upregulated and correlate with disease progression in the TDP-43(Q331K) mouse model of amyotrophic lateral sclerosis. J. Neuroinflammation 15, 171.

Lobsiger, C.S., et al., 2007. Toxicity from different SOD1 mutants dysregulates the complement system and the neuronal regenerative response in ALS motor neurons. Proc. Natl. Acad. Sci. U. S. A. 104, 7319–7326.

Loeffler, D.A., et al., 2006. Complement activation in the Parkinson's disease substantia nigra: an immunocytochemical study. J. Neuroinflammation 3, 29.

Morgan, B.P., 2018. Complement in the pathogenesis of Alzheimer's disease. Semin. Immunopathol. 40, 113–124

Nishimura, J. et al., 2014 Genetic Variants in C5 and Poor Response to Eculizumab N Engl J Med. 370:632-639

O'Barr, S.A., et al., 2001. Neuronal expression of a functional receptor for the C5a complement activation fragment. J. Immunol. 166, 4154–4162.

Perrin, F.E., et al., 2005. No widespread induction of cell death genes occurs in pure motoneurons in an amyotrophic lateral sclerosis mouse model. Hum. Mol. Genet. 14,3309–3320.

Shah DK, Betts AM, 2013. Antibody biodistribution coefficients: inferring tissue concentrations of monoclonal antibodies based on the plasma concentrations in several preclinical species and human. mAbs 5:297-305

Singhrao, S.K., et al., 1999. Increased complement biosynthesis by microglia and complement activation on neurons in Huntington's disease. Exp. Neurol. 159, 362–376

Sta, M., et al., 2011. Innate and adaptive immunity in amyotrophic lateral sclerosis: evidence of complement activation. Neurobiol. Dis. 42, 211–220.

Trbojevic-Cepe, M., et al., 1998. Cerebrospinal fluid complement activation in neurological diseases. J. Neurol. Sci. 154, 173–181.

Vissing J, O'Brien F, Wang JJ, Howard JF., 2018. Correlation between myasthenia gravis-activities of daily living (MG-ADL) and quantitative myasthenia gravis (QMG) assessments of anti-acetylcholine receptor antibody-positive refractory generalized myasthenia gravis in the phase 3 regain study. Muscle Nerve;58(2): E21-E22

Wang, H.A., et al., 2017. Complement C5a-C5aR1 signaling drives skeletal muscle macrophage recruitment in the hSOD1G93A mouse model of amyotrophic lateral sclerosis. Skelet. Muscle 7, 10.

Woodruff, T.M., et al., 2008. The complement factor C5a contributes to pathology in a rat model of amyotrophic lateral sclerosis. J. Immunol. 181, 8727–8734.

Woodruff, T.M., et al., 2010. The role of the complement system and the activation fragment C5a in the central nervous system. NeuroMolecular Med. 12, 179–192.

Woodruff, T.M., et al., 2014. Role for terminal complement activation in amyotrophic lateral sclerosis disease progression. Proc. Natl. Acad. Sci. U. S. A. 111, E3–E4.