APL2-ALS-206

A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF PEGCETACOPLAN IN SUBJECTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS)

MERIDIAN

AMENDMENT 6

13 JANUARY 2023

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SIGNATURE PAGE

Sponsor's Approval

The protocol has been approved by Apellis Pharmaceuticals, Inc.

PPD

Apellis Pharmaceuticals, Inc
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AMENDMENT 6: SUMMARY OF CHANGES FROM THE PREVIOUS VERSION

Protocol versions		
Summary of changes since last version of approved protocol		
Amendment 6	**Amendment date** **04 January 2023**	**Global**

Description of change	Section(s) affected by change	Rationale for change
Nonsubstantial editorial and technical changes that did not impact content of the document have been made for grammar, clarity, and document usability.	Entire document	Improved clarity of the protocol.
Changed name of company signatory	Signature Page	Responsible physician for the study changed.
Study period was extended from 33 months to 45 months and the planned length of a subject's participation went from 116 weeks to 168 weeks.	Synopsis, Section 6 Section 6.1, Figure 1	Added an open-label long-term extension period.
Updated exploratory endpoints to add the addition of a week 156 time point for capturing specific measures, including adding 3 new exploratory endpoints at week 156	Synopsis, Section 5.2.4, Section 10.2, Section 12.3.3	Updated some exploratory endpoints and added the 3 new exploratory endpoints to capture measures during the new open-label long-term extension time point.
Updated the open-label treatment period (Part 3) as follows: Subjects who complete Part 3 will enter Part 4~~, unless they enter the sponsor-planned long-term extension protocol~~.	Synopsis, Section 6.1.3, Section 6.1.5	Long-term extension is no longer planned, it is now Part 4 of the study.
Updated the study design to reflect the addition of the new open-label, long-term extension period (new Part 4) and described it throughout the protocol where needed, including a new schedule of assessments for this period. Updated the previous Part 4 (6-week off-treatment follow-up period) to now be called Part 5 due to the addition of the new open-label, long-term extension period	Synopsis, Section 6, Figure 1, Section 8.6.2, Section 11.1.2, Section 11.1.3, Section 11.1.4, Section 11.1.5, Section 11.1.8, Section 11.1.8.1, Section 11.5, Appendix 2 (Table 8, new)	Added an open-label long-term extension period, which then required the previous Part 4 to become the new Part 5.
Updated the exclusion criteria for both riluzole and edaravone to accurately reflect when they are excluded based on the addition of the new study period.	Synopsis, Section 7.2	Updated to accurately reflect when these medications are excluded based on the new study period.

Updated the blinding description The open-label ~~treatment period~~ and long-term extension ~~is~~ treatment periods are not blinded.	Synopsis	Changed language to reflect that the new long-term treatment period is also not blinded.
Updated the statistical methodology for the secondary efficacy endpoints.	Synopsis	Updated to align with Section 12.3
Added the newly approved medication, Relyvrio.	Section 4.1	Relyvrio was recently approved for the treatment of ALS.
Updated the study summaries to reflect more recent report results.	Section 4.4	Updates were needed to some of the originally presented study summaries.
Added the following paragraph which was from the French Addendum 5.1: Systemic hypersensitivity reactions (eg, facial swelling, rash, urticaria) have occurred in patients treated with pegcetacoplan. One patient (less than 1% in clinical studies) experienced a serious allergic reaction which resolved after treatment with antihistamines. If a severe hypersensitivity reaction (including anaphylaxis) occurs, discontinue pegcetacoplan infusion immediately, institute appropriate treatment, per standard of care, and monitor until signs and symptoms are resolved.	Section 4.5	Added to the protocol for additional information to the study sites, it was previously included with the French Addendum 5.1, Amendment 1.
Updated the language regarding vaccinations to provide further clarity.	Table 2 (footnote b), Section 8.4	Further clarity was needed regarding the vaccinations.
Updated the language regarding anti–pegcetacoplan peptide antibody and anti-PEG antibody collection.	Table 2 (footnote k), Table 3 (footnote i), Section 11.1.9	Updated this language to more accurately reflect the practice of assessing these antibodies.
Added a new footnote (p) regarding returning unused investigational product: [p] Only subjects not enrolling in Part 4 will return unused investigational product	Table 3 (footnote p)	Added to provide further instructions to the study sites.
Updated the language in footnote m to provide further clarity.	Table 3 (footnote m)	Further clarity was needed regarding IP dispensation.
Updated the definition of the end of the trial from the open-label treatment period to the open-label, long-term extension period	Section 6.5, Section 7.3	Updated as there is now a longer opportunity for treatment.
Updated Section 6.6.6 to be Early Termination Follow-Up Visit (previously was Section 6.6.5) Created a new Section 6.6.7, Unscheduled Visit(s) (previously was Section 6.6.6)	Section 6.6.6, Section 6.6.7	Sections needed to move down due to the addition of the new Section 6.6.5 which describes the new open-label long-term extension period.

Previous Section 6.6.6, Unscheduled Visit(s) has been moved to Section 6.6.7	Section 6.6.7	Moved to incorporate new section.
Added language regarding survival status for subjects who withdraw from the study: If a subject withdraws from the study, then the subject and/or their caregivers will be contacted by the study site to provide post-discontinuation survival status at 6-month intervals until the study completes.	Section 7.3	Added language to collect survival status of subjects who have withdrawn from the study.
Updated the following: Subjects are required to discontinue the investigational product and withdraw from the study if they meet the below criteria: • Administer a ~~prohibited medication(s)~~complement inhibitor during the period outlined in Section 8.6.1. • Intentionally unblinded themselves.	Section 7.3.1.1	Updated the language to more accurately reflect the intention of this reason for requiring a subject to withdraw.
Added language to clarify that both riluzole and edaravone cannot be initiated during Part 2 of the study. Also, the following new language was added to this section: • Subjects should not begin Relyvrio (AMX0035) during Part 2 of the study and if administered during Part 3 or 4, the dates of administration must be documented in the subject's source document and subject's eCRF.	Section 8.5	Clarification needed that riluzole and edaravone are not allowed to be initiated during Part 2 of the study. Relyvrio was newly approved for the treatment of ALS and this section provides guidance regarding if and when it can be concomitantly administered during this study
Added the number of collection time points for the new open-label, long-term extension period. Updated the sample volume amounts over the course of the study to reflect the additional collection time points.	Table 5	Updates necessary to reflect the newly added open-label, long-term extension period.
Added the following language: All death events should be reported as the fatal outcome of an SAE, with the date and cause of death included. The medical event leading to the subject's death (eg, respiratory failure, pneumonia) should be reported as the SAE term. If no alternative cause of death is identified, "progression of ALS" may be reported as the event term if deemed medically appropriate by the investigator.	Section 11.2.1.3	This change clarifies that all death events must be recorded as the outcome of an SAE.

Updated language as follows: Serious events (including events related to efficacy endpoints) that are considered ALS-related should be reported as "not related" SAEs. "ALS" or "disease progression" should not be reported as event terms if a more precise term for the ~~, but instead the~~ complication or actual cause of hospitalization/death (eg, respiratory failure) ~~should~~can be reported. "Disease progression" is considered a worsening of a subject's ALS symptoms (weakness, spasticity, respiratory insufficiency, respiratory arrest, dysphasia). It may reflect an increase in the severity of the disease or an increase in symptoms. Any event experienced by a subject which is solely regarded as part of disease progression and~~,~~ can be considered as a direct consequence of ALS, but does not result in death, should not be reported as an AE/SAE; examples include: respiratory insufficiency, dysphagia, respiratory failure, dysarthria, etc. However, if a subject should experience worsening of ALS-related disease symptoms that are not considered anticipated disease progression for that given subject, the investigator should report these findings as an AE. Examples of this might include: pneumonia, malnutrition, fall, or aspiration. If there is any uncertainty as to whether an event is due to anticipated disease progression, it should be reported as an AE.	Section 11.2.1.3.1	These changes reflect the update made in Section 11.2.1.3 and provide further clarification regarding adverse events associated with ALS disease progression.
Updated language as follows: The intent-to-treat (ITT) set will include all randomized subjects who receive at least one dose of randomized treatment (pegcetacoplan or placebo). Subjects will be analyzed according to their assigned treatment, regardless of the treatment actually received.	Section 12.2.3	Updated to clarify the ITT population more accurately.
Updated language as follows: The primary efficacy analysis for the primary endpoint (CAFS) will be conducted on the mITT set and will be repeated for the ~~ITT and~~ PP set~~s~~ to evaluate the robustness of the results from the primary analysis	Section 12.3.1	Updated to align with the SAP.

Updated Section 12.3.2 language as follows: (2nd, 3rd, and 4th paragraphs of Section 12.3.2) Absolute values and changes from baseline in secondary efficacy endpoints (ALSFRS-R, in-clinic percentage of predicted SVC, HHD, and ALSAQ-40) will be summarized, using descriptive statistics, by treatment and visit. Baseline will be taken as the measurement closest, but prior, to ~~randomization~~the first dose of investigational product. Changes from baseline in secondary efficacy outcomes (ALSFRS-R, in-clinic percentage of predicted SVC, HHD, and ALSAQ-40) will be summarized by treatment group and analyzed using a mixed model for repeated measures ~~repeated measurements analysis of covariance~~. The model will include fixed categorical effects for treatment, study visit, and the study visit-by-treatment interaction, as well as the continuous, fixed covariate of baseline and the visit-by-baseline interaction term, time from symptoms onset to the first dose of investigational product, and the randomization stratification factors. Initially an unstructured covariance matrix will be investigated. If this analysis fails to converge, other covariance structures will be used; details will be provided in the SAP. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. For the secondary endpoints of time to death and time to death, permanent tracheostomy, or permanent assisted ventilation, Kaplan-Meier analysis will be used to describe the survival data. The comparison of the survival time between treatment groups will be provided using a Cox proportional hazard model adjusting for the same covariates used in CAFS ANCOVA. For subjects who did not experience an event, the time to event will be censored at the last observation date for the Kaplan-Meier plot. ~~Subjects who were randomized but did not receive any treatment will be censored at the randomization date.~~ Subjects who are lost to follow-up or who discontinued the study will be censored at the date of discontinuation or lost to follow-up date.	Section 12.3.2	Updated to provide more clarity and to align with the SAP.

Updated Section 12.3.3 language as follows: Absolute values and changes from baseline in exploratory endpoints ~~(EQ-5D-5L, ZBI, at-home %SVC, NfL, pNfH, and EIM)~~ will be summarized, using descriptive statistics, by treatment and visit: • EQ-5D-5L, ZBI, NfL, pNfH, and EIM at weeks 52, 104, and 156). • At-home %SVC at weeks 52 and 104 • ALSFRS-R, % SVC in-clinic, HHD, and ALSAQ-40 at week 156 Baseline will be taken as the measurement closest to but prior to randomization~~, with the exception of at-home %SVC, for which baseline is the first assessment (which may be done after the first dose of study treatment)~~. Time to percutaneous endoscopic gastrostomy tube placement up to weeks 52, 104, and 156 will be computed and summarized by treatment group~~.~~, as will time to death, permanent tracheostomy, or permanent assisted ventilation up to week 156; and time to death up to week 156. Additional analyses might be performed for these endpoints and will be detailed in SAP.	Section 12.3.3	Updated due to the addition of the new exploratory endpoints.
Updated the amendment history to include the summary of changes from Amendment 5.	Appendix 1	Change made for accuracy.

1. SYNOPSIS

Name of Sponsor/Company: **Apellis Pharmaceuticals, Inc.**	
Name of Active Substance: Pegcetacoplan (also known as APL-2)	
Protocol Number: APL2-ALS-206	**Phase:** 2
Title of Study: A phase 2, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of pegcetacoplan in subjects with amyotrophic lateral sclerosis (ALS)	
Study period: Estimated 45 months	
Objectives	
Primary Objective: To assess the efficacy of twice per week subcutaneous (SC) doses of pegcetacoplan 1080 mg compared to placebo in subjects with sporadic ALS as measured by the Combined Assessment of Function and Survival (CAFS) rank score (joint-rank score)	
Secondary Objectives: • To assess the effect of pegcetacoplan compared to placebo as measured by the Revised ALS Functional Rating Scale (ALSFRS-R) score • To assess the effect of pegcetacoplan compared to placebo on disease progression as measured by respiratory function through percentage of slow vital capacity (%SVC) • To determine the effect of pegcetacoplan compared to placebo on muscle strength as measured by handheld dynamometry (HHD) • To determine the effect of pegcetacoplan compared to placebo on survival or specified state of disease progression • To assess the effect of pegcetacoplan compared to placebo on health-related quality of life as measured by ALS Assessment Questionnaire (ALSAQ-40) • To assess the safety of pegcetacoplan during the randomized and open-label treatment periods through incidence and severity of treatment-emergent adverse events (TEAEs), clinical laboratory tests (hematology, chemistry), vital signs, and physical examinations • To assess the long-term efficacy of pegcetacoplan using ALSFRS-R, %SVC, HHD, and ALSAQ-40 during the open-label treatment period	

Endpoints
Primary Efficacy Endpoint: • CAFS rank score (joint-rank score) at week 52 **Secondary Efficacy Endpoints:** • Change from baseline in ALSFRS-R at week 52 • Change from baseline in %SVC (at clinic visits) at week 52 • Change from baseline in HHD megascore at week 52 • Time to death, permanent tracheostomy, or permanent assisted ventilation up to week 52 • Time to death up to week 52 • Change from baseline in ALSAQ-40 at week 52 • Change from baseline of the randomized treatment period (visit 2) and of the open-label treatment period (visit 15) to week 104 for ALSFRS-R, %SVC, HHD, and ALSAQ-40 • Time to death, permanent tracheostomy, or permanent assisted ventilation up to week 104 • Time to death up to week 104
Primary Safety Endpoints: • Incidence and severity of TEAEs • Change from baseline in vital signs and clinical laboratory tests • Positive responses (Yes) to the Columbia Suicide Severity Rating Scale

Exploratory Endpoints:

- Change from baseline in European Quality of Life–5 Dimensions–5 Level at week 52, week 104, and week 156
- Change from baseline in Zarit Burden Interview score at week 52, week 104, and week 156
- Change from baseline of %SVC (home spirometry) at week 52 and week 104
- Time to percutaneous endoscopic gastrostomy tube placement up to week 52, week 104, and week 156
- Change from baseline in serum neurofilament light chain at week 52, week 104, and week 156
- Change from baseline in serum phosphorylated neurofilament heavy chain at week 52, week 104, and week 156
- Change from baseline in electrical impedance myography at week 52, week 104, and week 156 (only at select investigational sites chosen to complete this)
- Pegcetacoplan pharmacokinetic concentrations at week 52, week 104, and week 156
- Changes from baseline at week 52, week 104, and week 156 in complement biomarkers:
  - Classical hemolytic complement pathway activity
  - Alternative hemolytic complement pathway activity
  - C3 levels
- Immunogenicity: presence of antibodies to polyethylene glycol moiety and peptide moiety of pegcetacoplan during the randomized and open-label treatment periods
- Change from baseline of the randomized treatment period (week 1) and of the open-label treatment period (week 52) to week 156 for ALSFRS-R, %SVC (in-clinic), HHD, and ALSAQ-40
- Time to death, permanent tracheostomy, or permanent assisted ventilation up to week 156
- Time to death up to week 156

Study Design:

This is a phase 2, randomized, double-blind, placebo-controlled, multicenter, efficacy and safety study of SC pegcetacoplan 1080 mg twice per week conducted in approximately 228 subjects with ALS.

The planned length of participation in the study for each subject is a maximum of approximately 168 weeks. This study will consist of 5 parts:

- Part 1: Up to 6-week screening period
- Part 2: 52-week randomized treatment period
- Part 3: 52-week open-label (pegcetacoplan) treatment period
- Part 4: 52-week open-label long-term extension treatment period
- Part 5: 6-week off-treatment follow-up period

Part 1

Screening (Up to 6 Weeks)

- Informed consent will be obtained at screening prior to any study-related procedures being conducted
- Subjects (and/or caregiver) will be trained on the use of at-home assessments.

Part 2

Randomized Treatment Period (52 Weeks)

- Approximately 228 subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomized 2:1 to either the pegcetacoplan treatment group or to the placebo treatment group. Safety and efficacy will be assessed and will include once per week at-home measurements, monthly calls, and clinic visits.
- Pegcetacoplan treatment group
  - Subjects randomized to pegcetacoplan will receive SC pegcetacoplan 1080 mg twice per week for 52 weeks.
- Placebo treatment group
  - Subjects randomized to placebo will receive SC placebo twice per week for 52 weeks.

Subjects who discontinue treatment early and do not complete Part 2 will continue to Part 5.

Part 3

Open-Label (Pegcetacoplan) Treatment Period (52 weeks)

At the end of Part 2, all subjects from both treatment groups will continue to Part 3. All subjects participating in Part 3 will be treated with pegcetacoplan 1080 mg twice per week up to week 104. Subjects who complete Part 3 will enter Part 4. Subjects who do not continue to Part 3, or who have started Part 3 but discontinue treatment early, will continue to Part 5.

Part 4

Open-Label (Pegcetacoplan) Long-Term Extension Treatment Period (52 weeks)

At the end of Part 3, any subject who, in the opinion of the investigator, is experiencing clinical benefit from pegcetacoplan administration will be invited to continue to Part 4, the open-label long-term extension treatment period. All subjects participating in Part 4 will be treated with pegcetacoplan 1080 mg twice per week up to week 156. Subjects who complete Part 4 will enter Part 5. Subjects who do not continue to Part 4, or who have started Part 4 but discontinue treatment early, will continue to Part 5.

Part 5

Off-Treatment Follow-up Period (6 weeks)

During Part 5, all subjects who have discontinued the investigational product (blinded pegcetacoplan/placebo or open-label pegcetacoplan) will complete a follow-up visit 6 weeks later.

Diagnosis: Subjects with a diagnosis of sporadic ALS

Main Criteria for Inclusion:

1. Sporadic ALS diagnosed as definite, probable, or laboratory-supported probable as defined by the revised El Escorial criteria (Brooks et al. 2000)
2. At least 18 years of age
3. Slow vital capacity ≥60% of the predicted value at screening
4. Onset of ALS symptoms within 72 weeks prior to screening
5. Total ALSFRS-R score of ≥30 at screening
6. Women of childbearing potential defined as any woman who has experienced menarche and who is NOT permanently sterile or postmenopausal
    a. must have a negative pregnancy test at screening and
    b. must agree to use protocol defined methods of contraception for the duration of the study and 90 days after their last dose of investigational product.
        i. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause.
7. Males must agree to
    a. use protocol defined methods of contraception and
    b. refrain from donating sperm for the duration of the study and 90 days after their last dose of investigational product.
8. Have vaccination against *[illegible]*, *[illegible]* (types A, C, W, Y, and B), and *[illegible]* (type B) either within 5 years prior to baseline visit 2b, or agree to receive vaccination at least 7 days prior to baseline visit 2b. Vaccination is mandatory, unless documented evidence exists that subjects are nonresponders to vaccination (as evidenced by titers or display titer levels within acceptable local limits).
9. Willing and able to give informed consent and comply with study procedure and assessments (including at-home assessments)

Main Criteria For Exclusion:

1. Confirmed or suspected other causes of neuromuscular weakness
2. Diagnosis of another neurodegenerative disease(s)
3. Subject with significant cognitive impairment, clinical dementia, or psychiatric illness that in the opinion of the investigator may increase subject's risk by participating in the study or confound the outcome of the study
4. Subjects with a significant pulmonary disorder not attributed to ALS or who require treatments that might complicate the evaluation of the effect of ALS on respiratory function (eg, chronic obstructive pulmonary disease, pulmonary fibrosis, cystic fibrosis, pulmonary arterial hypertension)
5. Current use or anticipated need, in the opinion of the investigator, of a diaphragm pacing system during the randomized treatment period
6. Riluzole initiation or change in dose within 30 days prior to the start of the screening period or planned initiation during study participation. If using riluzole, the subject should remain on the drug throughout Part 2 of study participation, but the dosage may be altered or the drug discontinued at any time by the investigator for any safety concern. Riluzole-naïve subjects are allowed in the study.
7. Edaravone initiation or change in dose within 60 days prior to the start of the screening period or planned initiation during study participation. If using edaravone, the subject should remain on the drug throughout Part 2 of study participation, but the dosage may be altered or the drug discontinued at any time by the investigator for any safety concern. Edaravone-naïve subjects are allowed in the study.
8. Positive response to Item 4 or 5 of the Columbia Suicide Severity Rating Scale
9. Subjects with detectable hepatitis C by polymerase chain reaction at screening
10. Subjects with chronic inactive hepatitis B with viral loads >1000 IU/mL (>5000 copies/mL) at screening. Eligible subjects who are chronic active carriers (≤1000 IU/mL) must receive prophylactic antiviral treatment according to local country guidelines (eg, entecavir, tenofovir, lamivudine)
11. History of an aggressive lymphoma or presence of a lymphoma requiring therapy by itself
12. Active or overt malignant disease other than basal cell carcinoma or cutaneous squamous cell carcinoma
13. Received organ transplant
14. Presence or suspicion of liver dysfunction as indicated by elevated alanine aminotransferase, aspartate aminotransferase, or bilirubin levels >2 × the upper limit of normal
15. Presence or suspicion of severe recurrent or chronic infections that, in the opinion of the investigator, increase the subject's risk by participating in the study

16. Participation in any other investigational drug trial or exposure to other investigational agent, device, or procedure within 30 days or within 5-half lives of the treatment (whichever is longer) prior to the start of the screening period or during study participation
17. Use of any other complement inhibitor within 30 days or within 5-half lives of the treatment (whichever is longer) prior to the start of the screening period or during study participation
18. If breastfeeding, unwilling to discontinue for the duration of the study and for at least 6 months after final dose of drug
19. Inability to cooperate or any condition that, in the opinion of the investigator, could increase the subject's risk by participating in the study or confound the outcome of the study
20. Subjects with known allergy or hypersensitivity to pegcetacoplan or to any of the components
21. Known or suspected hereditary fructose intolerance

Investigational Product, Dosage, and Mode of Administration:

- Pegcetacoplan, 1080 mg twice per week, SC
- Placebo, twice per week, SC

Duration of Treatment:

168 weeks total (screening: up to 6 weeks; randomized treatment: 52 weeks; open-label [pegcetacoplan] treatment: 52 weeks; open-label [pegcetacoplan] long-term extension period: 52 weeks; follow-up: 6 weeks)

Blinding:

This is a double-blind study during the randomized treatment period. The open-label and long-term extension treatment periods are not blinded.

Statistical Methodology for Primary Efficacy Endpoint:

The primary efficacy endpoint is the CAFS rank score (joint-rank score) at week 52.

The CAFS ranks score will be summarized by treatment group using descriptive statistics.

The CAFS ranks score will be analyzed using analysis of covariance (ANCOVA) model with treatment as a fixed effect, adjusted for baseline ALSFRS-R total score, duration from symptoms onset to the first dose of study treatment, and stratification factors.

Statistical Methodology for Secondary Efficacy Endpoints:

To preserve the Type 1 error, a fixed-sequence testing strategy will be used. The ordering of the secondary endpoints in this testing strategy will match the order in which they are presented in the secondary endpoint section.

Changes from baseline in secondary efficacy outcomes will be summarized by treatment group and analyzed using a mixed model for repeated measures repeated measurements. The model will include fixed categorical effects for treatment, study visit, and the study visit-by-treatment interaction, as well as the continuous, fixed covariate of baseline and the visit-by-baseline interaction term, time from symptoms onset to the first dose of investigational product, and the randomization stratification factors. Initially, an unstructured covariance matrix will be investigated. If this analysis fails to converge, other covariance structures will be used; details will be provided in the statistical analysis plan. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

For the secondary endpoints of time to death and time to death, permanent tracheostomy, or permanent assisted ventilation, Kaplan-Meier will be used to describe the survival data. The comparison of the survival time between treatment groups will be provided using a Cox proportional hazard model adjusting for the same covariates used for the CAFS ANCOVA. For subjects who did not experience an event, the time to event will be censored at the last observation date for the Kaplan-Meier plot. Subjects who are lost to follow-up or discontinue study will be censored at the date of discontinuation or lost to follow-up.

Planned Interim Analysis:

No interim analysis is planned.

Statistical Methodology for Safety Endpoints:

All safety measures, including AEs and clinical laboratory results (hematology, chemistry if appropriate), will be descriptively summarized by treatment group at baseline and for each postbaseline visit.

The number and percentage of subjects with TEAEs will be presented. Treatment-emergent adverse events are defined as adverse events (AEs) that start or deteriorate on or after the date of the first dose of investigational product until the study follow-up visit or the early termination follow-up visit.

Pharmacokinetic concentration will be summarized by treatment group and visit using descriptive statistics.

Sample Size Justification:

A sample size of 180 randomized subjects (2:1 allocation ratio to pegcetacoplan:placebo) would provide approximately 86% power to detect a significant difference (33%) in the primary outcome (CAFS score) between the 2 treatment groups at a 2-sided alpha of 5% with 75% power to detect a 35% improvement in the rate of decline in the ALSFRS-R score and 39% power to detect a 10% improvement in survival.

The estimates were based on the following assumptions:

- Mean monthly rate of decline in ALSFRS-R is 1 unit for the placebo treatment group and pooled standard deviation of 0.84 units/month
- 52-week mortality rate with placebo at 20%
- Approximately 40-week subject enrollment period
- 52 weeks of follow-up for assessing survival outcomes after each subject enrolls
- 52 weeks of follow-up for assessing functional outcomes after each subject enrolls

Subjects will be randomized and stratified by location of first muscle weakness (limb or bulbar) and riluzole and edaravone use.

Approximately 228 subjects (152:76) will be randomized to account for an anticipated 20% of randomized subjects prematurely discontinuing the study without providing a postbaseline ALSFRS-R measurement.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
%SVC	percentage of slow vital capacity
ADA	anti-drug antibodies
AE	adverse event
AH50	50% alternative hemolytic complement pathway activity
AIHA	autoimmune hemolytic anemia
ALS	amyotrophic lateral sclerosis
ALSAQ-40	Amyotrophic Lateral Sclerosis Assessment Questionnaire, 40-item
ALSFRS-R	Revised Amyotrophic Lateral Sclerosis Functional Rating Scale
aPTT	activated partial thromboplastin time
CAD	cold agglutinin disease
CAFS	Combined Assessment of Function and Survival
CH50	50% classical hemolytic complement pathway activity
CNS	central nervous system
CRF	case report form
C-SSRS	Columbia Suicide Severity Rating Scale
DPS	diaphragm pacing system
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EIM	electrical impedance myography
EQ-5D-5L	5-Level EuroQoL-5 Dimension
ETFU	early termination follow-up
GA	geographic atrophy
GCP	Good Clinical Practice
HHD	handheld dynamometry
HRQoL	health-related quality of life

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IRB	institutional review board
ITT	intent-to-treat
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MN	motor neuron
NfL	neurofilament light chain
PCV13	pneumococcal conjugate vaccine 13
PD	pharmacodynamic
PEG	polyethylene glycol
PK	pharmacokinetic(s)
pNfH	phosphorylated neurofilament heavy chain
PP	per-protocol
PPSV23	pneumococcal polysaccharide vaccine 23
QTcF	QT interval corrected using Fridericia's method
SAE	serious adverse event
sALS	sporadic amyotrophic lateral sclerosis
SAP	statistical analysis plan
SC	subcutaneous
SVC	slow vital capacity
TEAE	treatment-emergent adverse event
WOCBP	women of childbearing potential
ZBI	Zarit Burden Interview

4. INTRODUCTION

This study is being conducted as part of a series of studies for the clinical development of pegcetacoplan (also known as APL-2). The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements. The subject population will comprise of adult male and female subjects with sporadic amyotrophic lateral sclerosis (sALS).

4.1. Amyotrophic Lateral Sclerosis and Unmet Medical Need

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder of unknown etiology for which there is no effective treatment. Progressive denervation of neuromuscular synapses in the peripheral nervous system and degeneration of upper and lower motor neurons in the central nervous system (CNS) result in muscle weakness, atrophy, paralysis, and ultimately death within 2-3 years from the onset of symptoms. Initial presentation of ALS varies between affected individuals, and typically presents as spinal-onset disease (muscle weakness of the limbs), or bulbar-onset disease (difficulty with speech and swallowing). Sporadic ALS accounts for 90% of cases and has no clear etiology, while familial ALS accounts for 10% of cases and contains an underlying genetic component. However, while these 2 forms differ in causation, they appear pathologically and clinically indistinguishable.

There is no known cure for ALS. There are 3 approved medications to treat ALS, riluzole, edaravone, and Relyvrio. Riluzole, approved in 1995 and available globally, is administered orally twice daily and delays time to tracheostomy or death in patients with ALS (Riluzole Package Insert 2016), prolonging survival by 2-3 months (Miller 2002). Edaravone, approved in the US in 2017, is administered in courses intravenously (Edaravone Package Insert 2017) and shows efficacy in only a small subset of patients with early ALS (Abe et al. 2017).

Relyvrio (AMX0035), approved in the United States in 2022, is administered orally or via feeding tube twice daily and slows the loss of physical function in patients with ALS as measured by ALSFRS-R (Relyvrio Package Insert 2022).

4.2. Information on the Investigational Product (Pegcetacoplan)

Pegcetacoplan, the active ingredient in pegcetacoplan solution for subcutaneous infusion 1080 mg/20 mL is a symmetrical molecule comprised of 2 pentadecapeptides covalently bound to the ends of a linear 40 kDa polyethylene glycol molecule. The peptide moieties bind to complement C3 and exert a broad inhibition of the complement cascade. The 40 kDa polyethylene glycol moiety imparts improved solubility and longer residence time in the body after administration of the drug product.

Pegcetacoplan is provided as a solution in acetate buffer solution containing sorbitol for subcutaneous (SC) administration.

Further details can be found in the current version of the pegcetacoplan Investigator's Brochure (IB).

4.3. Study Rationale

There is considerable evidence for the key role of neuroinflammation in ALS characterized by microglia activation, reactive astroglia, macrophage and lymphocyte infiltration, and overproduction of inflammatory cytokines, which correlate with motor neuron (MN) degeneration and disease progression (Chen et al. 2014; Murdock et al. 2017; Brettschneider et al. 2012; Turner et al. 2004; Ehrhart et al. 2015). Microglia maintain homeostasis by direct contact with the synaptic terminals and can respond to microenvironment signals and damage by removing defunct axon terminals (Kettenmann et al. 2013). During ALS progression, microglia transition from a protective phenotype to a proinflammatory and neurotoxic phenotype due to a proinflammatory stimuli, which results in synapse loss and the release of inflammatory factors that trigger the neurotoxic activity of astrocytes in the CNS (Liao et al. 2012; Chiu et al. 2013; Liddelow et al. 2017). Infiltrated muscle macrophages at the neuromuscular junction (NMJ) also result in denervation by phagocytizing presynaptic terminals (Wang et al. 2017). These neurotoxic mechanisms and interplays lead to self-destruction of MNs and, subsequently, the brain lose its ability to initiate and control the movement of muscles, including respiratory muscles. Uncontrolled inflammation is believed to drive, or actively participate, to disease progression. Therefore, therapy aimed at modulating the inflammatory and immune environment to preserve the remaining MNs may be beneficial in patients with ALS.

The complement system is a pivotal component of both innate and adaptive immunity, contributing to immune surveillance, inflammation, and homeostasis (Kolev et al. 2014). Its 3 activation pathways (alternative, lectin and classical) converge to C3 and lead to its cleavage into its effectors, C3a and C3b, which in turn will lead to the formation of C5 convertase and to C5 cleavage into C5a and C5b, and formation of the membrane attack complex. Overactivation of complement is a hallmark of many neurodegenerative diseases. Its diverse functions include C3a/C5a-triggered recruitment and activation of immune cells in particular microglia, macrophages, and lymphocytes, activation of glial cells by C3a/C3a receptor, C3b-mediated opsonization of neurons and synapse loss, and neuronal cell lysis by the membrane attack complex (Carpanini et al. 2019).

Investigations in ALS animal models and patients with ALS demonstrate that complement-driven immune response may contribute to MN degeneration and progression of the disease. In animal model of ALS, disease progression significantly correlates with an upregulation of all complement effectors in muscles, peripheral nervous system, and spinal cord tissues, and an increased number of activated microglia/macrophages in the CNS and at the NMJ (Lee et al. 2018; Wang et al. 2017; Chiu et al. 2009). Inhibition of the complement downstream of C3 has been identified as a potential therapeutic target to slow disease progression in ALS in animal models (Lee et al. 2017). In patients or donors with ALS, high levels of complement C3 and downstream active fragments are present in blood, cerebral serum fluid, and in CNS tissues, in particular deposited on microglia and damaged neurites of the spinal cord and brain (Kawamata et al. 1992; Goldknopf et al. 2006; Sta et al. 2011; Ganesalingam et al. 2011; El Idrissi et al. 2016). The deposition of complement effectors, including C3/C3b, at the NMJ occurs early in the progression of ALS and precedes both motor end-plate denervation and degeneration of MNs (El Idrissi et al. 2016).

The site of initiation of ALS is still unclear. Amyotrophic lateral sclerosis was initially described as a disease that causes the progressive loss of MNs in the CNS followed by axonal degeneration and muscle atrophy. Growing evidence in animal models and clinical neurophysiology support a second hypothesis in which MN pathology may begin as a distal axonopathy and proceed back to the CNS in a "dying back" pattern (Noto et al. 2011; Fischer et al. 2004). Others have proposed an independent and random degeneration of upper and lower MNs (Ravits and La Spada 2009; van den Bos et al. 2019). Whether the disease starts in the CNS or at the NMJ, stopping the inflammation and immune response driven by complement should demonstrate a positive effect on disease progression. Although pegcetacoplan does not cross the blood-brain barrier, there is growing evidence that the blood-brain barrier is compromised in patients with ALS (Garbuzova-Davis and Sanberg 2014) and pegcetacoplan may reach the brain in addition to its potential beneficial impact on inflammation and phagocytosis at the NMJ.

Studies of ALS pathology have involved all complement pathways and effectors. Given that C3 is acting as a point of convergence of all activation pathways, exerting direct effector functions, and helping to coordinate downstream immune responses, C3 is an attractive target to treat ALS. Taken together, targeting the complement system at the level of C3 using pegcetacoplan may reverse the immune response, which may stop or slow down ALS progression.

4.4. Summary of Clinical Experience With Pegcetacoplan

Pegcetacoplan is being studied in ALS and multiple other complement-mediated indications (paroxysmal nocturnal hemoglobinuria [PNH], cold agglutinin disease [CAD], complement-dependent nephropathies, and geographic atrophy [GA] secondary to age-related macular degeneration).

To date, pegcetacoplan at doses of ≥270 mg/day and 1080 mg twice weekly have been generally safe and well tolerated when administered via SC infusion. No expected serious adverse drug reactions have been identified, and no deaths have occurred that are considered related to treatment with pegcetacoplan.

Study APL2-302, a randomized, multicenter, open-label, active-comparator, controlled study in patients with PNH, demonstrated that pegcetacoplan 1080 mg twice weekly (and 1080 mg every third day dosing adjustment option) SC infusion produced consistent and meaningful effects on relevant clinical efficacy measures with a favorable safety profile. Pegcetacoplan demonstrated control of both intravascular and extravascular hemolysis by improving key hematological manifestations of PNH, reducing the burden of transfusions, and improving patient-reported symptoms of fatigue. Taken together, these analyses provide strong evidence that treatment with pegcetacoplan provides a clinically meaningful and significant treatment benefit in the treatment of PNH.

Study CCI [redacted] is an ongoing open-label, prospective, phase 2 study (Gertz et al. 2019) that includes subjects with warm autoimmune hemolytic anemia (wAIHA) and CAD that has completed the initial Part A (336 days) and is continuing with Part B, the long-term extension phase. Results from Part A comprised 24 subjects (12 diagnosed with wAIHA; 12 diagnosed with CAD) and indicate that pegcetacoplan is able to rapidly increase hemoglobin values within the first weeks of treatment and this effect persisted for 48 weeks. Results also showed improvements in hemolysis (shown by reduction of reticulocyte, lactate dehydrogenase, and indirect bilirubin).

Further, pegcetacoplan was generally well tolerated in this study. Subjects in this study are administered pegcetacoplan subcutaneously at doses of 270 mg/day or 360 mg/day.

Studies conducted in subjects with GA secondary to age-related macular degeneration include a phase 2 study (POT-CP121614), and 2 phase 3 studies (APL2-303 and APL2-304), as well as a long-term extension study CCI [redacted]. In all of these studies that have reported outcomes, up to 24 months, pegcetacoplan administered intravitreally (15 mg) monthly or every other month was found to be both efficacious and had a tolerable safety profile.

Although the administration route of pegcetacoplan in patients with GA (intravitreous) is not the one that will be used to treat patients with ALS (subcutaneous), the mechanism by which complement C3 and microglia cooperate to eliminate the targeted cells (retinal cells versus motor neurons) is believed to be similar.

Please refer to the latest version of the pegcetacoplan IB for more information on the clinical trials using pegcetacoplan.

4.4.1. Dose Rationale

In this study, pegcetacoplan will be administered as a subcutaneous infusion at a dose of 1080 mg twice per week. The dose selection is based on prior clinical experience with pegcetacoplan. Repeated SC doses of 1080 mg twice per week have been administered to healthy subjects in study CCI [redacted] for 4 weeks and adult subjects with PNH in Study APL2-302 for at least 16 weeks and were found to be well tolerated in both studies. Pharmacodynamic observations of sustained reduction of 50% alternative hemolytic complement pathway activity (AH50) levels and increased C3 levels from both studies were consistent with a conclusion that pegcetacoplan inhibits alternative complement activity. Statistically significant improvement in efficacy biomarker response (eg, increase in hemoglobin levels) were observed in PNH subjects in study APL2-302 after treatment with pegcetacoplan. Pegcetacoplan is expected to be pharmacologically active to regulate other complement-driven immune responses including those that may contribute to MN degeneration and progression of the disease in sALS patients. The SC doses of 1080 mg twice per week of pegcetacoplan is deemed the appropriate regimen for this clinical trial to treat adult male and female subjects with sALS.

Please refer to the latest version of the pegcetacoplan IB for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics (PK), efficacy, and safety of pegcetacoplan.

4.5. Clinical Risks/Benefits of Pegcetacoplan

Pegcetacoplan has the potential to slow the progression of ALS by targeting the complement system at the level of C3 and thus preventing the degeneration of motor neurons.

The safety of subcutaneous pegcetacoplan administration has been studied in multiple phase 2 and 3 studies for AIHA, C3 glomerulonephropathies, and PNH, with an acceptable safety profile to date. Nonetheless, a number of safety monitoring practices are being employed by this protocol to ensure subject safety, including physical examination, vital signs monitoring, hematology, serum chemistry, urinalysis, as well as prompt reporting of serious adverse events (SAEs).

Injection/infusion site/pump safety will be assessed during clinical visits when dosing coincides with clinic visit, and any significant finding from the assessment will be reported as an AE (see Section 11.2).

Systemic complement inhibition might predispose individuals to infections caused by encapsulated organisms, including *Streptococcus pneumoniae*, *Neisseria meningitidis* (serogroups A, C, W, Y, and B), and *Haemophilus influenzae* type B. Subjects will be required to have documented evidence of vaccination against these organisms or agree to receive the vaccines (see Section 8.4). Administration of prophylactic antibiotic therapy chronically may be conducted, at the discretion of the treating investigator, in accordance with local treatment guidelines.

Body temperature and vital signs will be monitored at all clinic visits, as well as relevant blood parameters throughout the study, to assess for signs of infection. Subjects will be provided with emergency study cards that include a list of symptoms associated with infections. This study card also guides subjects with instructions to contact their study physician or seek emergency medical care in the event they experience any of the listed symptoms. In the event of a suspected infection, the investigator should provide guidance on appropriate action to be taken.

Systemic hypersensitivity reactions (eg, facial swelling, rash, urticaria) have occurred in patients treated with pegcetacoplan. One patient (less than 1% in clinical studies) experienced a serious allergic reaction which resolved after treatment with antihistamines. If a severe hypersensitivity reaction (including anaphylaxis) occurs, discontinue pegcetacoplan infusion immediately, institute appropriate treatment, per standard of care, and monitor until signs and symptoms are resolved.

The use of silica reagents in coagulation panels should be avoided. Apellis previously conducted an investigation into prolonged activated partial thromboplastin times (aPTTs) observed in subjects treated with pegcetacoplan. It was confirmed that false positive aPTT prolongation occurred when coagulation panels were performed using a Stago Analyzer and, specifically, silica reagents. It was determined that there was interference between the silica reagents and PEGylated pegcetacoplan, resulting in artificially prolonged aPTTs.

Subjects should be instructed to take the investigational product (pegcetacoplan or placebo) as prescribed, and to contact the investigator immediately for guidance in the event of any missed doses. The sponsor's medical monitor should be contacted before interrupting or discontinuing the investigational product.

Apellis is not currently aware of any evidence associating pegcetacoplan use with specific risks or complications of COVID-19. Apellis recognizes the need to consider the public health risks of the COVID-19 pandemic within the context of conducting a clinical trial. Since these risks may change as the pandemic evolves, and may vary based on geographic location, Apellis will continue to evaluate the risk/benefit around study conduct on an ongoing and patient-by-patient basis.

4.5.1. Safety Measures With Enrollment

Because this is the first time pegcetacoplan is being studied in the ALS patient population, measurements are in place to closely monitor safety at the beginning of the study.

Enrollment will be limited to a maximum of 20 subjects in the 4 weeks following first subject enrolled, and a maximum of 40 subjects during the first 8 weeks of the study. After the 8 weeks, enrollment will not be limited.

The data monitoring committee (DMC) will meet after 20 subjects have completed visit 3 (week 4), and at regular intervals throughout the study as outlined in the DMC charter (see Section 12.9 for additional information).

4.5.2. COVID-19 Risk Mitigation Measures

In the event that an investigative site is closed, or subject is unable/unwilling to travel due to COVID-19, and, if in the opinion of the investigator it is in the subject's best interest to continue in the study, the following mitigation measures may be implemented for the study and utilized if deemed necessary and authorized by the sponsor, including but not limited to:

- In locations where home nursing services may be utilized, a home nursing vendor may be set up to complete assessments at a subject's home.
- Minimum safety assessments to be drawn at a certified local laboratory will be identified.
- The electronic data capture (EDC) system will capture any missed assessments related to COVID-19.
- Any change in COVID-19 status (serology or antigen), if available, will be captured separately in the EDC system.
- Where applicable, relevant study documentation will be updated and communicated to health authorities and/or institutional review board (IRBs)/independent ethics committee (IECs) as required.

5. TRIAL OBJECTIVES AND ENDPOINTS

5.1. Objectives

5.1.1. Primary Objective

The primary objective of this study is to assess the efficacy of twice per week SC doses of pegcetacoplan 1080 mg compared to placebo in subjects with sALS as measured by the Combined Assessment of Function and Survival (CAFS) rank score (joint-rank score).

5.1.2. Secondary Objectives

The following are the secondary objectives of this study:

- To assess the effect of pegcetacoplan compared to placebo as measured by the Revised ALS Functional Rating scale (ALSFRS-R) score
- To assess the effect of pegcetacoplan compared to placebo on disease progression as measured by respiratory function through percentage of slow vital capacity (%SVC)
- To determine the effect of pegcetacoplan compared to placebo on muscle strength as measured by handheld dynamometry (HHD)
- To determine the effect of pegcetacoplan compared to placebo on survival or specified state of disease progression
- To assess the effect of pegcetacoplan compared to placebo on health-related quality of life (HRQoL) as measured by ALS Assessment Questionnaire (ALSAQ-40)
- To assess the safety of pegcetacoplan during the randomized and open-label treatment periods through incidence and severity of TEAEs, clinical laboratory tests (hematology, chemistry), vital signs, and physical examinations
- To assess the long-term efficacy of pegcetacoplan using ALSFRS-R, %SVC, HHD, and ALSAQ-40 during the open-label treatment period

5.2. Endpoints

5.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the difference in CAFS rank score (joint-rank score) at week 52.

5.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Change from baseline in ALSFRS-R at week 52
- Change from baseline in %SVC (at clinic visits) at week 52
- Change from baseline in HHD megascore at week 52
- Time to death, permanent tracheostomy, or permanent assisted ventilation up to week 52
- Time to death up to week 52

- Change from baseline in ALSAQ-40 at week 52
- Change from baseline of the randomized treatment period (visit 2) and of the open-label treatment period (visit 15) to week 104 for ALSFRS-R, %SVC, HHD, and ALSAQ-40
- Time to death, permanent tracheostomy, or permanent assisted ventilation up to week 104
- Time to death up to week 104

5.2.3. Primary Safety Endpoints

The primary safety endpoints are as follows:

- Incidence and severity of TEAEs
- Change from baseline in vital signs and clinical laboratory tests
- Positive responses (Yes) to the Columbia Suicide Severity Rating Scale (C-SSRS)

5.2.4. Exploratory Endpoints

The exploratory endpoints are as follows:

- Change from baseline in European Quality of Life–5 Dimensions–5 Level (EQ-5D-5L) at week 52, week 104, and week 156
- Change from baseline in Zarit Burden Interview (ZBI) score at week 52, week 104, and week 156
- Change from baseline of %SVC (home spirometry) at week 52 and week 104
- Time to percutaneous endoscopic gastrostomy tube placement up to week 52, week 104, and week 156
- Change from baseline in serum neurofilament light chain (NfL) at week 52, week 104, and week 156
- Change from baseline in serum phosphorylated neurofilament heavy chain (pNfH) at week 52, week 104, and week 156
- Change from baseline in electrical impedance myography (EIM) at week 52, week 104, and week 156 (only at select investigational sites chosen to complete this)
- Pegcetacoplan PK concentrations at week 52, week 104, and week 156
- Changes from baseline at week 52, week 104, and week 156 in complement biomarkers:
  - Classical hemolytic complement pathway activity (CH50)
  - AH50
  - C3 levels
- Immunogenicity: presence of antibodies to PEG moiety and peptide moiety of pegcetacoplan during the randomized and open-label treatment periods

- Change from baseline of the randomized treatment period (week 1) and of the open-label treatment period (week 52) to week 156 for ALSFRS-R, %SVC (in-clinic), HHD, and ALSAQ-40
- Time to death, permanent tracheostomy, or permanent assisted ventilation up to week 156
- Time to death up to week 156

6. INVESTIGATIONAL PLAN

See Figure 1 for the study design, Table 2 for the schedule of assessments for the randomized treatment period, and Table 3 for the schedule of assessments for the open-label (pegcetacoplan) treatment period; Table 8 for the schedule of assessments for the open-label (pegcetacoplan) long-term extension treatment period.

6.1. Overall Study Design

This is a phase 2, randomized, double-blind, placebo-controlled, multicenter, efficacy and safety study of SC pegcetacoplan 1080 mg twice per week conducted in approximately 228 subjects with ALS. The study has been designed to minimize the burden on subjects with use of at-home assessments and limited number of clinic visits.

The planned length of participation in the study for each subject is a maximum of approximately 168 weeks. This study will consist of 5 parts:

- Part 1: Up to 6-week screening period
- Part 2: 52-week randomized treatment period
- Part 3: 52-week open-label (pegcetacoplan) treatment period
- Part 4: 52-week open-label (pegcetacoplan) long-term extension treatment period
- Part 5: 6-week off-treatment follow-up period

Throughout this protocol, “investigational product” refers to the blinded treatment, whether that is pegcetacoplan or placebo.

6.1.1. Part 1: Screening Period (Up to 6 Weeks)

- Informed consent will be obtained at screening prior to any study-related procedures being conducted.
- Subjects (and/or caregivers) will be trained on the use of at-home assessments.

6.1.2. Part 2: Randomized Treatment Period (52 Weeks)

Approximately 228 subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomized 2:1 to either the pegcetacoplan treatment group or the placebo group. Safety and efficacy will be assessed and will include once per week at-home measurements, monthly calls, and clinic visits. Subjects who discontinue treatment early and do not complete Part 2 will continue to Part 5.

6.1.2.1. Pegcetacoplan Treatment Group

- Subjects randomized to pegcetacoplan will receive SC pegcetacoplan 1080 mg twice per week for 52 weeks.

6.1.2.2. Placebo Treatment Group

- Subjects randomized to placebo will receive SC placebo twice per week for 52 weeks.

6.1.3. Part 3: Open-Label (Pegcetacoplan) Treatment Period (52 Weeks)

At the end of Part 2, all subjects from both treatment groups will continue to Part 3. All subjects participating in Part 3 will be treated with pegcetacoplan 1080 mg twice per week up to week 104. Subjects who complete Part 3, will enter Part 4. Subjects who do not continue to Part 3, or who have started Part 3 but discontinue treatment early, will continue to Part 5.

6.1.4. Part 4: Open-Label (Pegcetacoplan) Long-Term Extension Treatment Period (52 Weeks)

At the end of Part 3, any subject who, in the opinion of the investigator, is experiencing clinical benefit from pegcetacoplan administration will be invited to continue to Part 4, the open-label long-term extension treatment period. All subjects participating in Part 4 will be treated with pegcetacoplan 1080 mg twice per week up to week 156. Subjects who complete Part 4 will enter Part 5. Subjects who do not continue to Part 4, or who have started Part 4 but discontinue treatment early, will continue to Part 5.

6.1.5. Part 5: Off-Treatment Follow-up Period (6 Weeks)

During Part 5, all subjects who have discontinued the investigational product (blinded pegcetacoplan/placebo or open-label pegcetacoplan) will complete a follow-up visit 6 weeks later.

6.2. Number of Subjects

There will be approximately 228 subjects diagnosed with sALS enrolled in the study.

6.3. Treatment Assignment

All subjects who meet all the inclusion criteria and none of the exclusion criteria will be enrolled in the study, until such time that approximately 228 subjects have been enrolled in the study. At the first visit of Part 2, subjects will be randomized after confirmation of study eligibility in a ratio of 2:1 via a computer-generated randomization schedule to receive pegcetacoplan or placebo. The randomization will be performed centrally and stratified by location of first muscle weakness (limb or bulbar) and riluzole and edaravone use. The stratification by location of onset and riluzole use will ensure balance between treatment groups for the respective stratification factors. Fixed block randomization will be used to ensure that approximately equals number of subjects are assigned each treatment within strata.

6.4. Criteria for Study Termination

The sponsor reserves the right to suspend or discontinue this study for administrative and/or safety reasons, at any time. The investigator reserves the right to discontinue dosing subjects, at any time, for safety reasons.

Figure 1: Study Design

Abbreviations: ALSFRS-R = Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; EQ-5D-5L = European Quality of Life–5 Dimensions–5 Level; W = week(s); ZBI = Zarit Burden Interview.
Notes: The initial baseline (visit 2b) spirometry assessments will be conducted in the clinic; every subsequent spirometry assessment will be conducted at home. ALSFRS-R questionnaire will be administered via the phone, including at screening.

Table 2: Schedule of Assessments—Randomized Treatment Period (Core)

Study period	Screening	Baseline[q]		Randomized treatment period (core)												Follow-up (core)[s]	ETFU[t]
Study week	-6	1		4	8	12	16	20	24	28	32	36	40	44	48	52	58	
Study day	-42	0	1	29	57	85	113	141	169	197	225	253	281	309	337	365	407	
Study visit*	1	2aT	2b	3	4T	5	6T	7T	8	9T	10T	11	12T	13T	14T	15	15b	NA
Visit window (± days)	0	0	0	7	4	7	4	4	7	4	4	7	4	4	4	7	7	7
Informed consent	X																	
Demographics[a]	X		X															
Inclusion/exclusion criteria	X		X															
Medical and treatment history	X																	
Vaccination[b]	X																	
Physical examination[c]	X		X													X	X	X
Vital sign measurements[d]	X		X	X		X			X			X				X	X	X
12-lead ECG[e]	X		X	X		X			X			X				X	X	X
Height	X																	
Weight	X		X	X		X			X			X				X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ALSFRS-R[f]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D-5L[f]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ZBI[f,g]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ALSAQ-40			X	X		X			X			X				X	X	X
C-SSRS	X		X	X		X			X			X				X	X	X
EIM[h] (only at select investigational sites)			X	X		X			X			X				X	X	X
HHD			X	X		X			X			X				X	X	X
Urinalysis	X		X	X		X			X			X				X	X	X
Urine pregnancy test[i]			X	X		X			X			X		X		X	X	X
Blood[j]	X		X	X		X			X			X				X	X	X

Table 2: Schedule of Assessments—Randomized Treatment Period (Core)

Study period	Screening	Baseline[q]		Randomized treatment period (core)												Follow-up (core)[s]	ETFU[t]
Study week	-6	1		4	8	12	16	20	24	28	32	36	40	44	48	52	58	
Study day	-42	0	1	29	57	85	113	141	169	197	225	253	281	309	337	365	407	
Study visit*	1	2aT	2b	3	4T	5	6T	7T	8	9T	10T	11	12T	13T	14T	15	15b	NA
Visit window (± days)	0	0	0	7	4	7	4	4	7	4	4	7	4	4	4	7	7	7
Pregnancy (β-HCG and FSH)[i]	X																	
HCV, HBsAg	X																	
Hematology	X		X	X		X			X			X				X	X	X
Chemistry	X		X	X		X			X			X				X	X	X
Pharmacokinetics			X	X		X			X			X				X	X	X
Anti–pegcetacoplan peptide Ab and anti-PEG Ab assays[k]			X	X		X			X			X				X	X	X
Complement profile (C3, CH50 & AH50)			X	X		X			X			X				X	X	X
NfL			X	X		X			X			X				X	X	X
pNfH			X	X		X			X			X				X	X	X
At-clinic %SVC (using study-specific clinic spirometry device)	X		X	X		X			X			X				X	X	X
%SVC[l] (using study-specific at-home spirometry)			X															
Training for at-home assessments[l]			X															
At-home %SVC[m]				---------- Once per week →													X[u]	X[u]
Investigational product administration[n]				---------- Twice per week →														
Injection site assessment[o]				---------- Twice per week after dosing →														
Investigational product dispensation for home administration[p]		---------- →																

Table 2: Schedule of Assessments—Randomized Treatment Period (Core)

Study period	Screening	Baseline[q]		Randomized treatment period (core)													Follow-up (core)[s]	ETFU[t]
Study week	-6	1		4	8	12	16	20	24	28	32	36	40	44	48	52	58	
Study day	-42	0	1	29	57	85	113	141	169	197	225	253	281	309	337	365	407	
Study visit*	1	2aT	2b	3	4T	5	6T	7T	8	9T	10T	11	12T	13T	14T	15	15b	NA
Visit window (± days)	0	0	0	7	4	7	4	4	7	4	4	7	4	4	4	7	7	7
Return of unused investigational product																(X)[r]		X
Dispensation of at-home devices			X															
Return of at-home devices																	X	X

Abbreviations: %SVC = percentage of slow vital capacity; Ab = antibody(ies); AH50 = 50% alternative hemolytic complement pathway activity; ALS = amyotrophic lateral sclerosis; ALSAQ-40 = ALS Assessment Questionnaire; ALSFRS-R = Revised ALS Functional Rating Scale; β-HCG = β–human chorionic gonadotropin; C3 = complement component 3; CH50 = 50% classical hemolytic complement pathway activity; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EIM = electrical impedance myography; ETFU = early termination follow-up; EQ-5D-5L = 5-Level EuroQol-5 Dimension; FSH = follicle-stimulating hormone; HHD = handheld dynamometry; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; Hib = *Haemophilus influenzae* B vaccine; NA = not applicable; NfL = neurofilament light chain; PCV13 = pneumococcal conjugate vaccine 13; PEG = polyethylene glycol; pNfH = phosphorylated neurofilament heavy chain; PPSV23 = pneumococcal polysaccharide vaccine 23; SC = subcutaneous; T = telephone administered assessment; WOCBP = women of childbearing potential; ZBI = Zarit Burden Interview.

***Visits with a "T" are telephone administered visits.**

[a] Confirm age of subject at time of visit 2b.

[b] In order to receive the investigational product (pegcetacoplan or placebo), subjects must have documented evidence of vaccination against the following within 5 years of baseline visit 2b: *Neisseria meningitidis* types A, C, W, Y, and B (administered as 2 separate vaccinations - one for *N meningitidis* types A, C, W, Y and one for *N meningitidis* type B), *Streptococcus pneumoniae* (with a PCV13 or PPSV23), and *Haemophilus influenzae* type B (Hib vaccine). For subjects who do not have documented evidence of receiving any of the above vaccinations within 5 years prior to baseline visit 2b, the required missing vaccination(s) will be administered at least 7 days prior to baseline visit 2b. Vaccination is mandatory, unless documented evidence exists that subjects are nonresponders to vaccination (as evidenced by titers or display titer levels within acceptable local limits). The investigator will discuss with the sponsor regarding individual subject circumstances. If the subject requires vaccination against *N meningitidis*, both vaccinations (*N meningitidis* A, C, W, Y and *N meningitidis* B) will be administered at least 7 days prior to baseline visit 2b. If the subject requires vaccination against *Streptococcus pneumoniae*, PCV13 will be administered at least 7 days prior to baseline visit 2b, and PPSV23 will be administered after at least 8 weeks. Boosters and revaccination(s) should be administered according to vaccination guidelines (see Section 8.4). It is recommended that subjects also be vaccinated annually against influenza (flu) during study participation in accordance to guidelines in the country of residence.

[c] Full physical examination will be performed at the scheduled time points indicated. A symptom-driven physical examination may be performed at various unscheduled time points if deemed necessary by the investigator.

[d] At clinic visits, vital signs will be measured within 2 hours (± 30 mins) before blood sampling procedures. At baseline visit 2b, when investigational product is administered at the clinic, vital signs will be measured within 2 hours preinfusion and at 30 minutes (±5 minutes) postdose.

[e] A 12-lead ECG is to be performed before blood sampling procedures.

[f] With the exception of screening, Revised ALS Functional Rating Scale, EQ-5D-5L, and ZBI administration will be performed only via the telephone, on a dosing day, but prior to dosing (in the visit window prior to the visit, if applicable).

[g] Zarit Burden Interview will be administered to the same caregiver throughout the subject's study participation. If subject is not actively being assisted by a caregiver at baseline, ZBI will be administered to the subject's anticipated caregiver. If subject does not have an anticipated caregiver/relative at baseline, ZBI administration will begin when/if the subject starts requiring a caregiver. Please see Section 10.2.2 for the definition of a caregiver.
[h] At investigational sites selected to conduct EIM, EIM will occur before HHD.
[i] Blood pregnancy assessment and urine pregnancy test will be completed for WOCBP at the scheduled time points indicated.
[j] Blood samples will be taken after vital signs and 12-lead ECG have been completed.
[k] Additional samples for anti–pegcetacoplan peptide antibody and anti-PEG antibody will be collected every 6 months from last dose until it can be determined that the subject's antibody levels are at baseline or that further testing is not needed.
[l] At baseline visit 2b, in addition to the at-clinic %SVC using the clinic spirometer, subjects will also complete %SVC using their at-home devices. Training for the at-home SVC assessments will occur at baseline visit 2b after completion of the assessments using the at-home devices. Research personnel will provide training to the subject (and/or caregiver) until the subject (and/or caregiver) is able to perform the assessments independently. Only subjects (and/or caregivers) trained to perform the at-home assessments will be allowed to continue in the study.
[m] At-home %SVC will occur on a dosing day each week.
[n] Subjects (or caregiver) will administer SC pegcetacoplan, after receiving appropriate training by a nurse or other research personnel. The research personnel providing training will be made available for a minimum of 6 days on treatment (2 doses) to ensure the subject (or caregiver) has been trained to conduct self-administration; the duration can be shortened if ability to self-administer happens sooner. During training, the subject (or caregiver) must demonstrate to the research personnel his/her ability to safely and effectively administer study drug using the infusion pump. Following self-administration training, subject (or caregiver) may self-administer the SC infusions without supervision on all dosing days.
[o] Between clinic visits, subjects will be instructed to report any injection site reaction and/or any other AEs to the study coordinator.
[p] Investigational product dispensation for home administration may occur at different times throughout the study.
[q] Baseline is divided into visit 2a and visit 2b so questionnaires can be completed at the subject's home prior to dosing.
    a. Visit 2a will be conducted at home via the telephone one day prior to visit 2b.
    b. Visit 2b will be conducted at clinic; please confirm completion of visit 2a assessments before starting visit 2b assessments.
[r] Only subjects not enrolling in Part 3 will return unused investigational product.
[s] Visit 15b is only applicable for subjects who do not enter Part 3.
[t] Subjects who discontinue early should complete an early termination follow-up visit 6 weeks (±7 days) after treatment discontinuation.
[u] At-home measurements will be performed once per week on a dosing day through the last clinic visit.

Table 3: Schedule of Assessments—Open-Label (Pegcetacoplan) Treatment Period

Study period	Treatment period	Open-label (pegcetacoplan) treatment period													Follow-up (open-label)	ETFU[n]
Study week	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**110**	
Study day	**365**	**393**	**421**	**449**	**477**	**505**	**533**	**561**	**589**	**617**	**645**	**673**	**701**	**729**	**771**	
Study visit*	**15**	**16**	**17T**	**18T**	**19T**	**20T**	**21**	**22T**	**23T**	**24T**	**25T**	**26T**	**27T**	**28**	**28b**	**NA**
Visit window (± days)	7	7	4	4	4	4	7	4	4	4	4	4	4	7	7	7
Physical examination[a]	X														X	X
Vital sign measurements[b]	X	X					X							X	X	X
12-lead ECG[c]	X	X					X							X	X	X
Weight	X	X					X							X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ALSFRS-R[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D-5L[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ZBI[d,e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ALSAQ-40	X	X					X							X	X	X
C-SSRS	X	X					X							X	X	X
EIM[f] (only at select investigational sites)	X	X					X							X	X	X
HHD	X	X					X							X	X	X
Urinalysis	X	X					X							X	X	X
Urine pregnancy test[g]	X	X		X			X			X		X		X	X	X
Blood[h]	X	X					X							X	X	X
Hematology	X	X					X							X	X	X
Chemistry	X	X					X							X	X	X
Pharmacokinetics	X	X					X							X	X	X
Anti–pegcetacoplan peptide Ab and anti-PEG Ab assays[i]	X	X					X							X	X	X
Complement profile (C3, CH50 & AH50)	X	X					X							X	X	X

Table 3: Schedule of Assessments—Open-Label (Pegcetacoplan) Treatment Period

Study period	Treatment period	Open-label (pegcetacoplan) treatment period													Follow-up (open-label)	ETFU[n]
Study week	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**110**	
Study day	**365**	**393**	**421**	**449**	**477**	**505**	**533**	**561**	**589**	**617**	**645**	**673**	**701**	**729**	**771**	
Study visit*	**15**	**16**	**17T**	**18T**	**19T**	**20T**	**21**	**22T**	**23T**	**24T**	**25T**	**26T**	**27T**	**28**	**28b**	**NA**
Visit window (± days)	7	7	4	4	4	4	7	4	4	4	4	4	4	7	7	7
NfL	X	X					X							X	X	X
pNfH	X	X					X							X	X	X
At-clinic %SVC (using study-specific clinic spirometry)	X	X					X							X	X	X
At-home %SVC[j]	---------- Once per week ----------→														X[o]	X[o]
Pegcetacoplan administration[k]	---------- Twice per week ----------→															
Injection site assessment[l]	---------- Twice per week after dosing----------→															
Investigational product dispensation for home administration[m]	X	----------→														
Return of unused investigational product														X[p]		X
Return of at-home devices															X	X

Abbreviations: %SVC = percentage of slow vital capacity; Ab = antibody(ies); AH50 = 50% alternative hemolytic complement pathway activity; ALS = amyotrophic lateral sclerosis; ALSAQ-40 = ALS Assessment Questionnaire; ALSFRS-R = Revised ALS Functional Rating Scale; C3 = complement component 3; CH50 = 50% classical hemolytic complement pathway activity; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EIM = electrical impedance myography; ETFU = early termination follow-up; EQ-5D-5L = 5-Level EuroQol-5 Dimension; HHD = handheld dynamometry; NA = not applicable; NfL = neurofilament light chain; PEG = polyethylene glycol; pNfH = phosphorylated neurofilament heavy chain; SC = subcutaneous; T = telephone administered assessment; WOCBP = women of childbearing potential; ZBI = Zarit Burden Interview.

* **T = Telephone administered visit.**

[a] Full physical examination will be performed at the scheduled time points indicated. A symptom-driven physical examination may be performed at various unscheduled time points if deemed necessary by the investigator.

[b] At clinic visits, vital signs will be measured within 2 hours (±30 mins) before blood sampling procedures.

[c] A 12-lead ECG is to be performed before blood sampling procedures.

[d] Revised ALS Functional Rating Scale, EQ-5D-5L, and ZBI administration will be performed only via the telephone, on a dosing day, but prior to dosing (in the visit window prior to the visit, if applicable).

[e] Zarit Burden Interview will be administered to the same caregiver throughout the subject's study participation. If subject is not actively being assisted by a caregiver at baseline, ZBI will be administered to the subject's anticipated caregiver. If subject does not have an anticipated caregiver/relative at baseline, ZBI administration will begin when/if the subject starts requiring a caregiver. Please see Section 10.2.2 for the definition of a caregiver.
[f] At investigational sites selected to conduct EIM, EIM will occur before HHD.
[g] Urine pregnancy test will be completed for WOCBP.
[h] Blood samples will be taken after vital signs and 12-lead ECG have been completed.
[i] Additional samples for anti–pegcetacoplan peptide antibody and anti-PEG antibody will be collected every 6 months from last dose until it can be determined that the subject's antibody levels are at baseline or that further testing is not needed.
[j] At-home %SVC will occur on a dosing day each week.
[k] Subjects (or caregiver) will administer SC pegcetacoplan, after receiving appropriate training by a nurse or other research personnel.
[l] Between clinic visits, subjects will be instructed to report any injection site reaction and/or any other AEs to the study coordinator.
[m] Investigational product dispensation for home administration may occur at different times throughout the study. At weeks 64 and 88, which are between clinic visits, subjects or their caregiver(s) may be required to come into the clinic to pick-up additional IP and supplies. Depending on the length of time between the week 88 additional IP pick-up visit and the week 104 clinic visit, an unscheduled dispensation visit for pick-up of IP and/or supplies may be necessary.
[n] Subjects who discontinue early should complete an early termination follow-up visit 6 weeks (± 7 days) after treatment discontinuation.
[o] At-home measurements will be performed once per week, on the same day as when subject was receiving treatment, through the last clinic visit.
[p] Only subjects not enrolling in Part 4 will return unused investigational product.

6.5. End of Trial Definition

A participant is considered to have completed the study if he/she has completed all parts of the study including the last scheduled procedure shown in Table 8, Schedule of Assessments–Open-Label (Pegcetacoplan) Long-Term Extension Treatment Period. The end of the study is defined as the date of the last scheduled procedure shown in the schedule of assessments for the last participant in the trial globally.

6.6. Study Procedures

Please see the schedule of assessments (Table 2, Table 3, and Table 8) for a summary of the schedule of study participation and procedures. The schedule of visit dates for Part 2, randomized treatment period, and Part 3, open-label (pegcetacoplan) treatment period should be established, either prior to or at the time of screening, allowing subjects an opportunity to assess whether there are likely to be significant conflicts with other activities or planned absences.

6.6.1. Screening Period: Visit 1

The subject will be screened to confirm that the subject-selection criteria for the study has been met. Informed consent will be obtained at screening prior to any study-related procedures being conducted.

During the screening period (from week -6 to baseline), pulmonary function tests (slow vital capacity [SVC]) and clinical laboratory tests (eg, hematology, coagulation, serum chemistry, urinalysis) may be repeated once with written approval from the sponsor (including the assigned medical monitor), with no requirement to designate the subject as a screen failure, unless the subject fails the second time. Subjects who do not meet screening SVC of ≥60% or clinical laboratory-related screening criteria may still qualify for study entry without having to complete the full rescreening process as long as the %SVC and all clinical laboratory-related values meet the criteria for study entry within the screening period.

With the exception of %SVC and clinical laboratory-related entry criteria, subjects who have given informed consent and fail to meet at least 1 of the inclusion and/or exclusion criteria and have not been randomized or administered investigational product(s) will be designated as a screen failure. Any subject designated as a screen failure may only be rescreened once with written approval from the sponsor and will be required to recomplete the full screening process. Any %SVC or clinical laboratory test that is reconducted to confirm eligibility must be conducted within the screening period after written approval from the sponsor/medical monitor has been received, or the subject will be designated as a screen failure.

At the screening visit, the following assessments will be performed:

Note: 12-lead electrocardiogram (ECG) and vital sign measurements must be performed prior to blood sampling.

- Informed consent
- Demographics
- Medical and treatment history

- Inclusion and exclusion criteria, including
  - ALSFRS-R via the telephone at clinic
  - %SVC using clinic spirometer
  - C-SSRS
- Concomitant medications
- Vaccination history (see Section 8.4), administration of required vaccination(s)
- Physical examination
- Weight and height
- Vital sign measurements **(prior to blood sampling)**
- 12-lead ECG **(prior to blood sampling)**
- Urinalysis
- Blood **(after vital sign measurements and 12-lead ECG)**
  - Hematology
  - Chemistry
  - Pregnancy (β–human chorionic gonadotropin and follicle-stimulating hormone) for women of childbearing potential (WOCBP)
  - Hepatitis C virus, hepatitis B surface antigen
- Assess subject's (or caregiver's) ability to perform SVC measurements using the at-home devices. Subjects will *not* take home any of these devices from the screening visit.

Subjects missing documented evidence of any of the required vaccinations (within 5 years of baseline visit 2b) must receive the vaccinations at least 7 days prior to baseline visit 2b (see Section 8.4.1).

6.6.2. Baseline: Visit 2a and Visit 2b

6.6.2.1. Baseline: Visit 2a

At the baseline visit 2a, the following assessments will be performed at home:

- Questionnaires via the telephone:
  - ALSFRS-R
  - EQ-5D-5L
  - ZBI

6.6.2.2. Baseline: Visit 2b

At the baseline visit 2b, the following assessments will be performed at clinic:

Note: 12-lead ECG and vital sign measurements must be performed prior to blood sampling, EIM must be performed prior to HHD (if applicable). All assessments must be performed prior to dosing (with the exception of injection site assessments, adverse reaction review, and postdose vital sign measurements)

- Confirmation of inclusion and exclusion criteria
- Confirm age at time of visit 2b
- Concomitant medications
- Vaccination history (see Section 8.4)
- Physical Examination
- Weight
- Predose vital sign measurements **(prior to blood sampling and dosing)**
- 12-lead ECG **(prior to blood sampling and dosing)**
- Questionnaires:
  - ALSAQ-40
  - C-SSRS
- %SVC using clinic spirometer
- %SVC using at-home spirometer
- Training on at-home assessments
- EIM (only at select investigational sites) **(prior to HHD)**
- HHD **(after EIM, if applicable)**
- Urinalysis
- Urine pregnancy test for WOCBP
- Blood **(after vital sign measurements and 12-lead ECG)**
  - Hematology
  - Chemistry
  - Pharmacokinetics
  - Anti–pegcetacoplan peptide antibody and anti-PEG antibody assays
  - Complement profile (C3, CH50, and AH50)
  - NfL
  - pNfH

- Investigational product administration: baseline dosing will be administered at the clinic by a nurse.
  - Injection site assessment
  - Adverse events review
  - Postdose vital sign measurements

At the visit, subjects will receive the at-home devices. Trained research personnel will train the subject (and/or caregiver) to perform both the administration of pegcetacoplan and the at-home assessments independently. Only subjects/caregivers who have been trained to self-administer pegcetacoplan and the at-home assessments will be able to continue in the study. If subjects require caregiver assistance in administering pegcetacoplan and the at-home assessments, the caregiver must continue assisting in the administration of at-home assessments for the duration of study participation.

(Note: throughout this protocol, the term "self-administration" refers to administration of the at-home assessments/investigational product by either a trained subject or trained caregiver).

6.6.3. Randomized Treatment Period (Core) Visits

Part 2 (randomized treatment period) of this study is composed of 4 different types of visits:

- Clinic visits (Section 6.6.3.1)
- Home visits (Section 6.6.3.2)
- Telephone visits (Section 6.6.3.3)
- Follow-up (core) visit (Section 6.6.3.4)

6.6.3.1. Randomized Treatment Period (Core)—Clinic Visits: Visits 3, 5, 8, 11, 15

In the randomized treatment period, prior to the clinic visits, the following should be assessed on a dosing day, at home, within visit window before the day of the clinic visit:

- Questionnaires via the telephone:
  - ALSFRS-R
  - EQ-5D-5L
  - ZBI

At the clinic visits, the following assessments will be performed:

Note: 12-lead ECG and vital sign measurements must be performed prior to blood sampling, EIM must be performed prior to HHD (if applicable). If clinic visit coincides with a dosing day, all assessments must be performed prior to dosing (with the exception of injection site assessments and adverse reaction review).

- Concomitant medications
- Weight
- Vital sign measurements **(prior to blood sampling)**

- 12-lead ECG **(prior to blood sampling)**
- Questionnaires:
  - ALSAQ-40
  - C-SSRS
- %SVC using clinic spirometer
- EIM (only at select investigational sites) **(prior to HHD)**
- HHD **(after EIM, if applicable)**
- Urinalysis
- Urine pregnancy test for WOCBP
- Blood sample **(after vital sign measurements and 12-lead ECG)**
  - Hematology
  - Chemistry
  - Pharmacokinetics
  - Anti–pegcetacoplan peptide antibody and anti-PEG antibody assays
  - Complement profile (C3, CH50, and AH50)
  - NfL
  - pNfH
- Investigational product administration (if applicable)
- Injection site assessment (if applicable)
- AEs review
- Return of unused investigational product (only at visit 15 for subjects not enrolling in Part 3)

After visit 15, subjects will enroll in Part 3, the open-label (pegcetacoplan) treatment period. If the subject chooses not to participate in Part 3, they will complete the follow-up (core) visit (Study visit 15b), 6 weeks after visit 15.

6.6.3.2. Randomized Treatment Period (Core)—Home Assessments

During the randomized treatment period, on days when there are no clinic or telephone visits, the following assessments will be performed at the subject's home beginning after baseline:

- Twice per week:
  - Investigational product administration. Subjects and/or caregivers will be trained by research personnel before subject/caregiver can self-administer (see Section 9.4). Subjects should not deviate from their dosing schedule: Day 1 and Day 4 of each treatment week (eg, Tuesday/Friday/Tuesday).

- Once per week on a dosing day:
  - %SVC with handheld spirometry (self-administration)
- Throughout the randomized treatment period:
  - Self-reported injection site assessment
  - AEs review

6.6.3.3. Randomized Treatment Period (Core)—Telephone Visits: Visits 4T, 6-7T, 9-10T, 12-14T

At telephone visits in the randomized treatment period, the following assessments will be performed on a dosing day:

- Questionnaires via the telephone:
  - ALSFRS-R
  - EQ-5D-5L
  - ZBI
- Self-reported injection site assessment
- AEs review
- Urine pregnancy test for WOCBP (only at visit 13T)

6.6.3.4. Follow-Up (Core) Visit: Visit 15b

If the subject chooses not to participate in Part 3, they will complete the follow-up (core) visit, 6 weeks after visit 15.

Prior to the follow-up (core) visit, the following should be assessed, at home, within visit window before the day of the follow-up (core) visit:

- Questionnaires:
  - ALSFRS-R
  - EQ-5D-5L
  - ZBI

At the follow-up (core) visit, the following assessments will be performed:

Note: 12-lead ECG and vital sign measurements must be performed prior to blood sampling, EIM must be performed prior to HHD (if applicable).

- Concomitant medications
- Physical examination
- Weight
- Vital sign measurements **(prior to blood sampling)**

- 12-lead ECG **(prior to blood sampling)**
- Questionnaires:
  - ALSAQ-40
  - C-SSRS
- %SVC using clinic spirometer
- EIM (only at select investigational sites) **(prior to HHD)**
- HHD **(after EIM, if applicable)**
- Urinalysis
- Urine pregnancy test for WOCBP
- Blood sample **(after vital sign measurements and 12-lead ECG)**
  - Hematology
  - Chemistry
  - Pharmacokinetics
  - Anti–pegcetacoplan peptide antibody and anti-PEG antibody assays
  - Complement profile (C3, CH50, and AH50)
  - NfL
  - pNfH
- AEs review
- Return of at-home devices

6.6.4. Open-Label (Pegcetacoplan) Treatment Period Visits

Part 3 (open-label [pegcetacoplan] treatment period) of this study is composed of 4 different types of visits:

- Clinic visits (Section 6.6.4.1)
- Home assessments (Section 6.6.4.2)
- Telephone visits (Section 6.6.4.3)
- Follow-up (open-label) visit (Section 6.6.4.4)

6.6.4.1. Open-Label (Pegcetacoplan) Treatment Period—Clinic Visits: Visits 16, 21, 28

In the open-label (pegcetacoplan) treatment period, prior to the clinic visits, the following should be assessed on a dosing day, at home, within visit window before the day of the clinic visit:

- Questionnaires via the telephone:
  - ALSFRS-R
  - EQ-5D-5L
  - ZBI

At the clinic visits, the following assessments will be performed:

Note: 12-lead ECG and vital sign measurements must be performed prior to blood sampling, EIM must be performed prior to HHD (if applicable). If clinic visit coincides with a dosing day, all assessments must be performed prior to dosing (with the exception of injection site assessments and adverse reaction review).

- Concomitant medications
- Weight
- Vital sign measurements **(prior to blood sampling)**
- 12-lead ECG **(prior to blood sampling)**
- Questionnaires:
  - ALSAQ-40
  - C-SSRS
- %SVC using clinic spirometer
- EIM (only at select investigational sites) **(prior to HHD)**
- HHD **(after EIM, if applicable)**
- Urinalysis
- Urine pregnancy test for WOCBP
- Blood sample **(after vital sign measurements and 12-lead ECG)**
  - Hematology
  - Chemistry
  - Pharmacokinetics
  - Anti–pegcetacoplan peptide antibody and anti-PEG antibody assays
  - Complement profile (C3, CH50, and AH50)
  - NfL
  - pNfH
- Investigational product administration (if applicable)
- Injection site assessment (if applicable)
- AEs review
- Return of unused investigational product (only at visit 28)

6.6.4.2. Open-Label (Pegcetacoplan) Treatment Period—Home Assessments

During the open-label (pegcetacoplan) treatment period, on days when there are no clinic or telephone visits, the following assessments will be performed at home:

- Twice per week:
  - Pegcetacoplan administration. Subjects and/or caregivers will be trained by a nurse or other research personnel before subject can self-administer (see Section 9.4). Subjects should not deviate from their dosing schedule: day 1 and day 4 of each treatment week (eg, Tuesday/Friday/Tuesday).
- Once per week on a dosing day:
  - %SVC with handheld spirometry (self-administration)
- Throughout the open-label period:
  - Self-reported injection site assessment
  - AEs review

6.6.4.3. Open-Label (Pegcetacoplan) Treatment Period—Telephone Visits: Visits 17T-20T, 22T-27T

At telephone visits in the open-label (pegcetacoplan) treatment period, the following assessments will be performed on a dosing day:

- Questionnaires via the telephone:
  - ALSFRS-R
  - EQ-5D-5L
  - ZBI
- Self-reported injection site assessment
- AEs review
- Urine pregnancy test for WOCBP (only at visits 18T, 24T, and 26T)

6.6.4.4. Open-Label (Pegcetacoplan) Treatment Period—Follow-up Visit: Visit 28b

Prior to the follow-up (open-label) visit, the following should be assessed, at home, within visit window before the day of the follow-up (open-label) visit:

- Questionnaires via the telephone:
  - ALSFRS-R
  - EQ-5D-5L
  - ZBI

At the follow-up (open-label) visit, the following assessments will be performed:

Note: 12-lead ECG and vital sign measurements must be performed prior to blood sampling, EIM must be performed prior to HHD (if applicable).

- Concomitant medications
- Physical examination
- Weight
- Vital sign measurements **(prior to blood sampling)**
- 12-lead ECG **(prior to blood sampling)**
- Questionnaires:
  - ALSAQ-40
  - C-SSRS
- %SVC using clinic spirometer
- EIM (only at select investigational sites) **(prior to HHD)**
- HHD **(after EIM, if applicable)**
- Urinalysis
- Urine pregnancy test for WOCBP
- Blood sample **(after vital sign measurements and 12-lead ECG)**
  - Hematology
  - Chemistry
  - Pharmacokinetics
  - Anti–pegcetacoplan peptide antibody and anti-PEG antibody assays
  - Complement profile (C3, CH50, and AH50)
  - NfL
  - pNfH
- AEs review
- Return of at-home devices

6.6.5. Open-Label (Pegcetacoplan) Long-Term Extension Treatment Period

Part 4 (open-label [pegcetacoplan] long-term extension period) of this study is composed of 4 different types of visits:

- Clinic visits (Section 6.6.5.1)
- Home assessments (Section 6.6.5.2)
- Telephone visits (Section 6.6.5.3)
- Follow-up (open-label) visit (Section 6.6.5.4)

6.6.5.1. Open-Label (Pegcetacoplan) Long-Term Extension Treatment Period—Clinic Visits: Visits 31, 36, 41

In the open-label (pegcetacoplan) long-term extension treatment period, prior to the clinic visits, the following should be assessed on a dosing day, at home, within visit window before the day of the clinic visit:

- Questionnaires via the telephone:
  - ALSFRS-R
  - EQ-5D-5L
  - ZBI

At the clinic visits, the following assessments will be performed:

Note: 12-lead ECG and vital sign measurements must be performed prior to blood sampling, EIM must be performed prior to HHD (if applicable). If clinic visit coincides with a dosing day, all assessments must be performed prior to dosing (with the exception of injection site assessments and adverse reaction review).

- Concomitant medications
- Weight
- Vital sign measurements **(prior to blood sampling)**
- 12-lead ECG **(prior to blood sampling)**
- Questionnaires:
  - ALSAQ-40
  - C-SSRS
- %SVC using clinic spirometer
- EIM (only at select investigational sites) **(prior to HHD)**
- HHD **(after EIM, if applicable)**
- Urinalysis
- Urine pregnancy test for WOCBP
- Blood sample **(after vital sign measurements and 12-lead ECG)**
  - Hematology
  - Chemistry
  - Pharmacokinetics
  - Anti–pegcetacoplan peptide antibody and anti-PEG antibody assays
  - Complement profile (C3, CH50, and AH50)
  - NfL
  - pNfH

- Investigational product administration (if applicable)
- Injection site assessment (if applicable)
- AEs review
- Return of unused investigational product (only at visit 41)

6.6.5.2. Open-Label (Pegcetacoplan) Long-Term Extension Treatment Period—Home Assessments

During the open-label (pegcetacoplan) long-term extension treatment period, on days when there are no clinic or telephone visits, the following assessments will be performed at home:

- Twice per week:
  - Pegcetacoplan administration. Subjects and/or caregivers will be trained by a nurse or other research personnel before subject can self-administer (see Section 9.4). Subjects should not deviate from their dosing schedule: day 1 and day 4 of each treatment week (eg, Tuesday/Friday/Tuesday).
- Throughout the open-label period:
  - Self-reported injection site assessment
  - AEs review

6.6.5.3. Open-Label (Pegcetacoplan) Long-Term Extension Treatment Period—Telephone Visits: Visits 29T, 30T, 32T-35T, 37T-40T

At telephone visits in the open-label (pegcetacoplan) long-term extension treatment period, the following assessments will be performed on a dosing day:

- Questionnaires via the telephone:
  - ALSFRS-R
- Self-reported injection site assessment
- AEs review
- Urine pregnancy test for WOCBP (only at Visits 34T and 39T)

6.6.5.4. Open-Label (Pegcetacoplan) Long-Term Extension Treatment Period—Follow-up Visit: Visit 41b

Prior to the follow-up (open-label, long-term extension) visit, the following should be assessed, at home, within visit window before the day of the follow-up (open-label) visit:

- Questionnaires via the telephone:
  - ALSFRS-R
  - EQ-5D-5L
  - ZBI

At the follow-up (open-label) visit, the following assessments will be performed:

Note: 12-lead ECG and vital sign measurements must be performed prior to blood sampling, EIM must be performed prior to HHD (if applicable).

- Concomitant medications
- Physical examination
- Weight
- Vital sign measurements **(prior to blood sampling)**
- 12-lead ECG **(prior to blood sampling)**
- Questionnaires:
  - ALSAQ-40
  - C-SSRS
- %SVC using clinic spirometer
- EIM (only at select investigational sites) **(prior to HHD)**
- HHD **(after EIM, if applicable)**
- Urinalysis
- Urine pregnancy test for WOCBP
- Blood sample **(after vital sign measurements and 12-lead ECG)**
  - Hematology
  - Chemistry
  - Pharmacokinetics
  - Anti–pegcetacoplan peptide antibody and anti-PEG antibody assays
  - Complement profile (C3, CH50, and AH50)
  - NfL
  - pNfH
- AEs review
- Return of at-home devices

6.6.6. Early Termination Follow-Up Visit

Subjects who discontinue prior to the follow-up (core)/follow-up (open-label)/follow-up (open-label, long-term extension) visit will complete an early termination follow-up visit 6 weeks (±7 days) after their last dose of the investigational product.

Prior to the early termination follow-up visit, the following will be assessed, at home, within visit window before the day of the early termination follow-up visit:

- Questionnaires via the telephone:
  - ALSFRS-R
  - EQ-5D-5L
  - ZBI

At the early termination follow-up visit, the following assessments will be performed:

Note: 12-lead ECG and vital sign measurements must be performed prior to blood sampling, and EIM must be performed prior to HHD (if applicable).

- Concomitant medications
- Physical examination
- Weight
- Vital sign measurements **(prior to blood sampling)**
- 12-lead ECG **(prior to blood sampling)**
- Questionnaires:
  - ALSAQ-40
  - C-SSRS
- %SVC using clinic spirometer
- EIM (only at select investigational sites) **(prior to HHD)**
- HHD **(after EIM, if applicable)**
- Urinalysis
- Urine pregnancy test for WOCBP
- Blood sample **(after vital sign measurements and 12-lead ECG)**
  - Hematology
  - Chemistry
  - Pharmacokinetics
  - Anti–pegcetacoplan peptide antibody and anti-PEG antibody assays
  - Complement profile (C3, CH50, and AH50)
  - NfL
  - pNfH
- AEs review
- Return of at-home devices

6.6.7. Unscheduled Visit(s)

Subjects may be asked to return to the clinic for additional visits if considered necessary by the investigator. Unscheduled visits may include (but are not limited to) any of the procedures listed in the schedule of assessments (see Table 2, Table 3, and Table 8).

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

1. Sporadic ALS diagnosed as definite, probable, or laboratory-supported probable as defined by the revised El Escorial criteria (Brooks et al. 2000)
2. At least 18 years of age
3. SVC ≥60% of the predicted value based on age, sex, and height at screening
4. Onset of ALS symptoms within 72 weeks prior to screening
5. Total ALSFRS-R score of ≥30 at screening
6. WOCBP, defined as any woman who has experienced menarche and who is NOT permanently sterile or postmenopausal
    a. must have a negative pregnancy test at screening and
    b. must agree to use protocol defined methods of contraception for the duration of the study and 90 days after their last dose of the investigational product
        – Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause
7. Males must agree to
    a. use protocol defined methods of contraception and
    b. refrain from donating sperm for the duration of the study and 90 days after their last dose of the investigational product
8. Have vaccination against *Streptococcus pneumoniae, N meningitidis* (types A, C, W, Y, and B), and *H influenzae* (type B) either within 5 years prior to baseline visit 2b, or agree to receive vaccination at least 7 days prior to baseline visit 2b. Vaccination is mandatory, unless documented evidence exists that subjects are non-responders to vaccination (as evidenced by titers or display titer levels within acceptable local limits)
9. Willing and able to give informed consent and comply with study procedure and assessments (including at-home assessments)

7.2. Subject Exclusion Criteria

1. Confirmed or suspected other causes of neuromuscular weakness
2. Diagnosis of another neurodegenerative disease(s)
3. Subject with significant cognitive impairment, clinical dementia, or psychiatric illness that in the opinion of the investigator may increase subject's risk by participating in the study or confound the outcome of the study
4. Subjects with a significant pulmonary disorder not attributed to ALS or who require treatments that might complicate the evaluation of the effect of ALS on respiratory function (eg, chronic obstructive pulmonary disease, pulmonary fibrosis, cystic fibrosis, pulmonary arterial hypertension)

5. Current use or anticipated need, in the opinion of the investigator, of a diaphragm pacing system (DPS) during the randomized treatment period
6. Riluzole initiation or change in dose within 30 days prior to the start of the screening period or planned initiation during study participation. If using riluzole, the subject should remain on the drug throughout Part 2 of study participation, but the dosage may be altered or the drug discontinued at any time by the investigator for any safety concern. Riluzole-naïve subjects are allowed in the study.
7. Edaravone initiation or change in dose within 60 days prior to the start of the screening period or planned initiation during study participation. If using edaravone, the subject should remain on the drug throughout Part 2 of study participation, but the dosage may be altered or the drug discontinued at any time by the investigator for any safety concern. Edaravone-naïve subjects are allowed in the study.
8. Positive response to Item 4 or 5 of the C-SSRS
9. Subjects with detectable hepatitis C by polymerase chain reaction at screening
10. Subjects with chronic inactive hepatitis B with viral loads >1000 IU/mL (>5000 copies/mL) at screening. Eligible subjects who are chronic active carriers (≤1000 IU/mL) must receive prophylactic antiviral treatment according to local country guidelines (eg, entecavir, tenofovir, lamivudine)
11. History of an aggressive lymphoma or presence of a lymphoma requiring therapy by itself
12. Active or overt malignant disease other than basal cell carcinoma or cutaneous squamous cell carcinoma
13. Received organ transplant
14. Presence or suspicion of liver dysfunction as indicated by elevated alanine aminotransferase, aspartate aminotransferase, or bilirubin levels >2 × the upper limit of normal
15. Presence or suspicion of severe recurrent or chronic infections that, in the opinion of the investigator, increase the subject's risk by participating in the study
16. Participation in any other investigational drug trial or exposure to other investigational agent, device, or procedure within 30 days or within 5-half lives of the treatment (whichever is longer) prior to the start of the screening period or during study participation
17. Use of any other complement inhibitor within 30 days or within 5-half lives of the treatment (whichever is longer) prior to the start of the screening period or during study participation
18. If breastfeeding, unwilling to discontinue for the duration of the study and for at least 6 months after final dose of investigational product
19. Inability to cooperate or any condition that, in the opinion of the investigator, could increase the subject's risk by participating in the study or confound the outcome of the study
20. Subjects with known allergy or hypersensitivity to pegcetacoplan or to any of the components
21. Known or suspected hereditary fructose intolerance

7.3. Subject Completion and Withdrawal Criteria

Subjects will be considered to have completed the study when they have:

- Completed the open-label long-term extension period.

Subjects will be considered to have withdrawn from the study when they have:

- Completed any early termination activities.

A subject may withdraw from the study at any time, for any reason, without prejudice to his/her future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of the subject's safety). If a subject discontinues or is withdrawn from the investigational product for any reason, the study site must immediately notify the medical monitor. Once a subject is withdrawn from the study, the subject may not re-enter the study.

Subjects who discontinue the investigational product prior to the follow-up (core)/follow-up (open-label)/follow-up (open-label, long-term extension) visits will undergo all remaining visits and procedures through the relevant follow-up visit, unless unwilling or unable, or consent has been withdrawn. Subjects who wish to fully withdraw from the study before completion will complete the early termination follow-up visit 6 weeks (±7 days) after their last dose of the investigational product (see Table 2, Table 3, and Table 8).

If a subject withdraws from the study, then the subject and/or their caregivers will be contacted by the study site to provide post-discontinuation survival status at 6-month intervals until the study completes.

7.3.1. Reasons for Discontinuation

The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record and on the electronic case report form (eCRF). If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the eCRF.

The following list includes the reasons for discontinuation from treatment and/or withdrawal from the study:

- adverse events
- death
- lost to follow-up
- withdrawal by subject
- study terminated by sponsor
- physician decision
- pregnancy

- major protocol violation deemed, after consultation with study medical monitor, to potentially impact the subject's safety and study data interpretation
- lack of efficacy, defined as inadequate response to study drug in the investigator's opinion

7.3.1.1. Mandatory Study Discontinuation/Withdrawal Criteria

Subjects are required to discontinue the investigational product and withdraw from the study if they meet the below criteria:

- Administer a complement inhibitor during the period outlined in Section 8.6.1
- Intentionally unblinded themselves

7.3.2. Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point prior to the last scheduled contact. At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that he/she return to the site for final safety evaluations and to return any unused investigational product and study devices.

8. TREATMENT OF SUBJECTS

8.1. Identity of the Investigational Product

Throughout this protocol, "investigational product" refers to the blinded treatment, whether that is pegcetacoplan or placebo. Additional information on pegcetacoplan and placebo is available in Section 9.

8.2. Treatment Assignment

8.2.1. Blinding the Treatment Assignment

This is a randomized, double-blinded, placebo-controlled study. The intent of blinding is to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of the clinical study. Bias could arise from the influence that the knowledge of a specific treatment assignment may have on the recruitment and allocation of subjects, their subsequent care, the assessment of endpoints, the handling of withdrawals, and so on. The essential aim of blinding, therefore, is to prevent identification of the treatments by the subject and the blinded assessors associated with the conduct of the study until all such opportunities for bias have passed.

Designated blinded study staff (eg, research coordinators, nurses, technicians administering questionnaires, subjects, spirometry and dynamometer central reading centers, assigned evaluating physician(s), and the sponsor) will be blinded to treatment assignment. Only the drug supply distributor/logistics personnel who are not site personnel will be unblinded to study treatment. These individuals are not allowed to discuss treatment and/or subject outcome with blinded study staff, including the evaluating physician. The principal investigator must be blinded to subjects' treatment assignment.

8.2.2. Randomization

To prevent bias in treatment assignment, randomization will occur through the interactive response technology system.

The randomization will only be available to the drug supply distributor/logistics personnel. The randomization will not be made available to the sponsor, subjects, or clinic staff responsible for the monitoring and evaluation of safety assessments.

All subjects who meet all the inclusion criteria and none of the exclusion criteria will be enrolled in the study, until such time that approximately 228 subjects have been enrolled in the study. At the first visit of the randomized treatment period, subjects will be randomized after confirmation of study eligibility in a ratio of 2:1 via a computer-generated randomization schedule to receive pegcetacoplan or placebo. The randomization will be performed centrally and stratified by location of first muscle weakness (limb or bulbar), riluzole, and edaravone use. The stratification by location of onset and riluzole and edaravone use will ensure balance between treatment groups for the respective stratification factors. Fixed block randomization will be used to ensure that approximately equal number of subjects are assigned each treatment within strata.

8.2.3. Unblinding Prior to Study Completion

Breaking the blind is forbidden except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the subject, or in the event of an interim safety analysis. Managing serious reactions does not generally require unblinding a subject's treatment assignment. The investigator has the ability to unblind a trial subject's treatment in the interactive response technology (IRT) in the event of a medical emergency. In the event that emergency unblinding must be performed, the investigator should complete the unblinding notification form and send it to PPD PPD. Where medically feasible, all efforts should be taken to notify prior to breaking the blind. The investigator should contact the study's medical monitor to discuss case details. The unblinding process in IRT is outlined in the IRT manual.

The date and reason for the unblinding should be noted in the subject's source document. The personnel breaking the blind should not divulge the subject's treatment assignment to any individual not directly involved in managing the medical emergency, nor to personnel involved with the analysis and conduct of the study. Subjects who have had their treatment assignment unblinded secondary to medical emergency will no longer receive study treatment. However, they should continue to complete the early termination follow-up (ETFU) visit as outlined in the schedule of assessments.

8.3. Dosing of the Investigational Product

Subjects are administered the investigational product via SC infusion (20 mL) twice per week. In the randomized treatment period, subjects randomized to the pegcetacoplan treatment group will receive pegcetacoplan twice per week at a dose of 1080 mg and the placebo treatment group will receive placebo twice per week. In the open-label treatment and long-term extension periods, both treatment groups will receive pegcetacoplan at a dose of 1080 mg twice per week. Subjects should not deviate from their dosing schedule: day 1 and day 4 of each treatment week (eg, Tuesday/Friday/Tuesday).

Dosing diaries will be utilized for all subjects and are to be completed for each dose administered. In the randomized, open-label, and long-term extension treatment periods, the subjects (or caregivers) will complete the dosing diaries.

8.4. Vaccinations

In order to receive the investigational product, subjects must have documented evidence of vaccination against the following within 5 years of baseline visit 2b:

- *N meningitidis* types A, C, W, Y, and B (administered as 2 separate vaccinations - one for *N meningitidis* types A, C, W, Y and one for *N meningitidis* type B)
- *Streptococcus pneumoniae* (with a pneumococcal conjugate vaccine 13 [PCV13] or pneumococcal polysaccharide vaccine 23 [PPSV23])
- *H influenzae* type B (Hib vaccine)

For subjects who do not have documented evidence of receiving any of the above vaccinations within 5 years prior to baseline visit 2b, the required missing vaccination(s) will be administered during at least 7 days prior to baseline visit 2b; however, in the event that an expeditious study start is warranted, the vaccination schedule may be adjusted with written approval from the sponsor. Vaccination is mandatory, unless documented evidence exists that subjects are non-responders to

vaccination (as evidenced by titers or display titer levels within acceptable local limits). The investigator will discuss with the sponsor regarding individual subject circumstances.

If the subject requires vaccination against *N meningitidis*, both vaccinations (*N meningitidis* A, C, W, Y and *N meningitidis* B) should be administered at least 7 days prior to baseline visit 2b. If the subject requires vaccination against *Streptococcus pneumoniae*, PCV13 will be administered at least 7 days prior to baseline visit 2b, and PPSV23 will be administered after at least 8 weeks.

Revaccination should be consistent with the recommendations of the Centers for Disease Control and Prevention (or local guidelines) as follows:

- *N meningitidis* types A, C, W, Y: every 5 years
- *N meningitidis* type B: 1 year after the primary series and repeated every 2-3 years
- *Streptococcus pneumoniae* (PPSV23): 5 years after previous PPSV23 dose
- *Haemophilus influenzae* type B (Hib vaccine): no revaccination needed

It is recommended that subjects also be vaccinated annually against influenza (flu) during study participation in accordance with guidelines in the country of residence.

8.4.1. Prophylactic Antibiotics

Administration of prophylactic antibiotic therapy chronically may be conducted, at the discretion of the treating investigator, in accordance with local treatment guidelines.

8.5. Concomitant Medications

All medications administered and procedures performed within 12 weeks of screening will be collected as prior medications and procedures. Medications administered and procedures performed from the time of informed consent through the early termination follow-up/follow-up (core)/follow-up (open-label)/follow-up (long-term extension) visit will be documented.

- Use of riluzole during the study is allowed as long as the subject remains on the drug throughout Part 2 of study participation, but the dosage may be altered or the drug discontinued by the investigator at any time for any safety concern. Riluzole initiation or change in dose within 30 days prior to the start of the screening period or during Part 2 of study participation is not allowed. Riluzole-naïve subjects are allowed in study. If riluzole is initiated or discontinued or if dose is changed during Parts 3 or 4 of the study, the dates of administration must be documented in the subject's source document and subject's eCRF.
- Use of edaravone during the study is allowed as long as the subject remains on the drug throughout Part 2 of study participation, but the dosage may be altered or the drug discontinued at any time by the investigator for any safety concern. Edaravone initiation or change in dose within 60 days prior to the start of the screening period or during Part 2 of study participation is not allowed. Edaravone-naïve subjects are allowed in study. If edaravone is initiated or discontinued or if dose is changed during Parts 3 or 4 of the study, the dates of administration must be documented in the subject's source document and subject's eCRF.

- Subjects should not begin Relyvrio (AMX0035) during Part 2 of the study and if administered during Part 3 or 4, the dates of administration must be documented in the subject's source document and subject's eCRF.

Concomitant treatment refers to all treatment taken between the dates of the first dose of investigational product and the end of the follow-up period, inclusive. Concomitant treatment information must be recorded on the appropriate eCRF page. Except for complement inhibitors (other than pegcetacoplan [eg, eculizumab or ravulizumab]), any concomitant medication deemed necessary for the subject's standard of care during the study, or for the treatment of any AE (along with the allowed medications described below) may be given at the discretion of the investigator. It is the responsibility of the investigator to ensure that the details regarding all medications are recorded in full in the subject's eCRF.

8.6. Prohibited Medications or Procedures

8.6.1. Prohibited Medications

Subjects are prohibited from taking the below medications:

- Any other complement inhibitor within 30 days or within 5-half lives of the treatment (whichever is longer) prior to the start of the screening period or during study participation

8.6.2. Prohibited Procedures

Subjects are prohibited from having a DPS implanted prior to or during Part 2. Subjects who have a DPS implanted during Part 2 will be required to withdraw from the study. If a subject has a DPS implanted during Part 3 or 4, the date of the implantation must be documented in the subject's source document and subject's eCRF.

8.7. Treatment Compliance

Investigational product accountability will be performed to ensure subjects are dosing according to assigned treatment group. Subjects should not skip or deviate from their dosing schedule: day 1 and day 4 of each treatment week (eg, Tuesday/Friday/Tuesday). Dosing will be recorded in the dosing diaries.

Subjects must be instructed to bring their empty/unused investigational product packaging to every visit. The pharmacist/nominated person will record details on the drug accountability form. Refer to the Pharmacy Manual for further details.

9. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

9.1. Investigational Product

9.1.1. Pegcetacoplan

Pegcetacoplan (also known as APL-2) drug product (DP) solution for injection or infusion will be provided as a sterile solution of pegcetacoplan with a concentration of 54 mg/mL in 10 mM acetate buffer, pH 5.0, containing 4.1% sorbitol supplied in stoppered glass vials. Additional information is provided in the pegcetacoplan DP IB.

9.1.2. Placebo

Placebo will be provided as a sterile solution of 10 mM acetate buffer, pH 5.0, containing 4.1% sorbitol supplied in stoppered glass vials.

9.2. Investigational Product Packaging and Labeling

9.2.1. Packaging

Investigational product is supplied in 20-cc glass vials. Please refer to the Pharmacy Manual for details.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement, in advance, by the sponsor.

9.2.2. Labeling

Labels containing study information and pack identification are applied to the investigational product container.

All investigational product (pegcetacoplan DP or placebo) is labeled with a minimum of the following: protocol number, dosage form (including product name and quantity in pack), route of administration, directions for use, storage conditions, batch number and/or packaging reference, statements required per local regulations (eg, “For clinical trial use only”), and name and address of the sponsor.

Space is allocated on the label so that the clinic representative can record a unique subject identifier and date dispensed.

Additional labels may, on a case-by-case basis, be applied to the investigational product in order to satisfy national, local, or institutional requirements but must not do any of the following: contradict the clinical study label, obscure the clinical study label, identify the study subject by name.

Additional labels may not be added without the sponsor’s prior full agreement.

9.3. Investigational Product Storage and Handling

The investigational product is to be stored refrigerated at 2 to 8°C.

If the investigational product is stored at investigator site (or documented storage location outside of subjects' home), temperature monitoring is required to ensure that the investigational product is maintained within the established temperature range (2 to 8°C).

The site pharmacist is responsible for the following:

- ensuring that the investigational product is stored in a secure, limited-access location at the site
- ensuring that the temperature is monitored throughout the duration of the study when the investigational product is at site and/or shipped to subject
- ensuring that investigational product and supply records are maintained
- dispensing the vials of investigational product to the subject and/or caregiver
- entering the unique subject identifier on the investigational product bottle/carton labels as they are distributed

The investigator or trained research personnel is responsible for ensuring subjects and/or caregivers are trained on how to appropriately store the investigational product.

If the subject receives the investigational product from the site, it should be transported in a sponsor-approved bag or box, containing previously temperature-conditioned cold plates to ensure that the storage temperature (2 to 8°C) is maintained. Temperature monitoring will not be required at the subject's residence.

With sponsor prior approval, investigational product and/or ancillary supplies may be shipped from the study site to a subject's designated location. Such shipments will be implemented only at sites where this activity is approved by the IRB/IEC and health authority (if required). Subject consent will be required prior to any subject information being provided to a courier. The responsibility to return empty vials and any unused investigational product shall remain unchanged.

9.4. Administration

The investigational product will be administered as a 20-mL SC infusion.

The preferred site of infusion will be the abdomen. If administration into the abdomen is not feasible, alternative appropriate sites are acceptable (see Pump Instructions for Use for more details).

Nurses or other research personnel will train and supervise the self-administration of SC infusions. The nurses/research personnel will be made available for a minimum of 6 days on treatment (2 doses) to ensure the subject or caregiver has been trained to conduct administration; the duration could be shortened if ability to self-administer happens sooner. During training, the subject (or caregiver) must demonstrate to the research personnel his/her ability to safely and effectively administer study drug using the infusion pump. Following self-administration training, subjects (or caregiver) may self-administer the SC infusions without supervision. If subject (or caregiver) is unable to self-administer study drug, a nurse may be made available for longer periods of time for study drug administration following consultation with the sponsor.

9.5. Infusion Supplies

The sponsor will supply syringes, vial adapters, infusion sets, and ambulatory syringe infusion pumps, as required. Refer to the Pharmacy Manual for further details.

9.6. Investigational Product Accountability

Accountability for the investigational product at the study center is the responsibility of the investigator. The investigator will ensure that the investigational product is used only in accordance with this protocol. Where allowed, the investigator may choose to delegate investigational product accountability responsibilities to a pharmacist or other appropriate individual.

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator/designee will acknowledge receipt of the investigational product, and documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and participant numbers. The sponsor/designee will review investigational product accountability at the study center on an ongoing basis during monitoring visits. Investigational product must not be used for any purpose other than the present study. Investigational product that has been dispensed to a participant and returned unused must not be re-dispensed to a different participant. The investigator is responsible for ensuring the retrieval of all returnable study supplies from subjects.

9.7. Investigational Product Disposal

All unused and used study drug vials should be retained at the center until they are inventoried by the study monitor. At the conclusion of the study, any unused investigational product will either be destroyed or be returned to the sponsor or designee for destruction, and destruction will be documented appropriately. If no supplies remain, this fact will be documented appropriately.

10. EFFICACY AND EXPLORATORY ASSESSMENTS

10.1. Efficacy Assessments

10.1.1. Primary Efficacy Assessment

The primary efficacy assessment is the difference in the CAFS score at week 52.

10.1.1.1. CAFS Scale

The CAFS scale is a combined endpoint ranking subjects' clinical outcomes based on ALSFRS-R and survival time. The worst outcome is assigned to the subject who dies first in the study and the best is assigned to the subject who survives with the least functional decline. Each subject's outcome is compared to every other subject outcome in the trial in a series of pairwise comparisons, and the summed scores are ranked. A higher mean CAFS score indicates a better group outcome. Analysis will be completed by the sponsor.

10.1.1.1.1. ALSFRS-R Scale

The ALSFRS-R is a validated rating scale used to assess physical function in subjects with ALS. There are 12-items across 4 domains encompassing bulbar function, respiratory function, fine motor function, and gross motor function. Each question is scored from 0 (worst function) to 4 (best function), for a total maximum score of 48. The ALSFRS-R has been correlated to disease progression and survival and is validated for administration over the telephone to the subject. If the subject is unable to complete the ALSFRS-R assessment, the ALSFRS-R may be administered over the telephone to the caregiver (and must continue to be administered to the same caregiver for the rest of the subject's participation in the study). In this study, ALSFRS-R will be assessed by qualified research personnel via the telephone during monthly telephone visits and on a dosing day within the visit window prior to clinic visits (except for screening).

10.1.2. Secondary Efficacy Assessments

The following are the secondary efficacy assessments for this study:

- Change from baseline in ALSFRS-R at week 52
- Change from baseline in %SVC (at clinic visits) at week 52
- Change from baseline in HHD megascore at week 52
- Change from baseline in ALSAQ-40 at week 52
- Time to death, permanent tracheostomy, or permanent assisted ventilation up to week 52
- Time to death up to week 52
- Change from baseline of the randomized treatment period (visit 2) and of the open-label treatment period (visit 15) to week 104 for ALSFRS-R, %SVC, and HHD
- Time to death, permanent tracheostomy, or permanent assisted ventilation up to week 104
- Time to death up to week 104

10.1.2.1. Slow Vital Capacity—Clinic

Slow vital capacity is a pulmonary function test measured during spirometry which reflects the maximum amount of air that can be exhaled slowly. The %SVC is the percentage of the predicted SVC value based on age, sex, and height. Slow vital capacity has been shown to closely correlate with forced vital capacity and is a predictor of functional loss in ALS.

Slow vital capacity will be conducted at clinic visits with the clinic spirometer.

10.1.2.2. ALSAQ-40

The ALSAQ-40 is a 40-item validated questionnaire designed to assess HRQoL over the previous 2 weeks in subjects with ALS or other MN diseases. The instrument measures 5 dimensions of health status: physical mobility, activities of daily living and independence, eating and drinking, communication, and emotional functioning. Dimension scores are converted to a scale of 0 (perfect health as assessed by the measure) to 100 (worse health as assessed by the measure).

The ALSAQ-40 will be administered at clinic visits.

10.1.2.3. Handheld Dynamometry

Handheld Dynamometry (HHD) is a quantitative method to measure muscle strength used in subjects with ALS. Assessments will be evaluated by combined muscle groups called megascores, which average scaled individual strength measures to produce an overall measure. Strength expressed as megascores have been shown to decline with ALS disease progression.

The muscle groups that will be assessed are: first dorsal interosseous, wrist extension, elbow extension, elbow flexion, shoulder flexion, knee extension, knee flexion, and ankle dorsiflexion, on both sides of the body. HHD will be administered at clinic visits by qualified research personnel.

10.2. Exploratory Assessments

The following are the exploratory assessments for this study:

- Change from baseline in EQ-5D-5L at week 52, week 104, and week 156
- Change from baseline in ZBI score at week 52, week 104, and week 156
- Change from baseline of %SVC (home spirometry) at week 52 and week 104
- Time to percutaneous endoscopic gastrostomy tube placement up to week 52, week 104, and week 156
- Change from baseline in serum NfL at week 52, week 104, and week 156
- Change from baseline in serum pNfH at week 52, week 104, and week 156
- Change from baseline in EIM at week 52, week 104, and week 156 (only at select investigational sites chosen to complete this)
- Pegcetacoplan PK concentrations at week 52, week 104, and week 156

- Changes from baseline at week 52, week 104, and week 156 in complement biomarkers:
  - CH50
  - AH50
  - C3 levels
- Immunogenicity: presence of antibodies to PEG moiety and peptide moiety of pegcetacoplan during the randomized and open-label treatment periods
- Change from baseline of the randomized treatment period (week 1) and of the open-label treatment period (week 52) to week 156 for ALSFRS-R, %SVC (in-clinic), HHD, and ALSAQ-40
- Time to death, permanent tracheostomy, or permanent assisted ventilation up to week 156
- Time to death up to week 156

10.2.1. EQ-5D-5L

The EQ-5D-5L is a standardized measure of health status developed to assess HRQoL by the EuroQoL Group. The questionnaire consists of a descriptive system and a visual analogue scale. The descriptive system contains 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with 5 levels in each dimension.

EQ-5D-5L will be administered by qualified research personnel via the telephone during monthly telephone visits and within the visit window prior to clinic visits (but not in clinic).

10.2.2. Zarit Burden Interview

The ZBI is a 22-item self-reported measurement of caregiver burden. The caregiver responds to each item regarding the impact of the subject's disability on their life using a 5-point scale from 0 (Never) to 4 (Nearly Always). The total minimal score is 0 and the maximum score is 88, with higher scores signifying increased burden. The ZBI has been used in several studies to assess burden in caregivers of subjects with ALS.

The ZBI must be administered to the same caregiver throughout the subject's study participation. "Caregiver" is defined as the family member who lives with the subject, or individual who spends the most time providing physical and/or emotional care to the subject. The ZBI should not be administered by third party home care support staff. If the subject is not actively being assisted by a caregiver at baseline, ZBI will be administered to the subject's anticipated caregiver. If the subject does not have an anticipated caregiver/relative at baseline, ZBI administration will begin when/if the subject starts requiring a caregiver.

The ZBI will be administered by qualified research personnel via the telephone during monthly telephone visits and within the visit window of clinic visits (but not in clinic).

10.2.3. Slow Vital Capacity—Home

As outlined in Section 10.1.2.1, slow vital capacity is a pulmonary function test measured during spirometry that reflects the maximum amount of air that can be exhaled slowly. The %SVC is the percentage of the predicted SVC value based on age, sex, and height. Slow vital capacity has been shown to closely correlate with forced vital capacity and is a predictor of functional loss in ALS.

Slow vital capacity will be conducted once per week at home on a dosing day (with the exception of visit 2b) with a handheld spirometer. Slow vital capacity measured at subject's home will be collected via the GoSpiro device and transmitted to a provisioned device via Bluetooth radio. The data stored on the device is then sent to the CarePortal (data platform) via Wi-Fi or cellular transmission. The subject and/or caregiver will receive training from a research nurse or other research personnel on the use of the spirometer for home use.

10.2.4. Neurofilaments

Neurofilaments are intermediate filaments and structural proteins of neurons. The most commonly- assessed neurofilament subunits in clinical trials are NfL and pNfH. Neurofilament levels in serum and cerebral spinal fluid are reflective of neuronal injury and both NfL and pNfH have been shown to correlate with extent of clinical upper and lower MN involvement in subjects with ALS.

In this study, neurofilaments will be assessed with a blood sample.

10.2.5. Electrical Impedance Myography

Electrical impedance myography is a noninvasive, electrophysiological technique that has been shown to correlate with ALS disease progression. In this assessment, a high frequency, low-intensity electrical current is applied to a limb with the device and the resulting voltages are measured in the muscle. Changes in muscle structure such as atrophy, are detected as a change in impedance.

Electrical impedance myography measurements will be performed bilaterally on the following muscles: quadriceps, tibialis anterior, gastrocnemius, wrist extensor compartment, biceps, and deltoids.

Only select investigational sites will be chosen to perform this assessment on their subjects. Electrical impedance myography will be completed prior to HHD.

11. SAFETY ASSESSMENTS

11.1. Safety Parameters

11.1.1. Demographic/Medical History

Medical history will be recorded at screening. Investigators should document the occurrence, signs, and symptoms of the subject's pre-existing conditions, including all prior significant illnesses, up to and including 1 year before screening. Additional preexisting conditions, present at the time when informed consent is given, up to the time of first dosing, are to be regarded as concomitant. Medical history will include alcohol consumption and smoking history, if applicable. Information regarding genetic markers, identified to be linked to ALS, will also be collected, if available (Section 11.1.10).

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF in accordance with Section 11.5.

Additionally, demographic data will be collected for all subjects, as allowed per applicable regulations.

11.1.2. Vital Signs

Vital signs (body temperature, respiration rate, heart rate, and systolic and diastolic blood pressure measurements) will be evaluated at the visits indicated in the schedule of assessments tables (Table 2, Table 3, and Table 8). All vital signs will be measured after the subject has been resting in a sitting position for at least 5 minutes, except when they are supine or semireclined because of study procedures and/or AEs, or if deemed necessary by the investigator. Blood pressure measurements are to be taken in the same arm for the duration of the study.

Vital sign measurements will be repeated, if clinically significant or if machine/equipment errors occur. Out-of-range blood pressure, respiratory rate, or heart rate measurements will be repeated, at the investigator's discretion. Any confirmed, clinically significant vital signs measurements must be recorded as AEs.

When investigational product is administered at the clinic, vital signs will be measured within 2 hours preinfusion and at 30 minutes (±5 minutes) postdose.

11.1.3. Electrocardiogram

All 12-lead electrocardiograms (ECGs) will be measured once, prior to dosing (if applicable), at the time points outlined in the schedule of assessments (Table 2, Table 3, and Table 8). The ECG will be taken following resting in the supine position for at least10 minutes in a quiet environment and prior to any blood sampling procedures. The ECGs will be classified as normal, having a not clinically significant abnormality, or having a clinically significant abnormality. In addition, ECG parameters of ventricular rate, PR interval, QRS duration, and QT internal (uncorrected and corrected using Fridericia's method) will be reviewed for ongoing safety.

11.1.4. Weight and Height

Body weight and height (both assessed without shoes on) will be recorded as outlined in the schedule of assessments (see Table 2, Table 3, and Table 8).

11.1.5. Physical Examination

All full physical examinations, performed by the investigator or designee, will include, at a minimum, assessment of the following: general, head, ears, eyes, nose, throat, dentition, thyroid (endocrine), heart, chest, lungs, abdomen, skin, extremities, back/neck, musculoskeletal, and lymph nodes.

Brief physical examinations will include general appearance, heart, lungs, abdomen, extremities, and weight and are to be performed at all visits where a full physical examination does not occur.

Additional symptom-driven physical examinations may be performed at any time, as deemed necessary by the investigator.

See the schedule of assessments (Table 2, Table 3, and Table 8) for the details regarding which type of physical examination should be given at each visit.

11.1.6. Injection/Infusion Site/Pump Safety Assessment

Subjects (and/or caregivers) will be trained to administer the investigational product in the study.

Subjects will be instructed to notify the investigator or other study personnel if an injection/infusion site reaction occurs after self-administration of pegcetacoplan. All clinically significant findings related to injection/infusion procedures will be recorded as AEs.

11.1.7. C-SSRS

The C-SSRS is a measure used to identify and assess individuals at risk for suicide.
The questionnaire will assess suicidal thoughts and actions over the subject's lifetime, prior 6 months from screening and baseline, and changes from clinic visits. Questions are phrased for use in an interview format but can be completed as a self-report measure if necessary.
The C-SSRS measures 4 constructs: the severity of ideation, the intensity of ideation, behavior, and lethality and is made up of 10 categories. The outcome of the C-SSRS is a numerical score obtained from the aforementioned categories.

11.1.8. Laboratory Assessments

Laboratory assessment samples (Table 4) are to be obtained at designated visits as detailed in the schedule of assessments tables (Table 2, Table 3, and Table 8).

Labs will include, but will not be limited to, the following:

Table 4: Laboratory Assessments

Hematology	Serum Chemistry	Urine Studies
Hb Hematocrit Platelet count RBC count WBC count with differential	Albumin ALT ALP AST Bicarbonate Bilirubin (total, direct, and indirect) BUN Calcium Chloride Creatinine Creatine kinase Estimated glomerular filtration rate (using CKD-EPI formula) GGT Glucose HDL LDL Phosphorus Potassium Sodium Triglycerides Total cholesterol Total protein Uric acid	Urinalysis • Blood • Bilirubin • Glucose • Ketones • Leukocyte esterase • Microscopic examination of urine sediment, including for presence of RBCs, WBCs, and casts, will be performed on all urinalyses • Nitrite • pH • Pregnancy, when applicable • Protein • Specific gravity • Urobilinogen
Neurofilaments	**Additional**	
NfL pNfH	FSH (postmenopausal women) HBsAg HCV Serum pregnancy test Complement activation tests: (C3, AH50, and CH50) Anti–pegcetacoplan peptide antibody and anti-PEG antibody	

Abbreviations: AH50 = 50% alternative hemolytic complement pathway activity; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CH50 = 50% classical hemolytic complement pathway activity; CKD-EPI = Chronic Kidney Disease–Epidemiology Collaboration; FSH = follicle-stimulating hormone; GGT = gamma-glutamyltransferase; Hb = hemoglobin; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HDL = high-density lipoproteins; LDL = low-density lipoproteins; NfL = neurofilament light chain; pNfH = phosphorylated neurofilament heavy chain; RBC = red blood cells; WBC = white blood cells.
Note: The use of silica reagents in coagulation panels should be avoided in subjects treated with pegcetacoplan due to possible interference resulting in artificially prolonged aPTTs. Please refer to the IB for more details.

Blood and urine samples will be analyzed at a central laboratory facility, as defined in the Laboratory Manual. Urine samples will be analyzed by dipstick and a microscopic analysis. All laboratory reports must be reviewed, signed, and dated by the investigator. A legible copy of all reports must be filed with both the subject's eCRF and medical record (source document) for that visit.

Clinically significant abnormal values occurring during the study will be followed up until repeat test results return to normal, stabilize, or are no longer clinically significant.

Table 5 shows the blood volumes collected for the study.

Table 5: Blood Volumes Collected

Assay	Number of collection time points	Approximate volume per time point* (mL)	Approximate sample volume over course of study (mL)
Chemistry	Screening: 1 Randomized treatment visits: 6 Open-label visits: 4 Open-label Long-Term Extension: 4	3.5 or 5.0 mL	52.5 – 75.0
HBsAg, HCV	Screening: 1	8.5	8.5
CH50	Randomized treatment visits: 6 Open-label visits 4 Open-label Long-Term Extension: 4	4.0	56.0
AH50	Randomized treatment visits: 6 Open-label visits: 4 Open-label Long-Term Extension: 4	4.0	56.0
NfL and pNfH	Randomized treatment visits: 6 Open-label visits: 4 Open-label Long-Term Extension: 4	5.0	70.0
Pharmacokinetics	Randomized treatment visits: 6 Open-label visits: 4 Open-label Long-Term Extension: 4	4.0	56.0
Anti–pegcetacoplan peptide and anti-PEG Ab	Randomized treatment visits: 6 Open-label visits: 4 Open-label Long-Term Extension: 4	4.0	56.0

Table 5: Blood Volumes Collected

Assay	Number of collection time points	Approximate volume per time point* (mL)	Approximate sample volume over course of study (mL)
Hematology	Screening: 1 Randomized treatment visits: 6 Open-label visits: 4 Open-label Long-Term Extension: 4	2.0	30.0
		Total	**385 – 407.5**

Abbreviations: Ab = antibody; AH50 = 50% alternative hemolytic complement pathway activity; CH50 = 50% classical hemolytic complement pathway activity; HBsAg = surface antigen of the hepatitis B virus; HCV = hepatitis C virus; NfL = neurofilament light chain; PEG = polyethylene glycol; pNfH = phosphorylated neurofilament heavy chain.

11.1.8.1. Pregnancy Screen

For WOCBP, a serum pregnancy test will be performed at screening. Subjects with a positive result will be excluded or discontinued from the study. A urine pregnancy test will also be performed starting at baseline and at all indicated visits in the schedule of assessments (Table 2, Table 3, and Table 8). Male subjects will be counseled to avoid donating semen during the time between the first screening and the final follow-up (core)/follow-up (open-label)/open-label, long-term extension), and early termination follow-up visit and for 90 days after their last dose of investigational product.

11.1.9. Anti–Pegcetacoplan Peptide Antibody and Anti-PEG Antibody Assessments

The proposed anti-drug antibodies (ADA) sampling schedule was established to capture the ADA signal at baseline, along with any potential early onset and the dynamic profile (transient or persistent) of antibody formation.

Samples that test positive will be characterized by an assay that will determine antibody titer and measure neutralizing capacity. Discontinued subjects will have ADA follow-up every 6 months from last dose until it can be determined that the subject's antibody levels are at baseline or that further testing is not needed.

Subjects will need to have ADA samples collected as outlined in the schedule of assessments (Table 2, Table 3, and Table 8).

11.1.10. Genetic Mutation(s) Results

Testing for genetic mutations is not performed as part of the study. However, subjects who have confirmed genetic mutations linked with ALS (eg, C9orf72, TARDBP, FUS, etc.) will be asked to provide this information, which will be documented as part of their medical history. Providing genetic mutations testing results is optional and a subject's decision to not provide this information does not preclude them from participating in the study, if eligible. Genetic mutation data will be used in analysis for correlation with outcomes.

11.1.11. COVID-19 Assessment

If a subject has been tested for COVID-19, the results, if available, will be documented via eCRF.

11.2. Adverse and Serious Adverse Events

11.2.1. Definitions

11.2.1.1. Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug related. An AE can, therefore, be any unfavorable and unintended sign, including a clinically significant abnormal laboratory finding, symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.

Adverse events can be spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation and will be recorded during the study at the investigational site. All identified AEs must be recorded and described on the appropriate AE or SAE page of the eCRF.

Fluctuating or nonsignificant changes in laboratory values do not necessarily qualify for AE reporting. If changes in laboratory values are assessed as clinically significant and/or lead to discontinuation of administration of investigational product, they should be reported as an AE. If these laboratory values are linked to a diagnosis, only the diagnosis should be reported as an AE.

11.2.1.2. Unexpected Adverse Event

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Reference Safety Information section of the investigator brochure (IB) that is in effect at the time of event onset.

11.2.1.3. Serious Adverse Events

An SAE is any AE or suspected adverse reaction that, in the view of the investigator, results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Important medical events that may not result in death, be life threatening*, or require hospitalization may be considered serious when, according to appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in the above definition.

Examples of important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

**Life threatening* is defined as an AE or suspected adverse reaction that, in the view of either the investigator or sponsor, placed the subject at immediate risk of death as it occurred. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

All death events should be reported as the fatal outcome of an SAE, with the date and cause of death included. The medical event leading to the subject's death (eg, respiratory failure, pneumonia) should be reported as the SAE term. If no alternative cause of death is identified, "progression of ALS" may be reported as the event term if deemed medically appropriate by the investigator.

11.2.1.3.1. SAE Due to ALS

Serious events (including events related to efficacy endpoints) that are considered ALS-related should be reported as "not related" SAEs. "ALS" or "disease progression" should not be reported as event terms if a more precise term for the complication or actual cause of hospitalization/death (eg, respiratory failure) can be reported.

"Disease progression" is considered a worsening of a subject's ALS symptoms (weakness, spasticity, respiratory insufficiency, respiratory arrest, dysphasia). It may reflect an increase in the severity of the disease or an increase in symptoms.

Any event experienced by a subject which is solely regarded as part of disease progression and can be considered as a direct consequence of ALS, but does not result in death, should not be reported as an AE/SAE; examples include: respiratory insufficiency, dysphagia, respiratory failure, dysarthria, etc. However, if a subject should experience worsening of ALS-related disease symptoms that are not considered anticipated disease progression for that given subject, the investigator should report these findings as an AE. Examples of this might include: pneumonia, malnutrition, fall, or aspiration. If there is any uncertainty as to whether an event is due to anticipated disease progression, it should be reported as an AE.

11.3. Relationship to Investigational Product

The investigator will review each event and assess its relationship to investigational product treatment (not related, unlikely related, possibly related, or definitely related). The date and time of onset, time relationship to investigational product dosing, duration, and outcome (recovered/resolved, recovered/resolved with sequelae, recovering/resolving, not recovered/not resolved, fatal, or unknown) of each event will be noted.

Table 6 should be considered when evaluating the relationship of AEs/SAEs to study treatment.

Table 6: Definitions of Adverse Event Relatedness

Classification	Definition
DEFINITELY RELATED	Strong evidence of a causal relationship; the influence of other factors is unlikely
POSSIBLY RELATED	Some evidence of a causal relationship, but other factors may have caused or contributed to the event (eg, another illness or concomitant treatment)
UNLIKELY RELATED	A causal relationship is not a reasonable possibility, but it cannot be completely ruled out with the available evidence.
NOT RELATED	No evidence of a causal relationship

11.4. Severity of Events

The investigator will review each event and assess its severity. Note that severity is a measure of intensity, whereas seriousness is defined by the criteria in Section 11.2.1.2. An AE can be of severe intensity but not be considered serious.

Table 7 presents the severity definitions that should be considered when evaluating the severity of AEs and SAEs.

Table 7: Severity of Events

Severity	Definition/Description
Mild	Event results in mild or transient discomfort, not requiring intervention or treatment; does not limit or interfere with daily activities (eg, insomnia, mild headache).
Moderate	Event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment (eg, febrile illness requiring oral medication).
Severe	Event results in significant symptoms that prevents normal daily activities; may require hospitalization or invasive intervention (eg, anemia resulting in blood transfusion).

11.5. Recording Adverse Events

Adverse events and SAEs will be collected from the signing of the informed consent form (ICF) until one of the following occurs:

- follow-up (core)
- follow-up (open-label)
- follow-up (open-label, long-term extension)
- early termination follow-up (ETFU) visit, 6 weeks after the last dose of pegcetacoplan.

All SAEs will be followed until a final outcome of recovered, recovered with sequelae, or fatal, unless the subject withdraws consent or the investigator confirms that no additional information is available.

All SAEs that are suspected of being related to study treatment must be reported immediately to the sponsor if the investigator becomes aware of them, regardless of the time since the completion of the clinical trial.

Any events that occur prior to the start of dosing will be categorized as pretreatment events; events occurring after the start of dosing will be recorded as TEAEs (the start date of dosing and, therefore, categorization of the event will be dependent on randomization assignment).

For each AE, the investigator will evaluate and report the onset date (and time if applicable), resolution date (and time, if applicable), intensity, causality, action taken, seriousness criteria met (if applicable), and whether or not the subject discontinued the study as a result of the event.

If possible, the outcome of any AE resulting in permanent discontinuation or that was present at the end of the study should be reported, particularly if the AE was considered by the investigator to be related to the investigational product. Subjects experiencing AEs that cause interruption or

discontinuation of investigational product, or those experiencing AEs that are present at the follow-up (core)/follow-up (open-label)/follow-up (open-label, long-term extension)/ETFU visit should receive follow-up as appropriate.

All SAEs must be reported to the sponsor/Apellis Safety via eCRF immediately, without undue delay, under no circumstances later than 24 hours of becoming aware of the event, whether or not the event is deemed treatment-related. If the electronic data capture (EDC) system is not operational (or for paper-based studies), the site must complete the paper SAE form and email to PPD also immediately, without undue delay, under no circumstances later than 24 hours of becoming aware of the event. The reported information submitted as a paper SAE must be entered into the EDC system once it becomes operational.

Adverse events will be coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA). If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms.

11.6. Reporting Adverse Events

The sponsor has the responsibility to inform concerned health authorities, ethic committees, and investigators about SUSARs in line with GCP guidance and applicable regulatory requirements.

If required, specific SAEs should be reported to the concerned ethic committees in compliance with local requirements.

11.7. Pregnancy

Although pregnancy is not an AE, all pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) occurring with a female subject or the female partner of a male subject, must be followed to conclusion to determine their outcome and are considered immediately reportable events.

Any pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Apellis Safety within 24 hours of the Investigator becoming aware of the event. Pregnancies shall be reported on a Pregnancy Report Form, which must be signed and dated by the primary investigator and submitted via email to PPD

The investigator must follow the subject until completion of the pregnancy and must report the outcome of the pregnancy (eg, delivery, termination, etc.) and neonatal status up to 12 months postdelivery. An abnormal outcome is defined as the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. In the event of an abnormal outcome, an SAE must be reported using the SAE Report Form, as described in Section 11.4.

11.7.1. Acceptable Methods of Contraception

Approved methods of contraception include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral, intravaginal, or transdermal

- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral, injectable, or implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatments)
- Male condom with or without spermicide (for male study subjects with female partners of childbearing potential only)

Not all methods of contraception may be available in all of the countries in which the study is being conducted.

Note: Sexual abstinence is only accepted when it is the preferred and usual lifestyle of the subject.

Subjects must agree to use an approved method of contraception during the study and for 90 days after their last dose of investigational product.

11.8. Abuse, Misuse, Overdose, and Medication Error

Occurrences of events of drug abuse, drug misuse, drug overdose, and medication error must be reported to the sponsor.

Abuse of a medicinal product: Persistent or sporadic, intentional, excessive use of medicinal products, which is accompanied by harmful physical or psychological effects.

Misuse: Intentional and inappropriate use of a medicinal product not in accordance with the prescribed or authorized dose, route of administration, and/or intended indication(s), or not within the legal status of its supply.

Overdose: Administration of a quantity of study drug per administration or per day, which is above the assigned dose.

Medication Error: An error made in prescribing, dispensing, administration, and/or use of the study drug. Medication errors are reportable to the sponsor as defined below:

- The dispensing, administration, and/or use of unassigned study drug.
- The administration and/or use of an expired study drug.

All AEs or SAEs associated with drug abuse, drug misuse, drug overdose, or medication error must be reported as appropriate.

12. STATISTICS

A formal statistical analysis plan (SAP) will be developed and finalized prior to locking the database. The full details of data presentations and analyses will be provided in the SAP. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and included in the SAP. Any deviations from the final SAP or from what is outlined in the protocol will be discussed in the final study report.

12.1. Determination of Sample Size

A sample size of 180 randomized subjects (2:1 allocation ratio to pegcetacoplan:placebo) would provide approximately 86% power to detect a significant difference (33%) in the primary outcome (CAFS score) between the 2 treatment groups at a 2-sided alpha of 5% with 75% power to detect a 35% improvement in the rate of decline in the ALSFRS-R score and 39% power to detect a 10% improvement in survival.

The estimates were based on the following assumptions:

- Mean monthly rate of decline in ALSFRS-R is 1 unit for the placebo treatment group and pooled standard deviation of 0.84 units/month
- 52-week mortality rate with placebo at 20%
- Approximately 40-week subject enrollment period
- 52 weeks of follow-up for assessing survival outcomes after each subject enrolls
- 52 weeks of follow-up for assessing functional outcomes after each subject enrolls

Subjects will be randomized and stratified by location of first muscle weakness (limb or bulbar), riluzole and edaravone use.

Approximately 228 subjects (152:76) will be randomized to account for an anticipated 20% of randomized subjects prematurely discontinuing the study without providing a postbaseline ALSFRS-R measurement.

12.2. Analysis Set

12.2.1. Screened Set

The screened set will include all subjects who provide written informed consent. This set will be used only for the purpose of describing subject disposition.

12.2.2. Safety Set

The safety set will include all subjects who receive at least 1 dose of any double-blind investigational product. Subjects will be analyzed according to the treatment they received.

12.2.3. Intent-to-Treat Set

The intent-to-treat (ITT) set will include all randomized subjects who receive at least one dose of randomized treatment (pegcetacoplan or placebo). Subjects will be analyzed according to their assigned treatment, regardless of the treatment actually received.

12.2.4. Modified Intent-to-Treat Set

The modified intent-to-treat (mITT) set will include all subjects in the ITT set who have at least 1 postbaseline efficacy assessment.

12.2.5. Per-Protocol Set

The per-protocol (PP) set will include all subjects in the mITT set who have not violated any inclusion or exclusion criteria and/or deviated from the protocol in a way that could influence their efficacy assessment. Decisions concerning the exclusion of subjects from the PP analysis set will be made and documented prior to database lock.

12.2.6. Pharmacokinetic Set

The PK set will include all subjects in the safety set for whom the PK data are considered sufficient and interpretable.

12.2.7. Pharmacodynamic Set

The pharmacodynamic (PD) set will include all subjects in the safety set for whom the PD data are considered sufficient and interpretable.

12.2.8. Data Review for Analysis Set

After all the data have been verified/coded/entered into the database, a review will be performed. The purpose of this review will be to define the analysis populations. The review will also check the quality of the data, identifying outliers, and make decisions on how to deal with any data issues (eg, missing values, withdrawals, protocol deviations). After the preanalysis review, resolution of all issues and documentation of all decisions, the database will be locked.

12.3. Efficacy Analysis

12.3.1. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the CAFS score at week 52.

The CAFS score will be developed as follows:

- The functional and survival outcomes are determined for every subject in the pegcetacoplan and placebo treatment groups.
- All pairwise comparisons are performed and the scores of +1, 0, or –1 are assigned to a subject based on each pairwise comparison. The scores are assigned as follows:
  - If both subjects are deceased at the last point of contact, the subject with a longer survival receives a score of +1 and the other subject receives a score of –1.
  - If 1 subject is deceased and the other subject is alive at the last point of contact, the surviving subject receives a score of +1 and the deceased subject receives a score of –1.

- If both subjects are living at the last point of contact, the subject with a smaller change from baseline in the functional endpoint at the last point of contact receives a score of +1 and the other subject receives a score of –1.

The scores from each pairwise comparison are added up for each subject.

The CAFS ranks score will be summarized by treatment group using descriptive statistics.

The CAFS ranks score will be analyzed using analysis of covariance (ANCOVA) model with treatment as a fixed effect, adjusted for baseline ALSFRS-R total score, duration from symptoms onset to the first dose of study treatment, and stratification factors.

The primary efficacy analysis for the primary endpoint (CAFS) will be conducted on the mITT set and will be repeated for the PP set to evaluate the robustness of the results from the primary analysis.

Other sensitivity analyses will be explored, and details will be provided in the SAP.

12.3.2. Analysis of Secondary Efficacy Endpoints

To preserve the Type 1 error, a fixed-sequence testing strategy will be used. The ordering of the secondary endpoints in this testing strategy will match the order in which they are presented in the secondary endpoint section.

Absolute values and changes from baseline in secondary efficacy endpoints (ALSFRS-R, in-clinic percentage of predicted SVC, HHD, and ALSAQ-40) will be summarized, using descriptive statistics, by treatment and visit. Baseline will be taken as the measurement closest, but prior, to the first dose of investigational product.

Changes from baseline in secondary efficacy outcomes (ALSFRS-R, in-clinic percentage of predicted SVC, HHD, and ALSAQ-40) will be summarized by treatment group and analyzed using a mixed model for repeated measures. The model will include fixed categorical effects for treatment, study visit, and the study visit-by-treatment interaction, as well as the continuous, fixed covariate of baseline and the visit-by-baseline interaction term, time from symptoms onset to the first dose of investigational product, and the randomization stratification factors. Initially an unstructured covariance matrix will be investigated. If this analysis fails to converge, other covariance structures will be used; details will be provided in the SAP. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

For the secondary endpoints of time to death and time to death, permanent tracheostomy, or permanent assisted ventilation, Kaplan-Meier analysis will be used to describe the survival data. The comparison of the survival time between treatment groups will be provided using a Cox proportional hazard model adjusting for the same covariates used in CAFS ANCOVA. For subjects who did not experience an event, the time to event will be censored at the last observation date for the Kaplan-Meier plot. Subjects who are lost to follow-up or who discontinued the study will be censored at the date of discontinuation or lost to follow-up date.

12.3.3. Analysis of Exploratory Efficacy Endpoints

Absolute values and changes from baseline in exploratory endpoints will be summarized, using descriptive statistics, by treatment and visit:

- EQ-5D-5L, ZBI, NfL, pNfH, and EIM at weeks 52, 104, and 156
- At-home %SVC at week 52 and week 104
- ALSFRS-R, %SVC (in-clinic), HHD, and ALSAQ-40 at week 156

Baseline will be taken as the measurement closest to but prior to randomization. Time to percutaneous endoscopic gastrostomy tube placement up to weeks 52, 104, and 156 will be computed and summarized by treatment group, as will time to death, permanent tracheostomy, or permanent assisted ventilation up to week 156; and time to death up to week 156. Additional analyses might be performed for these endpoints and will be detailed in SAP.

12.4. Safety Analysis

All safety analyses will be summarized for the safety set.

Adverse events will be coded using MedDRA. All AEs, including TEAEs, will be summarized by System Organ Class, Preferred Term, treatment group for number of subjects, and proportion reporting the event. A similar summary will be produced for SAEs, AEs leading to termination, severe AEs, and AEs related to the investigational product. The intensity of AEs and the relationship to investigational product will be summarized for each System Organ Class and Preferred Term by treatment group.

Withdrawals due to AEs will be summarized for each body system and Preferred Term by treatment group.

Treatment-emergent adverse events are defined as those AEs that develop or worsen after the first dose of study medication until the study follow-up visit or the ETFU visit.

The AE summaries will be presented across all subjects. All AEs will be listed by subject, along with information regarding onset, duration, relationship, and severity to investigational product, action taken with investigational product, treatment of event, and outcome. In addition, the number and incidence of rejection episodes and graft loss will be tabulated.

Laboratory assessment and anti–pegcetacoplan peptide antibody/anti-PEG antibody test results will be summarized by treatment group using appropriate descriptive statistics.

Changes from baseline in clinical laboratory tests will be summarized, using descriptive statistics, by visit and nominal time postdose. Baseline will be taken as the measurement closest, but prior, to randomization. Out-of-range values will be flagged in data listings.

Changes from baseline in vital signs will be summarized, using descriptive statistics, by treatment, visit, and nominal time postdose. Baseline will be taken as the measurement closest, but prior, to randomization.

Values of potential clinical significance will be flagged in listings and summarized by treatment.

Changes in physical examinations will be described in a data listing.

Positive responses (Yes) to the C-SSRS will be summarized by treatment.

12.5. Pharmacokinetic Analysis

The PK concentrations will be evaluated using the PK set.

Concentrations will be summarized, using descriptive statistics, over time, in the randomized treatment group (pegcetacoplan group).

Individual subject concentration-time data will be plotted against actual sampling time. Median profiles of the concentration-time data, using nominal sampling times, will also be presented. Both linear-linear and linear-log plots will be presented.

12.6. Pharmacodynamic Analysis

The PD endpoints will be evaluated using the PD set.

Absolute values, changes from baseline, and percent changes from baseline will be summarized using descriptive statistics, over time by treatment group.

Individual subject time profiles will be plotted against actual sampling time. Median profiles, over time, using nominal sampling time, will also be presented.

The PD endpoints will be compared between treatment groups using mixed effect repeated measures analyses.

12.7. Other Analyses

Demographics, baseline characteristics, concomitant medication, medical history, and study medication exposure will be summarized by treatment group.

World Health Organization and MedDRA coding dictionaries will be used for the concomitant medications and medical histories, respectively.

12.8. Interim Analysis

No interim analysis is planned.

12.9. Data Monitoring Committee

A DMC will review cumulative safety/tolerability data (eg, physical examinations, vital signs, clinical laboratory tests, and AEs). The DMC will also review data related to efficacy for the week 52 analysis and final analysis. The DMC will have the responsibility to conduct a thorough safety assessment at regular predefined intervals during the treatment period of the study.

DMC meetings will be held according to the schedule in the DMC charter. An *ad hoc* DMC data review may be recommended by the DMC or requested by the sponsor at any time during the study. The first DMC meeting will be held after 20 subjects have completed visit 3 (week 4).

The remit, roles, and responsibilities of the DMC will be specified in a separate DMC charter.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Before an investigational site can enter a subject into the study, a representative of the sponsor will contact the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Apellis or its representatives. This will be documented in a Clinical Study Agreement between Apellis and the investigator.

Subject information will be captured and managed by study sites on eCRFs by a web-based EDC tool developed and supported by the contract research organization (CRO) assisting with the conduct of the study and configured by the sponsor. It is recommended that data be entered into the EDC system within 5 business days, including batched records and records with source documents.

Data management will be performed by the CRO according to their standard operating procedures. The data management plan will be approved by the sponsor.

During the study, a monitor from Apellis or representative will have regular contacts with the investigational site, for, but not limited to, the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm all participant data relating to the study will be recorded on printed or electronic case report form (CRF) unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF. Any subject records or data sets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- Ensure that the investigator must maintain accurate documentation (source data) that supports the information entered in the CRF
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- The sponsor/designee is responsible for the data management of this study, including quality checking of the data
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts). Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.
- Record and report any protocol deviations not previously sent to Apellis.

- Confirm that AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Apellis and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC.

The monitor will be available between visits if the investigator(s) or other staff need(s) information or advice.

13.1. Audits and Inspections

Authorized representatives of Apellis, a regulatory authority, an IEC or IRB may visit the site to perform audits or inspections, including source data verification. The purpose of an Apellis audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, local laws, GCP guidelines of the International Council for Harmonisation, and any applicable regulatory requirements. The investigator should contact Apellis immediately if contacted by a regulatory agency about an inspection.

13.2. Institutional Review Board/Independent Ethics Committee

The principal investigator must obtain IRB/IEC approval for the investigational protocol. Initial IRB approval, and all materials approved by the IRB for this study including the subject consent form and recruitment materials must be maintained by the investigator and made available for inspection.

14. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, Apellis, and/or authorized representatives of Apellis, may conduct a quality assurance audit(s) or pre–agency inspection visit(s). Please see Section 13.1 for more details regarding the audit process.

15. ETHICS

15.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to Apellis before he/she can enroll any subject into the study.

The principal investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The principal investigator is also responsible for providing the IRB with reports of any reportable serious adverse investigational product reactions from any other study conducted with the investigational product. Apellis will provide this information to the principal investigator.

Progress reports and notifications of serious adverse investigational product reactions will be provided to the IRB or IEC according to local regulations and guidelines.

15.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable national laws and regulations

15.3. Written Informed Consent

The principal investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, and possible risks and benefits of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject is to be given the opportunity to ask questions and allowed time to consider the information provided.

The subjects must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the subject, who will be required to give consent for their data to be used as described in the informed consent.

The subjects must be informed that their medical records may be examined by clinical quality assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The subject's signed and dated informed consent must be obtained before conducting any study procedures. The caregiver's signed and dated informed consent must be obtained before conducting any caregiver-related study procedures.

The principal investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject and caregiver, respectively.

16. DATA HANDLING AND RECORDKEEPING

16.1. Inspection of Records

Apellis will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the investigational product storage area, investigational product stocks, investigational product accountability records, subject charts and study source documents, and other records relative to study conduct.

16.2. Retention of Records

The principal investigator must maintain all documentation relating to the study for a period of 25 years end of the clinical trial. Medical files of subjects shall be archived in accordance with national law. If it becomes necessary for Apellis or the regulatory authority to review any documentation relating to the study, the investigator must permit access to such records.

17. PUBLICATION POLICY

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters), generated by the investigator and others performing the clinical study, will be subject to the terms of a clinical study agreement that will be agreed between the institution and the sponsor or its designee. With respect to such rights, the sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, investigators will be required to assign all such inventions, either to their institution or directly to the sponsor or its designee, as will be set forth in the clinical study agreement.

18. LIST OF REFERENCES

Abe K, Aoki M, Tsuji S, et al. Safety and efficacy of edaravone in well-defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2017;16(7):505-512.

Brettschneider J, Libon DJ, Toledo JB, et al. Migroglial activation and TDP-43 pathology correlate with executive dysfunction in amyotrophic lateral sclerosis. *Acta Neuropathol*. 2012;123(3):395-407.

Brooks B, Miller R, Swash M, Munsat T, World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord*. 2000;1(5):293-299.

Carpanini SM, Torvell M, Morgan BP. Therapeutic inhibition of the complement system in diseases of the central nervous system. *Front Immunol*. 2019;10:362.

Chen X, Feng W, Huang R, et al. Evidence for peripheral immune activation in amyotrophic lateral sclerosis. *J Neurol Sci*. 2014;347(1-2):90-95.

Chiu IM, Morimoto ET, Goodarzi H, et al. A neurodegeneration-specific gene-expression signature of acutely isolated microglia from an amyotrophic lateral sclerosis mouse model. *Cell Rep*. 2013;4(2):385-401.

Chiu IM, Phatnani H, Kuligowski M, et al. Activation of innate and humoral immunity in the peripheral nervous system of ALS transgenic mice. *Proc Nat Acad Sci*. 2009;106(49):20960-20965.

de Castro C, Weitz I, Deschatelets P, et al. Treatment with APL-2 in patients who remain anemic despite treatment with Soliris® leads to increases in hemoglobin, transfusion avoidance and broad control of hemolysis [abstract]. In: Brazilian Congress of Hematology, Hemotherapy and Cell Therapy - HEMO 2018 meeting program; 31 Oct-03 Nov 2018; São Paulo, Brazil; 2018:Abstract 161.

Edaravone [package insert]. Jersey City, NJ: MT Pharma America, Inc.; 2017.

Ehrhart J, Smith AJ, Kuzmin-Nichols N, et al. Humoral factors in ALS patients during disease progression. *J Neuroinflammation*. 2015;12:127.

El Idrissi NB, Bosch S, Ramaglia V, Aronica E, Baas F, Troost D. Complement activation at the motor end-plates in amyotrophic lateral sclerosis. *J Neuroinflammation*. 2016;13:72.

Fischer LR, Culver DG, Tennant P, et al. Amyotrophic lateral sclerosis is a distal axonopathy: evidence in mice and man. *Exp Neurol*. 2004;185(2):232-240.

Ganesalingam J, An J, Shaw CE, Shaw G, Lacomis D, Bowser R. Combination of neurofilament heavy chain and complement C3 as CSF biomarkers for ALS. *J Neurochem*. 2011;117(3):528-537.

Garbuzova-Davis S, Sanberg PR. Blood-CNS barrier impairment in ALS patients versus an animal model. *Front Cell Neurosci*. 2014;8(21):1-9.

Gertz M, Roman E, Fattizzo B, et al. Inhibition of C3 with APL-2 controls haemolysis and increases haemoglobin levels in subjects with autoimmune haemolytic anemia (AIHA). Paper presented at: 24th Congress of the European Haematology Association. 13-16 June 2019; Amsterdam, Netherlands.

Goldknopf IL, Sheta EA, Bryson J, et al. Complement C3c and related protein biomarkers in amyotrophic lateral sclerosis and Parkinson's disease. *Biochem Biophys Res Commun*. 2006;342(4):1034-1039.

Kawamata T, Akiyama H, Yamada T, McGeer PL. Immunologic reactions in amyotrophic lateral sclerosis brain and spinal cord tissue. *Am J Path*. 1992;140(3):691.

Kettenmann H, Kirchhoff F, Verkhratsky A. Microglia: new roles for the synaptic stripper. *Neuron*. 2013;77(1):10-18.

Kolev M, Le Friec G, Kemper C. Complement—tapping into new sites and effector systems. *Nat Rev Immunol*. 2014;14(12):811-820.

Lee JD, Kumar V, Fung JN, Ruitenberg MJ, Noakes PG, Woodruff TM. Pharmacological inhibition of complement C5a-C5a$_1$ receptor signaling ameliorates disease pathology in the hSOD1^{G93A} mouse model of amyotrophic lateral sclerosis. *Br J Pharmacol*. 2017;174(8):689-699.

Lee JD, Levin SC, Willis EF, Li R, Woodruff TM, Noakes PG. Complement components are upregulated and correlate with disease progression in the TDP-43^{Q331K} mouse model of amyotrophic lateral sclerosis. *J Neuroinflammation*. 2018;15:171.

Liao B, Zhao W, Beers DR, Henkel JS, Appel SH. Transformation from a neuroprotective to a neurotoxic microglial phenotype in a mouse model of ALS. *Exp Neurol*. 2012;237(1):147-152.

Liao DS, Grossi FV, El Mehdi D, et al. Complement C3 inhibitor pegcetacoplan for geographic atrophy secondary to age-related macular degeneration. *Ophthalmology*. 2020;127(2):186-195.

Liddelow SA, Guttenplan KA, Clarke LE, et al. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature*. 2017;541(7638):481-487.

Miller RG, Mitchell JD, Lyon M, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). *Cochrane Database Syst Rev*. 2002;CD001447.

Murdock BJ, Zhou T, Kashlan SR, Little RJ, Goutman SA, Feldman EL. Correlation of peripheral immunity with rapid amyotrophic lateral sclerosis progression. *JAMA Neurol*. 2017;74(12):1446-1454.

Noto Y, Kanai K, Misawa S, et al. Distal motor axonal dysfunction in amyotrophic lateral sclerosis. *J Neurol Sci*. 2011;302(1-2):58-62.

Ravits JM, La Spada AR. ALS motor phenotype heterogeneity, focality, and spread: deconstructing motor neuron degeneration. *Neurology*. 2009;73(10):805-811.

Relyvrio [package insert]. Cambridge, MA: Amylyx Pharmaceuticals, Inc.;2022

Riluzole [package insert]. Cary, NC: Covis Pharmaceuticals Inc.;2016.

Sta M, Sylva-Steenland R, Casula M, et al. Innate and adaptive immunity in amyotrophic lateral sclerosis: evidence of complement activation. *Neurobiol Dis*. 2011;42(3):211-220.

Turner MR, Cagnin A, Turkheimer FE, Miller CC, Shaw CE, Brooks DJ, et al. Evidence of widespread cerebral microglial activation in amyotrophic lateral sclerosis: an [11C] (R)-PK11195 positron emission tomography study. *Neurobiol Dis*. 2004;15(3):601-609.

van den Bos MA, Geevasinga N, Higashihara M, Menon P, Vucic S. Pathophysiology and diagnosis of ALS: insights from advances in neurophysiological techniques. *Int J Mol Sci*. 2019;20(11):2818.

Wang H, Ricklin D, Lambris JD. Complement-activation fragment C4a mediates effector functions by binding as untethered agonist to protease-activated receptors 1 and 4. *Proc Natl Acad Sci USA*. 2017;114(41):10948-10953.

Wong RS, Pullon HW, Deschatelets P, et al. Inhibition of C3 with APL-2 results in normalisation of markers of intravascular and extravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH). *Blood*. 2018;132:2314.