STATISTICAL ANALYSIS PLAN

PEGCETACOPLAN
PHASE 2

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)

PROTOCOL IDENTIFIER: APL2-ALS-206

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REVISION HISTORY

Version	Issue Date	Summary of Changes	Rationale
1.0	06 September 2022	Not applicable	
2.0	31 March 2023	Added MI-based CAFS in Section 6.4.2.1	Response to FDA question
		Added CAFS analysis for SVC (Section 6.5.2.2.1) and HHD (Section 6.5.3.2.1)	Response to FDA question
		Added analysis plan for OLP in Section 6.7	To prespecify analysis for OLP
		Changed stratification variable in the model and added baseline Log NfL in model as a covariate	To fit model better and adjust for prognostic factor
		Updated subgroup model; Added 2 subgroups; Added one AE summary by ADA response	Statistical consideration
		Adding change of NfL at week 52 to the list of secondary endpoints and positioned it at the last of the testing hierarchy	Update per understanding of increasing importance of NfL
		Changed pNfH model to ANCOVA	Longitudinal data not available
		Added clarification languages	

APPROVAL SIGNATURES

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ABBREVIATIONS

ADA	antidrug antibodies
ADAY	analysis study day
AE	adverse event
ALP	alkaline phosphatase
ALS	amyotrophic lateral sclerosis
ALSAQ-40	ALS Assessment Questionnaire
ALSFRS	ALS Functional Rating Scale
ALSFRS-R	Revised ALS Functional Rating Scale
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AR	autoregressive
AST	aspartate aminotransferase
BLQ	below the limit of quantification
BUN	blood urea nitrogen
CAFS	Combined Assessment of Function and Survival
CI	confidence interval
CKD-EPI	Chronic Kidney Disease–Epidemiology Collaboration
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	data monitoring committee
DPS	diaphragm pacing system
ECG	electrocardiogram
EIM	electrical impedance myography
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HDL	high-density lipoproteins
HHD	handheld dynamometry
ICE	intercurrent event
ITT	intent-to-treat
LDL	low-density lipoproteins
LLN	lower limit of normal
LS	least squares
MAR	missing at random
MedDRA	medical dictionary for regulatory activities
MI	multiple imputation
mITT	modified intent-to-treat
MMRM	mixed model for repeated measures
MNAR	missing not at random
NfL	neurofilament light chain
PCS	potentially clinically significant

PD	pharmacodynamic
PEG	polyethylene glycol
PK	pharmacokinetic
pNfH	phosphorylated neurofilament heavy chain
PP	per protocol
PT	Preferred Term
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SE	standard error
SI	système international
SOC	System Organ Class
SVC	slow vital capacity
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VAS	visual analogue scale
WBC	white blood cell
WHO	World Health Organization
ZBI	Zarit Burden Interview

1. INTRODUCTION

1.1. Background

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

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy, safety, and pharmacokinetic (PK) data as described in the final study protocol dated 13 January 2023 incorporating the most recent Amendment 6. Specifications for tables, figures, and listings are contained in a separate document.

The current SAP describes analysis of randomized controlled period (ie, up to week 52). An outline for efficacy analyses for the open-label periods is provided in Section 6.7. The details for analysis of the open-label periods will be provided in a separate SAP.

1.2. Exceptional Circumstances

Two exceptional circumstances, which require special consideration, occurred during the conduct of this trial:

- COVID-19 pandemic
- war in Ukraine.

The war in Ukraine had a number of impacts on study conduct, including discontinuation of subjects from treatment and study follow-up, transfer of affected subjects to sites outside Ukraine, and data not entered in the database.

The handling of these circumstances with respect to the study's estimands is described in Section 6.3 and Table 1 for the primary and secondary endpoints, and in Section 6.6 and Table 3 for the exploratory endpoints, and a supplemental analysis of the primary endpoint accounting for treatment interruptions due to COVID-19 is described in Section 6.4.3.2.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

The primary objective of the study is 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)

2.1.2. 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 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

2.2. Endpoints

2.2.1. Primary Endpoint

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

2.2.2. Secondary 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 in serum neurofilament light chain (NfL) 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

2.2.3. 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)

2.2.4. Exploratory Endpoints

The exploratory endpoints are as follows:

- CAFS rank score (joint-rank score) at Week 104 and Week 156
- Change from baseline in European Quality of Life–5 Dimensions–5 Level (EQ5D5L) 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 in %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 104, and Week 156
- Change from baseline in serum phosphorylated neurofilament heavy chain (pNfH) at Week 52, Week 104, and Week 156
- 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 polyethylene glycol (PEG) moiety and/or 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

3. STUDY DESIGN

3.1. General Description

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 diagnosis of sporadic ALS.

The planned length of participation in the study for each subject is a maximum of approximately 116 weeks. This study will consist of 5 parts (as shown in Figure 1):

- 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.

Figure 1: Study Design

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. Subjects randomized to pegcetacoplan will receive SC pegcetacoplan 1080 mg twice per week for 52 weeks. 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 4, all subjects will discontinue the investigational product (blinded pegcetacoplan/placebo or open-label pegcetacoplan) and complete a follow-up visit 6 weeks later, unless they enter the sponsor-planned long-term extension protocol.

3.2. Randomization

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

Access to randomization codes will be strictly controlled as mandated in the study's Blinding Management Plan. The randomization codes will not be made available to the sponsor, subjects, or clinic staff responsible for the monitoring and evaluation of efficacy or 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 (1) location of onset and (2) riluzole and edaravone use will ensure balance between treatment groups by the respective stratification factors. Fixed block randomization will be used to ensure that approximately equal number of subjects are assigned to each treatment within strata.

3.3. Blinding

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. Access to unblinded study treatment information will be strictly limited as mandated in the study's Blinding Management Plan; any individuals who are unblinded 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.

Both pegcetacoplan and placebo are supplied in sterile solutions of 10 mM acetate buffer, pH 5.0, containing 4.1% sorbitol in stoppered 20-cc glass vials.

In the OLP all participants will receive pegcetacoplan. However, to limit bias in data analyses for registrational purpose, a blinded analysis team will be established to conduct the analyses of OLP.

3.4. Sample Size and Power Considerations

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 use of riluzole and edaravone (neither, riluzole, edaravone, or both riluzole and edaravone).

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.

3.5. Analysis Timing and Unblinding

The analysis of data from the randomized treatment period of the study will be performed when all subjects have completed the randomized treatment period or discontinued early and all corresponding data have been entered into the database, reviewed, cleaned, and finalized, and the Week 52 analysis database locked. At that time, the sponsor analysis team will be unblinded to the treatment codes, and the primary analysis will be performed; this will include all efficacy and safety analyses for the randomized treatment period (ie, week 52 endpoints).

The analysis of the data from the open-label treatment period and open-label long-term extension period will be performed once all subjects have completed the open-label treatment period or open-label long-term extension period or discontinued early and all corresponding data have

been entered into the database, reviewed, cleaned, and finalized, and the analysis database locked.

4. STATISTICAL ANALYSIS SETS

4.1. 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.

4.2. Safety Set

The safety set will include all subjects who receive at least one dose of randomized treatment (pegcetacoplan or placebo). Subjects will be analyzed according to the treatment they actually received. Subjects will be presented under the pegcetacoplan group if they received at least one injection of pegcetacoplan during the study, but will be presented under the placebo group only if they did not receive any dose of pegcetacoplan. This population will be used for all safety analyses.

4.3. 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. The ITT set will be used for all efficacy analyses except the primary endpoint, for which the mITT set will be used.

4.4. Modified Intent-to-Treat Set

The modified intent-to-treat (mITT) set will include all randomized subjects who receive at least one dose of randomized treatment (pegcetacoplan or placebo), and who die or have a postbaseline assessment of the endpoint that are used in CAFS. For example, in CAFS analysis of ALSFRS-R, it will be all randomized subjects who receive at least one dose of randomized treatment (pegcetacoplan or placebo), and who die or have a postbaseline assessment of ALSFRS-R. Subjects will be analyzed according to their assigned treatment, regardless of the treatment actually received.

4.5. Per-Protocol Analysis Set

The per-protocol (PP) set will include all subjects in the ITT 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 Week 52 analysis database lock.

The review and classification of protocol deviations is described in Section 5.8 and the study's Protocol Deviation Handling Plan, where the criteria for major and minor deviations are also defined. Deviations that effect exclusion from the PP analysis set are a subset of protocol deviations; major protocol deviations do not necessarily result in exclusion of the subject from the PP analysis set.

4.6. Pharmacokinetic Set

The PK set will include all subjects in the safety set who have at least one quantifiable postdose concentration of pegcetacoplan (even with values below the limit of quantification [BLQ]) during the randomized treatment period.

4.7. Pharmacodynamic Set

The pharmacodynamic (PD) set will include all subjects in the safety set who have at least one quantifiable postdose PD endpoint (NfL, pNfH, C3, CH50, or AH50) evaluated.

5. STUDY SUBJECTS

In general, descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented for continuous endpoints and number and percentage will be presented for categorical endpoints.

5.1. Disposition of Subjects

A listing of all Screen Failures (ie, subjects who were screened but not randomized) will be presented. The number of subjects screened, passed screening, screened failed and randomized will be presented overall based on screened set.

The number of subjects who were included in each defined analysis set (ie, ITT, mITT, safety, and PP, PK, and PD) will be summarized by treatment group and overall, except for the screened set, which will be summarized only overall.

The overall summary of subject disposition will be based on ITT set and provided by treatment group and by phase (randomized control period or open-label period) and overall, including the following:

- Number of subjects completed treatment [through Week 52, as appropriate]
- Number of subjects discontinued from treatment and reason for discontinuation (prior to Week 52)
- Number of subjects completed study (through Week 52, as appropriate)
- Number of subjects discontinued from study and reason for discontinuation (prior to Week 52)

In addition, to assess the impact of the COVID-19 pandemic and the Ukraine conflict on disposition of subjects, the number of subjects discontinued from treatment due to each reason will be summarized.

The number of subjects screened, randomized and completed will be tabulated by site and country.

5.2. Demographic and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented by treatment group and overall for ITT set and safety set if the 2 sets are different. The following demographic characteristics will be summarized in the following order in the tables:

- Age at baseline (<45, ≥45 – <65, ≥65 – <75, ≥75 years)
- Sex
- Childbearing Potential
- Ethnicity
- Race
- Race defined by (American Thoracic Society/European Respiratory Society) ATS/ERS standards
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Having reported ALS related genetic mutations
- Stratification factors (at randomization):
  - location of first muscle weakness (limb or bulbar),
  - riluzole and edaravone use
- Actual Stratification factors:
  - location of first muscle weakness (limb or bulbar),
  - riluzole and edaravone use
- ALSFRS-R at baseline
- ALSAQ-40 at baseline
- HHD at baseline
- % Predicted SVC at baseline
- Neurofilament light chain (NfL) at baseline
- Location of onset, including limb location and bulbar ALS functions affected
- Time (months) from ALS symptom onset calculated as (date of first dose of study treatment – ALS symptom start date)/30.4375, or (date of randomization – ALS symptom start date)/30.4375 for untreated subjects
- Time (months) from ALS diagnosis calculated as (date of first dose of study treatment – ALS diagnosis date)/30.4375, or (date of randomization – ALS diagnosis date)/30.4375 for untreated subjects; (continuous; <= 6 months, >6 and ≤12 months; >12 months)
- El Escorial Criteria assessment for ALS
  - Presence of signs of lower motor neuron (LMN) degeneration by clinical, electrophysiological or neuropathologic examination

- Presence of signs of upper motor neuron (UMN) degeneration by clinical examination
- Presence of progressive spread of signs within a region or to other regions, as determined by history or examination
- Absence of electrophysiological evidence of other disease processes that might explain the signs of LMN and/or UMN degenerations
- Absence of neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs

5.3. Medical History

Medical history will be collected at the screening visit (visit 1) and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. Summaries will be presented for the safety set and will be done by System Organ Class (SOC) and Preferred Term (PT) with counts and percentages by treatment group and overall. Each subject will be counted only once in each SOC or SOC/PT summary.

5.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary version WHO Drug Global B3-format March 2020. Prior and concomitant medications will be summarized by Anatomical Therapeutic Class (ATC) level 2 and PT with the number and percentage of subjects for the safety set. Prior medications are defined as medications that started prior to the first dose of study drug. Concomitant medications are defined as medications that are taken on or after first dose of study drug. Medications that started before the first dose of study drug and continued on or after first dose of study drug will be considered as both prior and concomitant medications. Multiple medication usage by a subject in the same category will be counted only once.

Use of riluzole only, edaravone only, or both riluzole and edaravone will be tabulated for prior use and concomitant use. Discrepancies between the values used for randomization stratification by riluzole and edaravone and actual usage of the 2 medications will be listed.

All prior and concomitant medications will be listed for the ITT set.

5.5. Prior and Concomitant Procedures

Prior and concomitant procedures will be coded using MedDRA version 23.0 and will be presented for the safety set by SOC and PT with counts and percentages by treatment group and overall. A subject who had more than one procedure will be counted only once in the summary per SOC and PT. Prior procedures are defined as those that were started prior to the first dose of study drug. Concomitant procedures are defined as those that were started on or after first dose of study drug or ended on or after the first dose of study drug. Procedures that started before the first dose of study drug and continued on or after first dose of study drug will be considered as both prior and concomitant procedures. A data listing of all procedures will be provided for the ITT set.

5.6. Exposure to Investigational Product

Exposure to investigational product will be summarized for the safety set by treatment group and overall using the parameters below. Exposure will be summarized for the randomized and open-label treatment periods separately, and for the 2 periods combined.

- Total dose administered (mg)
- Duration of treatment (days), which is calculated as the number of days from the date of first dose of investigational product taken to the date of the last dose of investigational product taken (ie, treatment duration = date of last study drug infusion in the randomized treatment period – date of first study drug infusion + 4 [to account for twice weekly dosing]), inclusively
- Number and percentage of subjects who received infusions in the following categories:
  - Number and percentage of subjects with all infusions completed
  - Number and percentage of subjects who received numbers of infusions (completed or not) in the following categories: 1 - 21 (1% - 20%), 22 - 42 (21% - 40%), 43 - 62 (41% - 60%), 63 - 83 (61% - 80%), 84 - 104 (81% - 100%)
- Total number of infusions
  - Number and percentage of infusions completed
  - Number and percentage of infusions interrupted

A listing will be presented by subject number and week giving the date and time of dose administration.

5.7. Measurements of Treatment Compliance

Percent compliance will be calculated for the randomized and open-label treatment periods separately using the safety set. The percent compliance for twice weekly dosing is defined as:

$$Percent\ Compliance = \frac{Total\ Number\ of\ Infusions\ Received}{[(Last\ Dose\ Date - First\ Dose\ Date + 3.5)/7] \times 2} \times 100$$

The number and percentage of subjects will be presented by percentage of drug compliance in 10 percentage point increments (ie, ≥ 80% − <90%, ≥ 90 − ≤100%, >100% − <110%, with additional ranges added as needed) by treatment and overall.

A subject listing will be produced for treatment compliance and exposure. Calculated compliance data for each subject will be listed.

5.8. Protocol Deviations

Protocol deviations will be recorded outside the clinical database. The study team will classify major and minor protocol deviations per the agreed Protocol Deviation Handling Plan.
The Apellis study team will review the protocol deviations and their classification throughout the study and before the Week 52 analysis database lock and treatment unblinding.

Decisions of the review will include:

- Categorization of protocol deviations
- Classification of major and minor protocol deviations

A protocol deviation is classified as major if it has the potential to significantly impact the completeness, accuracy, and/or reliability of the study's efficacy or safety data. As defined in Section 4.5, subjects with protocol deviations that could influence their efficacy assessment result in exclusion from the PP set; these deviations are a subset of protocol deviations; major protocol deviations do not necessarily result in exclusion of the subject from the PP analysis set.

All protocol deviations occurring during the randomized treatment period will be identified, categorized, and classified prior to the Week 52 analysis database lock for the analysis of the randomized treatment period, and those occurring during the open-label treatment period will be identified, categorized, and classified prior to the week 104 analysis database lock for the open-label treatment period. Confirmed major and minor protocol deviations will be documented in the protocol deviation tracker for the study and finalized prior to database lock or treatment unblinding. Major/minor protocol deviations will be summarized by category and site for each treatment group and overall, for the safety set. Major/minor protocol deviations will be listed for the ITT set.

6. EFFICACY ANALYSES

The primary efficacy analysis (ie, CAFS at week 52) will be done on the mITT set while all other efficacy analyses will be based on the ITT set; in both cases, subjects will be analyzed according to the treatment assigned at randomization. Baseline for all efficacy analyses is defined as the last observed value for the efficacy assessment prior to taking the first dose of investigational product (based on dates or date/times), or prior to the randomization date for subject who are not treated.

All statistical tests will be performed at 2-sided 5% level of significance and all confidence intervals will be two-sided 95% confidence intervals.

Unless otherwise noted, analysis of efficacy endpoints in the overall population will be adjusted for the following randomization stratification factors:

- Location of first muscle weakness (limb or bulbar)
- Use of riluzole and edaravone (4 values: neither, riluzole only, edaravone only, or both riluzole and edaravone)

Because very few subjects used edaravone only, use of riluzole and edaravone was recategorized into 3 levels and will be included as a covariate in analyses (ie, neither, only one, or both). If subjects are found to have had the incorrect stratum assigned at randomization, they will be analyzed according to the randomization stratum.

For baseline variables that are adjusted in models, missing values will be imputed as mean or mode of that variable at baseline. Due to skewness in distribution, natural log transformed baseline NfL value will be used as a covariate for adjustment in the analysis models.

6.1. Analysis Models

In general, data will be analyzed with the approaches described below.

Analysis of covariance (ANCOVA)

Analysis of covariance (ANCOVA) will be used to analyze the ranks of the CAFS score with treatment as a fixed effect, adjusted for baseline ALSFRS-R total score, time from symptom onset (defined in Section 5.3), baseline Log NfL, and the randomization stratification factors (location of first muscle weakness and use of riluzole and edaravone). Least squares (LS) means will be presented for each treatment group, along with the between-treatment difference and 95% confidence interval (CI). In addition, the relative benefit of pegcetacoplan to placebo will be presented (difference in LS mean CAFS score between the pegcetacoplan group and the placebo group, divided by the LS mean CAFS score in the placebo group).

Mixed-effect model for repeated measures (MMRM) for continuous outcomes

Longitudinal assessments for changes from baseline in continuous outcomes (with the exception of home % predicted SVC, which is measured weekly and which will use the *Mixed Effects model for slope analysis of continuous outcomes* below) will be analyzed using a MMRM. The model will include fixed categorical effects for treatment, visit, and the visit-by-treatment interaction, as well as the continuous, fixed covariate of the baseline value of the endpoint, and the visit-by-baseline interaction, time from symptoms onset to the first dose of investigational product, baseline Log NfL and the randomization stratification factors (location of first muscle

weakness and use of riluzole and edaravone). LS means with standard errors (SEs) and 95% CIs of the change from baseline will be presented by treatment group and visit; between-treatment differences and 95% CIs and p-values will be presented by visit. LS means (±SE) will be plotted over time-by-treatment group.

The sandwich estimator (Diggle et al. 1994) will be used to estimate the SEs of the fixed effects parameters. Initially an unstructured covariance matrix [*c*=91, number of covariance parameters for endpoints assessed monthly] will be used. If the model fails to converge, the following covariance structures will be fit in this order with more and more constrained structures until convergence is met: (*i*) heterogenous first-order autoregressive AR(1) [*c*=14], (*ii*) Toeplitz [*c*=13], (*iii*) AR(1) + random effects for intercept and linear slope [*c*=5], (i*v*) AR(1) + random intercept [*c*=3], and (*v*) compound symmetry [*c*=2].

Mixed effects model for slope analysis of continuous outcomes

For slope analysis of continuous outcomes, a mixed effects model using the baseline and all postbaseline assessments will be used and will include a random intercept and random slope over time, along with linear fixed effect for time, the time-by-treatment interaction, as well as the continuous, fixed covariate of the baseline value of the endpoint, time from symptoms onset to the first dose of investigational product, baseline Log NfL, and the randomization stratification factors (location of first muscle weakness and use of riluzole and edaravone). An unstructured covariance structure will be used for estimating correlation between random intercept and random slope. The estimated slope over a 4-week period (with 95% CI) will be presented by treatment group, along with the estimate, 95% CI, and P value for the between-treatment difference in slopes.

Nonlinearity in the association between the outcome and time will be examined adding fixed effects for time^2 and the interaction term between treatment and time^2, and the random quadratic effect across time If there are no convergence issues, the models with and without these 3 additional terms will be compared based on the Akike Information Criteria (AIC); inference for the slope analysis will be based on better model based on AIC. If there are convergence issues, the quadratic random effect will be dropped, and the models with and without the 2 quadratic fixed effect terms will be then compared based on AIC. If model with quadratic effect is used as the final model, then the LSmean estimate and 95% CI by treatment group, along with difference in LS means between treatment group and P value will be presented every 4 weeks.

Cox proportional hazards model

For time-to-event endpoints, comparisons between treatment groups will be done using Cox proportional hazard models (Cox 1972) stratified by the randomization stratification factors (location of first muscle weakness and use of riluzole and edaravone) and adjusted for baseline ALSFRS-R, score and time from symptoms onset to the first dose of investigational product and baseline Log NfL. The number of events in each treatment group, the hazard ratio, 95% CI, and P value will be presented for the treatment over placebo.

6.2. Multiplicity Adjustment

The primary endpoint of the study will be tested at the 2-sided 0.05 level, and if the null hypothesis for the primary endpoint is rejected, the secondary endpoints will be tested. The secondary endpoints

will be tested sequentially in order in which they are presented in the secondary endpoint section above (Section 2.2.2); the testing will stop once a null hypothesis is not rejected. This fixed-sequence testing procedure will ensure that trial-wise error rate is controlled to be 0.05. Below is the ordering of the primary and secondary efficacy endpoints to be tested:

- difference in CAFS rank score (joint-rank score) at Week 52.
- change from baseline in ALSFRS-R at Week 52 (total score)
- change from baseline in % predicted 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 (total score)
- change from baseline in serum NfL at week 52

6.3. Estimands

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 sporadic ALS as measured by the CAFS rank score (joint-rank score).

The estimands and their attributes for the primary and all *comparative* secondary endpoints are shown in Table 1 below. This includes strategies for addressing the following intercurrent events (ICEs):

- Dth = Death
- RxDxIndep = Discontinuations from study treatment that are considered definitely unrelated to efficacy or safety; these included the Ukraine conflict and COVID-19 (illness or site effect., eg, site closure).
- RxDxRel = Discontinuations from study treatment that are potentially related to efficacy or safety; these include adverse events and lack of efficacy. Any other treatment discontinuation reason not included in RxDxIndep prior to database lock will be included here.
- RxIntExc = Treatment interruptions longer than 2 weeks that are due to exceptional circumstances (ie., COVID-19 or the Ukraine conflict).
- ALS-CM-Inc = increases (starting or dose increases) in concomitant use of ALS medications (riluzole or edaravone).
- ALS-CM-Dec = decreases (stopping or dose decreases) in concomitant use of ALS medications (riluzole or edaravone).
- CompInhib = use of any other complement inhibitor (Note: usage is prohibited within 30 days or within 5-half lives of the medication [whichever is longer] prior to the start of the screening period or during study participation)

- DPS = diaphragm pacing system (DPS) implanted during randomized treatment period. (Note: implantation of a DPS is prohibited prior to and during the randomized treatment period, and subjects who have a DPS implanted during this period are required to withdraw from the study.)

Table 1: Estimands and Attributes for Primary and Secondary Endpoints

For all estimands:

A. Population: subjects with sporadic ALS diagnosed as definite, probable, or laboratory-supported probable as defined by the revised El Escorial criteria and further defined in the protocol's inclusion and exclusion criteria

B. Treatment regimens of interest:

- twice per week SC doses of pegcetacoplan 1080 mg plus concomitant use of riluzole or edaravone (or neither or both) for 52 weeks of treatment
- twice per week SC doses of placebo plus concomitant use of riluzole or edaravone (or neither or both) for 52 weeks of treatment

C: Variable (or endpoint)	D: Strategies for addressing ICEs (event†: strategy‡)	E: Population-level summary
Primary Estimand		
CAFS rank score (joint-rank score)	Dth: composite strategy RxDxIndep: hypothetical strategy RxDxRel, RxIntExc, ALS-CM-Inc/Dec, CompInhib, DPS: treatment policy strategy	Difference in mean CAFS score between the pegcetacoplan group and the placebo group.
Secondary Estimands (for comparative endpoints)		
Change from baseline in ALSFRS-R at week 52	Dth: hypothetical strategy RxDxIndep: hypothetical strategy RxDxRel, RxIntExc, ALS-CM-Inc/Dec, CompInhib, DPS: treatment policy strategy	Difference in mean change from baseline in ALSFRS-R at week 52 between the pegcetacoplan and placebo arms
Change from baseline in % predicted SVC (at clinical visits) at week 52	Dth: hypothetical strategy RxDxIndep: hypothetical strategy RxDxRel, RxIntExc, ALS-CM-Inc/Dec, CompInhib, DPS: treatment policy strategy	Difference in mean change from baseline in %SVC (at clinic visits) at week 52 between the pegcetacoplan and placebo arms
Change from baseline in HHD megascore at week 52	Dth: hypothetical strategy RxDxIndep: hypothetical strategy RxDxRel, RxIntExc, ALS-CM-Inc/Dec, CompInhib, DPS: treatment policy strategy	Difference in mean change from baseline in HHD megascore at week 52 between the pegcetacoplan and placebo arms
Time to death, permanent tracheostomy or permanent assisted ventilation up to week 52	Dth: not applicable RxDxIndep: hypothetical strategy RxDxRel, RxIntExc, ALS-CM-Inc/Dec, CompInhib, DPS: treatment policy strategy	Hazard ratio (pegcetacoplan vs placebo arms) for time to death, permanent tracheostomy or permanent assisted ventilation

Table 1: Estimands and Attributes for Primary and Secondary Endpoints

Time to death up to week 52	Dth: not applicable RxDxIndep: hypothetical strategy RxDxRel, RxIntExc, ALS-CM-Inc/Dec, CompInhib, DPS: treatment policy strategy	Hazard ratio (pegcetacoplan vs placebo arms) for time to death
Change from baseline in ALSAQ-40 at week 52	Dth: hypothetical strategy RxDxIndep: hypothetical strategy RxDxRel, RxIntExc, ALS-CM-Inc/Dec, CompInhib, DPS: treatment policy strategy	Difference in mean change from baseline in ALSAQ-40 at week 52 between the pegcetacoplan and placebo arms

†ICE definitions:

- Dth = Death
- RxDxIndep = Discontinuations from study treatment that are considered definitely unrelated to efficacy or safety; these included the Ukraine conflict and COVID-19 (illness or site effect., eg, site closure). Other reasons may be added prior to database lock(other than due to death or COVID-19)
- RxDxRel = Discontinuations from study treatment due to COVID-19 impact (illness or site effect) that are potentially related to efficacy or safety; these include adverse events and lack of efficacy. Any other treatment discontinuation reason not included in RxDxIndep prior to database lock will be included here.
- RxIntExc = Treatment interruptions longer than 2 weeks that are due to exceptional circumstances (ie., COVID-19 or the Ukraine conflict).
- ALS-CM-Inc = Increases (starting or dose increases) in concomitant use of ALS medications (riluzole or edaravone)
- ALS-CM-Dec = Decreases (stopping or dose decreases) in concomitant use of ALS medications (riluzole or edaravone)
- CompInhib = use of any other complement inhibitor
- DPS = diaphragm pacing system

‡Strategies**:**

- Composite strategy: the occurrence of the ICE is considered part of the endpoint
- Hypothetical strategy: values are considered as if the ICE had not occurred; in all cases above, this strategy is addressed by excluding the data after the ICE
- Treatment policy strategy: the ICE is ignored; values after the ICE are used as if the ICE had not occurred.

6.4. Analyses of Primary Efficacy Endpoint

The primary efficacy endpoint is the CAFS rank score (joint-rank score) at week 52. The null ($H_{1,0}$) and alternative ($H_{1,1}$) hypotheses for the primary efficacy analysis are:

$H_{1,0}$: There is no difference in CAFS rank scores between the pegcetacoplan and placebo treatment groups

$H_{1,1}$: There is a difference in CAFS rank scores between the pegcetacoplan and placebo treatment groups.

The CAFS score will be developed as follows (and as proposed by Berry et al. 2013):

- The functional (ALSFRS-R) 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 the 2 subjects died on the same day, both receive a score of 0
  - Otherwise, if one subject is deceased and the other subject is alive at the last point of contact and this last point of contact is on or after the day of death, the surviving subject receives a score of +1 and the deceased subject receives a score of –1
  - Otherwise, the subject with a smaller decrease from baseline in ALSFRS-R at the last mutual time point receives a score of +1 and the other subject receives a score of –1
  - If the 2 subjects have the same decline from baseline in ALSFRS-R, or if they cannot be compared (eg, due to a lack of a mutual time point), both receive a score of 0.

The scores from all pairwise comparisons are added up for each subject are used as the CAFS score, which will then be ranked and used in the analyses described in *Analysis of Covariance* in Section 6.1.

6.4.1. Main Analysis of Primary Efficacy Endpoint

ANCOVA will be used to analyze the CAFS ranks score with treatment as a fixed effect, adjusted for baseline ALSFRS-R total score, time from symptoms onset to the first dose of investigational product, baseline Log NfL, and the randomization stratification factors (location of first muscle weakness and use of riluzole and edaravone). Further details on the presentation of the results are described in the Analysis of Covariance section in Section 6.1 above.

6.4.2. Sensitivity Analyses of Primary Efficacy Endpoint

The following sensitivity analyses will be done to examine the robustness of the main analyses of CAFS endpoint under the main estimand. These analyses impute missing ALSFRS-R values under the assumptions of both missing at random (MAR) and missing not at random (MNAR).

6.4.2.1. Multiple Imputation for Missing ALSFRS-R for CAFS Under MAR

Sensitivity analysis with multiple imputation for missing ALSFRS-R scores will be performed based on MAR assumption. For subjects who died by week 52, ALSFRS-R score will only be imputed before the death date. The imputation method will be implemented in SAS using the 3 standard steps to generate inference from imputed data: imputation step, analysis step, and pooling step.

- Missing ALSFRS-R are filled 100 times to generate 100 complete data sets and thus CAFS are derived for 100 times.
- The 100 data sets are analyzed using the CAFS method as described in Section 6.1.
- The results from 100 data sets are combined for inference.

The method for the imputation step is described below.

- The imputation model separate for each treatment group includes the following covariates: stratification variables, baseline Log NfL, duration from symptoms onset to the first dose of investigational product, ALSFRS-R values at baseline and all previous visits.
- The Markov chain Monte Carlo (MCMC) method in PROC MI will be invoked with multiple chains (CHAIN=MULTIPLE), 200 burn-in iterations (NBITER=200) and a noninformative prior (PRIOR=JEFFREYS) to produce complete data set. The seed to be used is in Table 2.

Combination of the results across the imputed data sets is described in Section 17.2.1.

Table 2: Seed for Multiple Imputation

Endpoints	Seed
ALSFRS-R	975321
SVC	123456
HHD	230323

6.4.2.2. Control-Based Multiple Imputation for CAFS

Sensitivity analysis with control-based multiple imputation for ALSFRS-R will be performed to consider the MNAR mechanism for monotone missing data in ALSFRS-R according to the reasons as describe in Section 6.5.1.2.1.

Using the resulting complete data sets, the CAFS scores will be recalculated (as described above in Section 6.4). The analysis model and presentation of the multiply imputed data sets will be done as for the main analysis of CAFS using the ANCOVA model described in Section 6.1 above, but with the results across the imputed data sets combined as in Section 17.2.1.

6.4.2.3. Tipping Point Analysis for CAFS

Multiple imputation based on the delta-adjusted stress testing (tipping point) analysis will be used to impute ALSFRS-R as described in Sections 6.5.1.2.2 and 17.2.2. The tipping point imputation approach will be based on the delta-adjusted stress testing method, also known as the

tipping point analysis (O'Kelly and Ratitch, 2014, Chapter 7). This method assumes that subjects who discontinue from the pegcetacoplan group experience worsening of ALSFRS-R defined by an adjustment (from -0.2 to -1 grid by -0.2) at all visits that are missing.

Using the resulting complete data sets, the CAFS scores will be recalculated (as described above in Section 6.4). The analysis model and presentation of the imputed data sets will be done as for the main analysis of CAFS using the ANCOVA model described in Section 6.1 above, but with the results across the imputed data sets combined as in Section 17.2.2.

6.4.3. Supplemental Analyses of Primary Efficacy Endpoint

6.4.3.1. Excluding Data After Changes in Concomitant ALS Treatment and Supportive Care

For this estimand, the treatment regimens of interest are:

- twice per week SC doses of pegcetacoplan 1080 mg for 52 weeks of treatment
- twice per week SC doses of placebo for 52 weeks of treatment

with **no** changes in background ALS therapy (riluzole or edaravone).

For the ALS-CM-Inc, ALS-CM-Dec, CompInhib, and DPS ICEs defined above (increases and decreases in the concomitant use of ALS treatments, use of other complement inhibitors, and DPS implantation respectively), the hypothetical strategy will be used: all ALSFRS-R and survival data after these ICEs will be excluded when deriving the CAFS score. Strategies for handling other ICEs will be the same as in the primary analysis.

CAFS scores and then ranks will be re-derived based on steps laid out in Section 6.4, and ANCOVA will be used to analyze the new scores.

6.4.3.2. Interruptions due to COVID-19 and Ukraine Conflict

For this estimand, the treatment regimens of interest are:

- twice per week SC doses of pegcetacoplan 1080 mg for 52 weeks of treatment
- twice per week SC doses of placebo for 52 weeks of treatment

with **no** interruptions longer than 2 weeks due to COVID-19 or the Ukraine conflict.

For the RxIntExc (treatment interruptions longer than 2 weeks that are due to exceptional circumstances, ie, COVID-19 or the Ukraine conflict) the hypothetical strategy will be used: all ALSFRS-R and survival data after these ICEs will be excluded when deriving the CAFS score. Strategies for handling other ICEs will be the same as in the primary analysis.

CAFS scores and then ranks will be re-derived based on steps laid out in Section 6.4, and ANCOVA will be used to analyze the new scores.

6.4.3.3. PP Set

The primary analysis described in Section 6.4.1 will be repeated using the PP set, as defined in Section 4.5.

6.4.4. Subgroup Analyses of Primary Efficacy Endpoint

Subgroup analyses will be performed to evaluate the consistency of the primary analysis results across subgroups defined by demographic and baseline characteristics. Analyses will be performed for the primary efficacy endpoint for each of the subgroups below (as appropriate per actual subgroup sample size, levels with small sample size [<10%] may be pooled to allow for an analysis to be conducted). The CAFS scores from the overall analysis will be used. The primary analysis as described in Section 6.4.1 will be repeated for each subgroup.

- Age at ALS symptom onset: <45, ≥45 – <65, ≥65, where age at symptom start is calculated as age at baseline - round((informed consent date – date of symptom onset)/365.25,0.1)
- Sex: male, female
- Race, defined by ATS/ERS standards: Caucasian, non-Caucasian
- Geographic region: Europe (Belgium, Czech Republic, France, Germany, Ireland, Italy, Netherlands, Poland, Spain, Ukraine, United Kingdom), Japan, South America (Argentina, Brazil), and Other (Australia, USA)
- Location of onset: limb, bulbar; the reported (actual) location will be used, not necessarily the value of the stratification factor
- Time (months) from ALS symptom onset (based on tertiles, rounded to the nearest month)
- Time (months) from ALS diagnosis to first dose (based on tertiles, rounded to the nearest month)
- Time (months) from ALS diagnosis to first dose (6 months, >6-12 months, and >12 months)
- Categorized baseline ALSFRS-R scores (based on tertiles, with cutoffs rounded to the nearest whole number)
- El Escorial Criteria assessment
- Baseline NfL (<=Median, > median)

6.4.5. Analysis of Covariates

ALS is a highly heterogeneous disease with various risk factors for disease progression. Although randomization is employed to achieve the potential of balancing risk factors between treatment groups, chance imbalance may occur. The baseline risk factors identified below will be evaluated for imbalance and additional supportive analyses of the primary and secondary endpoints will be performed adjusting for additional risk factors with major imbalance.

- Age at symptom onset
- Limb vs bulbar onset
- Body mass index
- Time from symptom onset to diagnosis
- Baseline ALSFRS score

- Baseline %SVC
- Neurofilament light chain.

In addition, risk predicted based on baseline characteristics using advanced analytic methods such as AI may be explored for adjusted analysis.

6.5. Analyses of Secondary Efficacy Endpoints

The following subsections describe the analyses of the secondary efficacy endpoints of the study.

All analyses of secondary endpoints will be done on the ITT set.

6.5.1. Change From Baseline in ALSFRS-R at Week 52 (Total Score)

The secondary efficacy endpoint of change from baseline in ALSFRS-R at week 52 (total score) will be examined with the following null ($H_{2.1,0}$) and alternative ($H_{2.1,1}$) hypotheses:

$H_{2.1,0}$: There is no difference in change from baseline in ALSFRS-R at Week 52 (total score) between the pegcetacoplan and placebo treatment groups

$H_{2.1,1}$: There is a difference in change from baseline in ALSFRS-R at Week 52 (total score) between the pegcetacoplan and placebo treatment groups.

Derivations and data handling conventions for the ALSFRS-R endpoint are described in Section 13.5.1. Absolute values and changes from baseline in ALSFRS-R total scores as well as domain subscores [bulbar function, fine motor, gross motor, and respiratory] will be presented by treatment group and visit (up to week 52) using descriptive statistics.

Changes from baseline in ALSFRS-R total scores up to week 52 will be analyzed using the MMRM described in *Mixed-effect model for repeated measures (MMRM) for continuous outcomes* in Section 6.1 above, with results presented as described there.

6.5.1.1. Supportive Analyses of ALSFRS-R

The following supplemental analyses will be done to further examine the change from baseline in ALSFRS-R scores.

6.5.1.1.1. Slope Analysis

The mean slope (rate of change) in observed ALSFRS-R scores will be compared between treatment groups using the mixed effects model for slope analysis of continuous outcomes described above in *Mixed effects model for slope analysis of continuous outcomes* in Section 6.1. Subjects with no postbaseline ALSFRS-R assessment will not be included.

6.5.1.2. Sensitivity Analyses of ALSFRS-R

The following sensitivity analyses will be done to further examine the robustness of the results for the analysis of change from baseline in ALSFRS-R scores.

6.5.1.2.1. Control-Based Multiple Imputation

Control-based multiple imputation approach will be used as a sensitivity analysis to consider the MNAR mechanism for monotone missing data. Changes from baseline in ALSFRS-R will be

analyzed based on the data observed while the subject remains on study treatment as well as the data imputed using multiple imputation (MI) methodology for the time points with missing values. The following strategy will be used:

- In the placebo group, all missing values will be imputed based on the MAR assumption using the placebo group
- In the pegcetacoplan group:
  - Nonmonotone missing values (ie, not due to dropout) will be imputed based on the MAR assumption using the pegcetacoplan group.
  - Monotone missing values (ie, postdropout) will be imputed as follows:
    - If the reason for treatment or study discontinuation is not potentially related to safety or efficacy, ie, 'SITE TERMINATED BY SPONSOR', the values will be imputed based on the MAR assumption using the pegcetacoplan group. ‘SITE TERMINATED BY SPONSOR’ is the coded reason for discontinuation due to Ukraine conflicts or COVID-19 external factors.
    - If the reason for treatment or study discontinuation is potentially related to safety or efficacy, the values will be imputed based on the placebo imputation model above. These reasons include all reasons except 'SITE TERMINATED BY SPONSOR'.

This approach does not assume a sustained benefit of pegcetacoplan after discontinuation but rather assumes a postdiscontinuation effect like that of placebo.

Details of the control-based MI procedure are given in Section 17.2.1. The analysis model and presentation of the multiply imputed data sets will be done as for the main analysis of the ALSFRS-R using the MMRM described in *Mixed-effect model for repeated measures (MMRM) for continuous outcomes* in Section 6.1 above, but with the results across the imputed data sets combined as in Section 17.2.1.

6.5.1.2.2. Tipping Point Analysis

MI based on the delta-adjusted stress testing (tipping point) analysis will be performed for ALSFRS-R and will be analyzed using the MMRM model used in the main analysis of this endpoint.

The tipping point imputation approach will be based on the delta-adjusted stress testing method, also known as the tipping point analysis (O’Kelly and Ratitch, 2014). This method assumes that subjects who discontinue from the pegcetacoplan group experience worsening of ALSFRS-R defined by a prespecified adjustment (from -0.2 to -1 grid by -0.2) at each following visit. Then each imputed data set will be analyzed using MMRM and the results across the imputed data sets will be combined as in Section 17.2.1.

Details of the delta-adjusted stress testing method procedure are given in Section 17.2.2. The analysis model and presentation of the multiply imputed data sets will be done as for the main analysis of the ALSFRS-R using the MMRM described in *Mixed-effect model for repeated measures (MMRM) for continuous outcomes* in Section 6.1 above.

6.5.1.3. Supplemental Analyses of ALSFRS-R

The following supplemental analyses will be done to examine other estimands for the change from baseline in ALSFRS-R scores.

6.5.1.3.1. Excluding Data After Changes in Concomitant ALS Therapy

For this estimand, the treatment regimens of interest are:

- twice per week SC doses of pegcetacoplan 1080 mg for 52 weeks of treatment
- twice per week SC doses of placebo for 52 weeks of treatment

with no changes in background ALS therapy (riluzole or edaravone), usage of complement inhibitors, or DPS.

For the ALS-CM-Inc, ALS-CM-Dec, and CompInhib ICEs defined above (increases and decreases in the concomitant use of ALS treatments, and use of other complement inhibitors, respectively), the hypothetical strategy will be used: all ALSFRS-R after the ICE will be excluded from the analysis. The strategies for handling other ICEs listed in Section 6.2 are the same as the primary analysis. MMRM will be used assuming there is no change of background ALS therapy and ALSFRS-R score will follow the same trend as before the ICE occurs.

6.5.1.4. Interruptions due to COVID-19 and Ukraine Conflict

For this estimand, the treatment regimens of interest are:

- twice per week SC doses of pegcetacoplan 1080 mg for 52 weeks of treatment
- twice per week SC doses of placebo for 52 weeks of treatment

with **no** interruptions longer than 2 weeks due to COVID-19 or the Ukraine conflict.

For the RxIntExc (treatment interruptions longer than 2 weeks that are due to exceptional circumstances, ie, COVID-19 or the Ukraine conflict) the hypothetical strategy will be used: all ALSFRS-R and survival data after these ICEs will be excluded when deriving the CAFS score. Strategies for handling other ICEs will be the same as in the primary analysis. MMRM will be used assuming there is no change of background ALS therapy and ALSFRS-R score will follow the same trend as before the ICE occurs.

6.5.1.4.1. PP Set

The analysis described in Section 6.5.1 will be repeated using the PP set, which is defined in Section 4.5.

6.5.1.5. Subgroup Analyses of ALSFRS-R

Subgroup analyses will be performed for ALSFRS-R to evaluate the consistency of the results of the analyses across the subgroups specified in Section 6.4.4 above. Levels with low sample size may be pooled to allow for an analysis to be conducted.

The MMRM used for the main analysis of ALSFRS-R will be repeated for each subgroup level respectively.

6.5.2. Change from Baseline in % Predicted SVC (at Clinic Visits) at Week 52

The secondary efficacy endpoint of change from baseline in % predicted SVC (at clinic visits) at week 52 will be examined with the following null ($H_{2.2,0}$) and alternative ($H_{2.2,1}$) hypotheses:

$H_{2.2,0}$: There is no difference in change from baseline in % predicted SVC (at clinic visits) at Week 52 between the pegcetacoplan and placebo treatment groups

$H_{2.2,1}$: There is a difference in change from baseline in % predicted SVC (at clinic visits) at Week 52 between the pegcetacoplan and placebo treatment groups.

Derivations and data handling conventions for the % predicted SVC endpoint are described in Section 13.5.2. Absolute values and changes from baseline in % predicted SVC will be presented by treatment group and visit (up to week 52) using descriptive statistics. Means (±SE) will also be plotted over time.

Changes from baseline in % predicted SVC up to week 52 will be analyzed using the MMRM described in Section 6.1, with results presented as described there.

6.5.2.1. Sensitivity Analyses of % Predicted SVC (at Clinic Visits)

The following sensitivity analyses will be done to further examine the robustness of the results for the analysis of change from baseline in % predicted SVC (at clinic) scores.

6.5.2.1.1. Control-Based MI

Control-based MI approach will be used as a sensitivity analysis to consider the MNAR mechanism for monotone missing data. Changes from baseline in % predicted SVC will be analyzed based on the data observed while the subject remains on study treatment as well as the data imputed using MI methodology for the time points with missing values.

Details of the control-based MI procedure are given in Section 6.5.1.2.1 and Section 17.2.1. The analysis model and presentation of the multiply imputed data sets will be done as for the main analysis of the % predicted SVC using the MMRM described in *Mixed-effect model for repeated measures (MMRM) for continuous outcomes* in Section 6.1, but with the results across the imputed data sets combined as in Section 17.2.1.

6.5.2.2. Supplemental Analyses of % Predicted SVC

6.5.2.2.1. CAFS Analysis for %Predicted SVC (at Clinic Visits)

CAFS score and rank score will be derived combining %predicted SVC and death similarly as in Section 6.4 and analyzed by the ANCOVA model adjusting for baseline %predicted SVC, time from symptom onset (defined in Section 5.3), the randomization stratification factors (details in Section 6.1 and baseline Log NfL. The analysis will be done based on mITT set.

6.5.2.2.2. PP Set

The analysis described in Section 6.5.2 will be repeated using the PP set, which is defined in Section 4.5.

6.5.2.3. Subgroup Analyses of % Predicted SVC (at Clinic)

Subgroup analyses will be performed for % predicted SVC to evaluate the consistency of the results of the analyses across the subgroups specified in Section 6.4.4. Levels with low sample size may be pooled to allow for an analysis to be conducted).

The MMRM used for the main analysis of % predicted SVC will be applied for each subgroup level respectively.

6.5.3. Change from Baseline in HHD Megascore at Week 52

The secondary efficacy endpoint of change from baseline in HHD megascore at week 52 will be examined with the following null ($H_{2.3,0}$) and alternative ($H_{2.3,1}$) hypotheses:

$H_{2.3,0}$: There is no difference in change from baseline in HHD megascore at Week 52 between the pegcetacoplan and placebo treatment groups

$H_{2.3,1}$: There is a difference in change from baseline in HHD megascore at Week 52 between the pegcetacoplan and placebo treatment groups.

Derivations and data handling conventions for the HHD megascore endpoint are described in Section 13.5.3. Absolute values and changes from baseline in HHD megascore will be presented by treatment group and visit (up to week 52) using descriptive statistics. Means (±SE) will also be plotted over time.

Changes from baseline in HHD megascore up to week 52 will be analyzed using the MMRM described in Section 6.1, with results presented as described there.

6.5.3.1. Sensitivity Analyses of HHD

The following sensitivity analyses will be done to further examine the robustness of the results for the analysis of change from baseline in HHD megascores.

6.5.3.1.1. Control-Based MI

Control-based MI approach will be used as a sensitivity analysis to consider the MNAR mechanism for monotone missing data. Changes from baseline in HHD megascores will be analyzed based on the data observed while the subject remains on study treatment as well as the data imputed using MI methodology for the time points with missing values.

Details of the control-based MI procedure are given in Section 6.5.1.2.1 and Section 17.2.1. The analysis model and presentation of the multiply imputed data sets will be done as for the main analysis of the HHD megascores using the MMRM described in *Mixed-effect model for repeated measures (MMRM) for continuous outcomes* in Section 6.1, but with the results across the imputed data sets combined as in Section 17.2.1.

6.5.3.2. Supplemental Analyses of HHD

6.5.3.2.1. CAFS Analysis for HHD

CAFS score and rank score will be derived combining HHD and death similarly as in Section 6.4 and analyzed by the ANCOVA model adjusting for baseline HHD, time from symptom onset

(defined in Section 5.3), baseline Log NfL, and the randomization stratification factors (details in Section 6.1. The analysis will be based on mITT set.

6.5.3.2.2. PP Set

The analysis described in Section 6.5.3 will be repeated using the PP set, which is defined in Section 4.5.

6.5.3.3. Subgroup Analyses of HHD Megascores

Subgroup analyses will be performed for HHD megascores to evaluate the consistency of the results of the analyses across the subgroups specified in Section 6.4.4. Levels with low sample size may be pooled to allow for an analysis to be conducted).

The MMRM used for the main analysis of HHD megascores will be applied to each level of subgroups respectively.

6.5.4. Time to Death, Permanent Tracheostomy, or Permanent Assisted Ventilation up to Week 52

The secondary efficacy endpoint of time to death, permanent tracheostomy, or permanent assisted ventilation up to week 52 will be examined with the following null ($H_{2.6,0}$) and alternative ($H_{2.6,1}$) hypotheses:

$H_{2.6,0}$: There is no difference in time to death, permanent tracheostomy, or permanent assisted ventilation between the pegcetacoplan and placebo treatment groups

$H_{2.6,1}$: There is a difference in time to death, permanent tracheostomy, or permanent assisted ventilation between the pegcetacoplan and placebo treatment groups.

For this endpoint, the first instance of any of the 3 events at or prior to week 52 will be considered an event. Subjects with an event after an ICE that is handled by a hypothetical strategy will be considered censored on the day of the ICE. Subjects with none of the events by the minimum of the week 52 visit date or date of first dose + 364 if week 52 is missing will be considered censored at the minimum of the last date of contact or their treatment discontinuation date for subjects whose ICE dictates hypothetical strategy, or their week 52 visit or first dose date+364 if week 52 is missing. Subjects who were randomized but did not receive any treatment will be censored at the randomization date. Time-to-event (or censor) will be calculated as date of event (or censor date) − date of randomization + 1.

Time to death, permanent tracheostomy, or permanent assisted ventilation will be summarized with the Kaplan-Meier method (Kaplan and Meier 1958), using plots and presentation of median (and 95% CIs) for time-to-event. Analysis will be done by a Cox proportional hazards model as described in Section 6.1.

6.5.5. Time to Death up to Week 52

The secondary efficacy endpoint of time to death up to week 52 will be examined with the following null ($H_{2.5,0}$) and alternative ($H_{2.5,1}$) hypotheses:

$H_{2.5,0}$: There is no difference in time to death up to Week 52 between the pegcetacoplan and placebo treatment groups

$H_{2.5,1}$: There is a difference in time to death up to Week 52 between the pegcetacoplan and placebo treatment groups.

Deaths that occurred at or prior to week 52 will be included in the time to death analysis. Subjects who are alive at their week 52 visit date or date of first dose + 364 days if week 52 visit is missing will be censored. Subjects who had the ICE of discontinued treatment unrelated to efficacy or safety will also be censored at treatment discontinuation. Time to death is calculated as date of death – randomization date +1. Time to censoring for subjects who are alive is calculated as min (last contact date, week 52 visit date or first dose date+ 364 days if missing, treatment discontinuation date for ICE subjects) – randomization data +1. Time to death will be summarized with the Kaplan-Meier method, using plots and presentation of median (and 95% CIs) for time-to-event. Analysis will be done by a Cox proportional hazards model as described in Section 6.1.

6.5.6. Change from Baseline in ALSAQ-40 at Week 52 (Total Score)

The secondary efficacy endpoint of change from baseline in ALSAQ-40 at week 52 (total score) will be examined with the following null ($H_{2.4,0}$) and alternative ($H_{2.4,1}$) hypotheses:

$H_{2.4,0}$: There is no difference in change from baseline in ALSAQ-40 at Week 52 (total score) between the pegcetacoplan and placebo treatment groups

$H_{2.4,1}$: There is a difference in change from baseline in ALSAQ-40 at Week 52 (total score) between the pegcetacoplan and placebo treatment groups.

Derivations and data handling conventions for the ALSAQ-40 endpoint are described in Section 13.5.4; all presentation and analysis of ALSAQ-40 will use the scaled scores. Absolute values and changes from baseline in ALSAQ-40 score will be presented by treatment group and visit (up to week 52) using descriptive statistics. Means (±SE) will also be plotted over time.

Changes from baseline in ALSAQ-40 score up to week 52 will be analyzed using the MMRM described in Section 6.1, with results presented as described there.

6.5.7. Change from Baseline in Serum NfL at week 52

The efficacy endpoint of change from baseline in serum NfL at week 52 will be examined with the following null ($H_{3.5,0}$) and alternative ($H_{3.5,1}$) hypotheses:

$H_{3.5,0}$: There is no difference in change from baseline in serum NfL at week 52 between the pegcetacoplan and placebo treatment groups

$H_{3.5,1}$: There is a difference in change from baseline in serum NfL at week 52 between the pegcetacoplan and placebo treatment groups.

NfL values are expected to be highly skewed, so before analysis and presentation, values will be natural log transformed. The handling of values below a limit of detection (LOD) is described in Section 13.7.7. Geometric means will be presented for descriptive statistics. Geometric means and geometric mean ratios relative to baseline will be presented by treatment group and visit (up to week 52) using descriptive statistics. Geometric means (with 95% CIs) will also be plotted over time.

Log-transformed NfL up to week 52 compared to baseline will be analyzed using the MMRM described in Section 6.1, with results presented as described there, with the exception that differences in LS means will reflect geometric mean ratios.

6.6. Analyses of Exploratory Endpoints

All analyses of exploratory endpoints will be done on the ITT set. Estimands and their attributes for comparative exploratory endpoints are stated in Table 3.

Table 3: Estimands and Attributes for Comparative Exploratory Endpoints

For all estimands:

A. Population: subjects with sporadic ALS diagnosed as definite, probable, or laboratory-supported probable as defined by the revised El Escorial criteria and further defined in the protocol's inclusion and exclusion criteria

B. Treatment regimens of interest:

a. twice per week SC doses of pegcetacoplan 1080 mg plus concomitant use of riluzole or edaravone (or neither or both) for 52 weeks of treatment

b. twice per week SC doses of placebo plus concomitant use of riluzole or edaravone (or neither or both) for 52 weeks of treatment

C: Variable (or endpoint)	D: Strategies for addressing ICEs (event†: strategy‡)	E: Population-level summary
Primary Estimand		
Change from baseline in % predicted SVC (home spirometry) at week 52	Dth: hypothetical strategy RxDxIndep: hypothetical strategy RxDxRel, RxIntExc, ALS-CM-Inc/Dec, CompInhib, DPS: treatment policy strategy	Difference in mean change from baseline in % predicted SVC (at-home visits) at week 52 between the pegcetacoplan and placebo arms
Change from baseline in EQ-5D-5L at week 52	Dth: hypothetical strategy RxDxIndep: hypothetical strategy RxDxRel, RxIntExc, ALS-CM-Inc/Dec, CompInhib, DPS: treatment policy strategy	Difference in mean change from baseline in EQ-5D-5L at week 52 between the pegcetacoplan and placebo arms
Change from baseline in ZBI score at week 52	Dth: hypothetical strategy RxDxIndep: hypothetical strategy RxDxRel, RxIntExc, ALS-CM-Inc/Dec, CompInhib, DPS: treatment policy strategy	Difference in mean change from baseline in ZBI) score at week 52 between the pegcetacoplan and placebo arms
Time to percutaneous endoscopic gastrostomy tube placement up to week 52	Dth: not applicable RxDxIndep: hypothetical strategy RxDxRel, RxIntExc, ALS-CM-Inc/Dec, CompInhib, DPS: treatment policy strategy	Hazard ratio (pegcetacoplan vs placebo arms) for time to percutaneous endoscopic gastrostomy tube placement
Change from baseline in serum NfL at week 52	Dth: hypothetical strategy RxDxIndep: hypothetical strategy RxDxRel, RxIntExc, ALS-CM-Inc/Dec, CompInhib, DPS: treatment policy strategy	Difference in mean change from baseline in serum NfL at week 52 between the pegcetacoplan and placebo arms
Change from baseline in serum pNfH at week 52	Dth: not applicable RxDxIndep: hypothetical strategy RxDxRel, RxIntExc, ALS-CM-Inc/Dec, CompInhib, DPS: treatment policy strategy	Difference in mean change from baseline in serum pNfH at week 52 between the pegcetacoplan and placebo arms

Table 3: Estimands and Attributes for Comparative Exploratory Endpoints

Change from baseline in EIM at week 52 (only at select investigational sites chosen to complete this)	Dth: hypothetical strategy RxDxIndep: hypothetical strategy RxDxRel, RxIntExc, ALS-CM-Inc/Dec, CompInhib, DPS: treatment policy strategy	Difference in mean change from baseline in EIM at week 52 between the pegcetacoplan and placebo arms

†ICE definitions:

- Dth = Death
- RxDxIndep = Discontinuations from study treatment that are considered definitely unrelated to efficacy or safety; these included the Ukraine conflict and COVID-19 (illness or site effect., eg, site closure). Other reasons may be added prior to database lock(other than due to death or COVID-19)
- RxDxRel = Discontinuations from study treatment due to reasons that are potentially related to efficacy or safety; these include adverse events and lack of efficacy. Any other treatment discontinuation reason not included in RxDxIndep prior to database lock will be included here.
- RxIntExc = Treatment interruptions longer than 2 weeks that are due to exceptional circumstances (ie., COVID-19 or the Ukraine conflict).
- ALS-CM-Inc = Increases (starting or dose increases) in concomitant use of ALS medications (riluzole or edaravone)
- ALS-CM-Dec = Decreases (stopping or dose decreases) in concomitant use of ALS medications (riluzole or edaravone)
- CompInhib = use of any other complement inhibitor
- DPS = diaphragm pacing system

‡Strategies**:**

- Composite strategy: the occurrence of the ICE is considered part of the endpoint
- Hypothetical strategy: values are considered as if the ICE had not occurred; in all cases above, this strategy is addressed by the MMRM model assuming the effect at Week 52 excluding the data after the ICE
- Treatment policy strategy: the ICE is ignored; values after the ICE are used as if the ICE had not occurred.

6.6.1. Change from Baseline in % Predicted SVC (Home Spirometry) at Week 52

The exploratory efficacy endpoint of change from baseline in % predicted SVC (home spirometry) at week 52 will be examined with the following null ($H_{3.1,0}$) and alternative ($H_{3.1,1}$) hypotheses:

$H_{3.1,0}$: There is no difference in change from baseline in % predicted SVC (home spirometry) at Week 52 between the pegcetacoplan and placebo treatment groups

$H_{3.1,1}$: There is a difference in change from baseline in % predicted SVC (home spirometry) at Week 52 between the pegcetacoplan and placebo treatment groups.

Derivations and data handling conventions for the at-home % predicted SVC endpoint are described in Section 13.5.2. Absolute values and changes from baseline in at-home % predicted SVC will be presented by treatment group and week (up to week 52) using descriptive statistics. Means (±SE) will also be plotted over time.

Observed values for % predicted SVC up to week 52 will be analyzed using the *Mixed effects model for slope analysis of continuous outcomes* described in Section 6.1, with results presented as described there.

6.6.2. Change from Baseline in EQ-5D-5L at Week 52

Two endpoints will be presented for the EQ-5D-5L:

- visual analog scale (VAS)
- descriptive summary.

The exploratory efficacy endpoint of change from baseline in EQ-5D-5L at week 52 will be examined with the following null ($H_{3.2,0}$) and alternative ($H_{3.2,1}$) hypotheses for the VAS component:

$H_{3.2,0}$: There is no difference in change from baseline in EQ-5D-5L VAS at Week 52 between the pegcetacoplan and placebo treatment groups

$H_{3.2,1}$: There is a difference in change from baseline in EQ-5D-5L VAS at Week 52 between the pegcetacoplan and placebo treatment groups.

Derivations and data handling conventions for the EQ-5D-5L endpoint are described in Section 13.5.5. Absolute values and changes from baseline in the VAS will be presented by treatment group and visit (up to week 52) using descriptive statistics. Means (±SE) will also be plotted over time.

Changes from baseline in the VAS up to week 52 will be analyzed using the MMRM described in Section 6.1, with results presented as described there.

For the descriptive summary, the number and percentage of subjects will be presented by category (no problems, slight problems, moderate problems, severe problems, extreme problems/unable to do) at baseline, week 24 and week 52. A shift table from baseline to last observed value (LOV) will also be presented.

6.6.3. Change from Baseline in ZBI Scores at Week 52

The exploratory efficacy endpoint of change from baseline in ZBI scores at week 52 will be examined with the following null ($H_{3.3,0}$) and alternative ($H_{3.3,1}$) hypotheses:

$H_{3.3,0}$: There is no difference in change from baseline in ZBI scores at Week 52 between the pegcetacoplan and placebo treatment groups

$H_{3.3,1}$: There is a difference in change from baseline in ZBI scores at Week 52 between the pegcetacoplan and placebo treatment groups.

Derivations and data handling conventions for the ZBI endpoint are described in Section 13.5.6. Absolute values and changes from baseline will be presented by treatment group and visit (up to week 52) using descriptive statistics. Means (±SE) will also be plotted over time.

Changes from baseline up to week 52 will be analyzed using the MMRM described in Section 6.1, with results presented as described there.

6.6.4. Time to Percutaneous Endoscopic Gastrostomy Tube Placement up to Week 52

The exploratory efficacy endpoint of time to percutaneous endoscopic gastrostomy tube placement up to week 52 will be examined with the following null ($H_{3.4,0}$) and alternative ($H_{3.4,1}$) hypotheses:

$H_{3.4,0}$: There is no difference in time to percutaneous endoscopic gastrostomy tube placement between the pegcetacoplan and placebo treatment groups

$H_{3.4,1}$: There is a difference in time to percutaneous endoscopic gastrostomy tube placement between the pegcetacoplan and placebo treatment groups.

Subjects who did not have the procedure at or prior to week 52 in study will be censored at the minimum of the last date of contact or their treatment discontinuation date for subjects whose ICE dictates hypothetical strategy, or their week 52 visit or first dose date+364 if week 52 is missing.. Subjects who were randomized but did not receive any treatment will be censored at the randomization date. Time to percutaneous endoscopic gastrostomy tube placement (or censor) will be calculated as date of death (or censor date) – date of randomization + 1.

Time to percutaneous endoscopic gastrostomy tube placement will be summarized with the Kaplan-Meier method, using plots and presentation of median (and 95% CIs) for time-to-event. Analysis will be done by a Cox proportional model as described in Section 6.1.

6.6.5. Change from Baseline in Serum pNfH at Week 52

The exploratory efficacy endpoint of change from baseline in serum pNfH at week 52 will be examined with the following null ($H_{3.6,0}$) and alternative ($H_{3.6,1}$) hypotheses:

$H_{3.6,0}$: There is no difference in change from baseline in serum pNfH at Week 52 between the pegcetacoplan and placebo treatment groups

$H_{3.6,1}$: There is a difference in change from baseline in serum pNfH at Week 52 between the pegcetacoplan and placebo treatment groups.

Values of pNfH are expected to be highly skewed, so before analysis and presentation, they will be natural log transformed. The handling of values below a LOD is described in Section 13.7.7. Geometric means will be presented for descriptive statistics. Geometric means and geometric mean ratios relative to baseline will be presented by treatment group and visit (up to week 52) using descriptive statistics.

Due to operational reasons, samples are only analyzed for NfH at week 52 visit or the last visit if the patient early withdrew. Thus, log-transformed NfH at week 52 compared to baseline will be

analyzed using the ANCOVA described in Section 6.1, with results presented as described there, with the exception that differences in LS means will reflect geometric mean ratios. LS means of geometric means (with 95% CIs) at week 52 will also be plotted.

6.7. Analyses of Open-Label Periods (OLP)

Data collected from OLP, ie, part 3 and part 4, will be analyzed with data from RCP to provide long-term efficacy and safety assessment. Baseline will be the same as defined for Week 52 analysis, and day 1 is the day of first dose in RCP. Patients will be analyzed according to the treatment assigned at randomization. CAFS analysis will be performed based on mITT set while other efficacy endpoints will be analyzed based on ITT set. The analyses compare early-start with delated-start of pegcetacoplan and provide further support for treatment effect to be observed in the randomized treatment period. For efficacy endpoints in OLP specified in Section 2.2, absolute value and change from baseline will be summarized by visits by the randomized treatment groups. The same strategies to hand ICEs and models will be used as specified for week 52 analyses. Statistical tests will be conducted in the order specified below. For other long-term endpoints that are not included in multiplicity control below, models used for week 52 analyses may still be used for analysis but only nominal p-values will be reported with estimates and 95% CI.

Multiplicity control

To control the overall type I error in OLP analyses, the endpoints will be tested in the following order:

1. Change from baseline in ALSFRS-R at week 104
2. Change from baseline in %SVC at week 104
3. Change from baseline in HHD at week 104
4. CAFS rank score at week 104
5. Time to death up to week 104
6. Time to death, permanent tracheostomy, or permanent assisted ventilation up to week 104

Analysis methods as described for the randomized treatment period will be used. Additional analysis using external control may be explored to evaluate the long-term effect of pegcetacoplan. Further details will be provided in a separate SAP.

7. SAFETY ANALYSIS

The safety analysis will be performed using the safety set. Safety variables include AEs, clinical laboratory variables, vital signs, and ECG variables. For each safety variable, the last value collected before the first dose of investigational product will be used as baseline for all analyses of that safety variable.

All safety analyses will be conducted according to the treatment the subject actually received.

7.1. Adverse Events

Adverse events will be coded using version 23.0 of MedDRA.

An AE will be considered treatment emergent (ie, a TEAE) if it has a start date on or after the first dose of randomized treatment or if it has a start date before the date of the first dose of double-blind investigational product, but increases in severity on or after the date of the first dose of double-blind investigational product. AEs that occur more than 56 days after the date of the last dose of investigational product will not be considered treatment emergent. (Eight weeks [56 days] is approximately 5 times the half-life of pegcetacoplan, which is about 10 days.)

All summaries of adverse events will be restricted to TEAEs. Therefore, TEAEs are referred to as AEs, and treatment emergent serious AEs are referred to as serious adverse events (SAEs) in this document.

An overall summary of the number of subjects with AEs will be presented, including the number and percentage of subjects with

- any AE
- AEs related to investigational product (evaluated by the investigator as definitely or possibly related)
- AEs related to infusion procedure (evaluated by the investigator as definitely or possibly related)
- injection/infusion site reactions
- SAEs
- SAEs related to investigational product (evaluated by the investigator as definitely or possibly related)
- any AE by maximum severity
- SAEs by maximum severity
- severe AEs
- AEs leading to interruption of study treatment
- AEs leading to discontinuation of study treatment
- AEs leading to study discontinuation
- AEs leading to death
- AEs in the following categories (with specific terms declared prior to unblinding):
  - hypersensitivity
  - sepsis

– infections

The overall summary will also include the total number of events reported for all categories above.

The number and percentage of subjects reporting AEs in each treatment group and overall will be tabulated alphabetically by SOC and PT for all of the itemized categories above. If more than one AE occurs with the same PT for the same subject, then the subject will be counted only once for that PT using the most severe and most related occurrence for the summarization by severity and by relationship to investigational product. The number of events will also be presented. These presentations will be sorted alphabetically by SOC then sorted within SOC using PT in the following hierarchy: (*i*) decreasing incidence in the pegcetacoplan group, (*ii*) decreasing incidence in the placebo group, and (*iii*) alphabetically.

AEs will also be presented without classification by SOC sorted by PT in the following hierarchy (*i*) decreasing incidence in the pegcetacoplan group, (*ii*) decreasing incidence in the placebo group, and (*iii*) alphabetically.

AEs will be summarized by SOC and PT by ANTI-PEG response status (see Section 7.6.2.2).

All AEs (treatment emergent or not) will be listed by subject, along with information regarding onset, duration, relationship to study treatment and infusion procedure, treatment emergent flag, severity, action taken with investigational product, seriousness, and outcome.

7.2. Injection/Infusion Site Assessment

Injection sites are to be assessed after each injection regardless of where the injection is done (home or clinic) and if there is a reaction, the attributes of the reaction are to be collected: redness, induration, swelling, bruising, rash, and other; and if the reaction is clinically significant, it is to be reported on the AE form. The incidence of injection site reactions, each attribute, and clinically significant injection site reactions will be summarized by treatment group. Injection site reactions reported as AEs will be presented in the appropriate AE sections.

7.3. Clinical Laboratory Data

Laboratory assays were to be done by a central laboratory. If laboratory parameters were assayed at a local laboratory, they will be normalized relative to central laboratory's upper and lower limits of normal.

Descriptive statistics for clinical laboratory values in SI units and changes from baseline at each assessment time point as well as shift tables (normal, abnormal low, and abnormal high) from baseline to each visit for quantitative variables will be presented by treatment group and overall for the following clinical laboratory variables:

Hematology hemoglobin, hematocrit, platelet count, red blood cell (RBC) count, white blood cell (WBC) count with differential, and absolute neutrophil and lymphocyte counts

Biochemistry albumin, alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), bicarbonate, bilirubin (total, direct, and indirect), blood urea nitrogen (BUN), calcium, chloride, creatinine, creatine kinase, estimated glomerular filtration rate (using Chronic Kidney Disease–Epidemiology

Collaboration [CKD-EPI] formula), gamma-glutamyltransferase (GGT), glucose, high-density lipoproteins (HDL), low-density lipoproteins (LDL), phosphorus, potassium, sodium, triglycerides, total cholesterol, total protein, and uric acid

Urinalysis blood, bilirubin, glucose, ketones, leukocyte esterase, microscopic examination of urine sediment (including for presence of RBCs, WBCs, and casts), nitrite, pH, pregnancy (when applicable), protein, specific gravity, and urobilinogen.

For hematology and biochemistry tests, the number and percentage of subjects with abnormal clinical laboratory test values (<lower limit of normal [LLN] or >upper limit of normal [ULN]) will be tabulated by treatment group and overall. For urinalysis tests, the number and percentage of subjects with positive results (>0, 'positive', or '+' or greater depending on the test) will be tabulated by treatment group and overall. The denominator is the total number of subjects with at least 1 postbaseline laboratory value for the parameter. All laboratory data will be listed for the safety set, and out-of-range values (ie, below LLN or above the ULN will be flagged. A listing of all abnormal laboratory values will also be presented.

7.4. Vital Signs

Descriptive statistics for vital signs (ie, systolic and diastolic blood pressure, heart rate, respiratory rate, temperature, and body weight) and their changes from baseline at each post-baseline visit and the LOV will be presented by treatment group and overall.

Vital sign values will be considered potentially clinically significant (PCS) if they meet the criteria listed in Table 4. The number and percentage of subjects with PCS post-baseline values will be tabulated by treatment group and overall. The percentages will be calculated relative to the number of subjects with baseline and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 PCS post-baseline vital sign value. A supportive listing of subjects with post-baseline PCS values will be provided including the subject number, site, baseline, and post-baseline PCS values.

Table 4: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign	Criteria
Heart Rate	≥100 bpm <40 bpm
Systolic blood pressure	≥130 mm Hg ≥160 mm Hg ≥180 mm Hg ≥20 mm Hg increase from baseline <90 mm Hg ≥20 mm Hg decrease from baseline
Diastolic blood pressure	≥90 mm Hg ≥15 mm Hg increase from baseline <40 mm Hg ≥15 mm Hg decrease from baseline

Table 4: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign	Criteria
Temperature	≥38°C

All vital signs data will be listed for the safety set.

7.5. Electrocardiogram

Descriptive statistics for ECG variables (ventricular rate, PR interval, QRS duration, QT interval, and QTcF interval) and their changes from baseline at each assessment time point will be presented by treatment group. ECG interpretation will be summarized by visit, and a shift table from baseline to each visit for qualitative ECG results will be presented.

ECG values will be considered PCS if they meet or exceed the upper limit values listed in Table 5. The number and percentage of subjects with post-baseline PCS values will be tabulated by treatment group. The percentages will be calculated relative to the number of subjects with baseline and at least 1 post-baseline assessment. The numerator is the total number of subjects with at least 1 PCS post-baseline ECG value. A listing of all subjects with post-baseline PCS value will be provided including the subject number, site, baseline, and post-baseline PCS values.

Table 5: Criteria for Potentially Clinically Significant ECG Values

ECG Parameter	Abnormal
Ventricular Rate	<40 bpm >100 bpm
PR interval	>200 msec
QRS interval	>120 msec
QTcF	>450 msec >480 msec >500 msec
QTcF increase from baseline	>30 msec >60 msec

7.6. Other Safety Data

7.6.1. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS asks about suicidal ideation and behavior; at both screening and baseline, the questions refer to both lifetime and the past 6 months, while at postbaseline visits, the questions refer to the time since the previous visit.

The C-SSRS will be categorized as follows with binary response (yes/no):

- Suicidal ideation questions
  - Category 1 – Wish to be Dead

  - Category 2 – Nonspecific Active Suicidal Thoughts
  - Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
  - Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
  - Category 5 – Active Suicidal Ideation with Specific Plan and Intent
- Suicidal behavior questions
  - Category 6 – Preparatory Acts or Behavior
  - Category 7 – Aborted Attempt
  - Category 8 – Interrupted Attempt
  - Category 9 – Actual Attempt (nonfatal)
  - Category 10 – Completed Suicide

The number and percentage of subjects for following endpoints will be summarized by visit:

- Suicidal ideation: A "yes" answer to any one of the 5 suicidal ideation questions
- Suicidal behavior: A "yes" answer to any one of the 5 suicidal behavior questions
- Suicidal ideation or behavior: A "yes" answer to any one of the 10 suicidal ideation and behavior questions

For screening and baseline, both the lifetime and past 6-month intervals will be presented.
A shift table from baseline (lifetime and past 6 months) to postbaseline (by visit and worst-case postbaseline) will be presented.

All C-SSRS data will be presented in a listing.

7.6.2. Immunogenicity

7.6.2.1. Sample-Level ADA Assay Data

Number and percentage of samples will be presented for the following. Samples will be classified as follows:

- **Evaluable Sample** – when a sample could be tested for ADA status and has a result.
- **ADA-Positive Sample** – when the sample is positive in the confirmatory assay
- **ADA-Negative Sample** – when the sample is negative in the screening assay or the confirmatory assay, and drug is at a level that does not interfere with the ADA method
- **ADA-Inconclusive Sample** – when the sample is negative in the screening assay or the confirmatory assay, and drug is at a level that interferes with the ADA method, then the sample is considered inconclusive
- **Unevaluable Sample** – when a sample could not be tested for ADA status due to inadequate sample volume, mishandling, or errors in sample collection, processing, storage, etc.
- **NAb Positive**– when the sample is positive in the antipeptide neutralizing antibody assay.
- **NAb Negative** - when the sample is negative in the antipeptide neutralizing antibody assay.
- **NAb Inconclusive**- when the sample is negative in the antipeptide neutralizing antibody assay, and drug is at a level that interferes with the method, then the sample is considered inconclusive

The titer range will also be presented for each ADA positive sample (predose, and post--dose) by treatment and overall.

7.6.2.2. ADA Response

Subject-level responses for anti–pegcetacoplan peptide antibodies and anti-PEG antibodies will be presented as a number and percentage by treatment and total.

The number of subjects with evaluable baseline samples will be presented, and the number (and percentage) of those subjects who have a positive baseline sample will be presented as subjects with pre-existing ADA.

Subject-level response will be summarized in the following categories:

- **Evaluable Subject** – A subject with at least one sample taken with a reportable result after first dosing during the treatment or follow-up period. The number (percentage) of evaluable subjects will be presented for the following categories
    - **ADA-Positive Subjects/ADA Incidence** – An evaluable subject with at least one predose sample and one treatment-emergent or treatment-boosted ADA-positive

sample at any time after dosing. All ADA positive subjects are equal to the ADA incidence

- **Treatment-Emergent ADA response**: An evaluable patient with a baseline ADA-negative sample and an ADA positive sample after treatment. ADA developed de novo.

- **Treatment Boosted ADA response:** An evaluable patient with a baseline ADA positive sample and a postdose ADA positive sample that was ≥ 4x the baseline titer (eg, baseline titer of 10 vs Postdose titer of 40)

- For treatment-emergent or treatment boosted ADA response, the following subcategories will be presented:

  - **Transient ADA Response**
    - Treatment-emergent positive subjects were classified as having a transient response if they had only a single ADA positive sample (that was not the last assessment), or more than 1 ADA positive sample within < 112 days (16 weeks) and not thereafter.
    - Treatment Boosted ADA positive subjects were classified as having a transient response if they had only a single ADA boosted sample (that was not the last assessment), or more than 1 positive boosted sample within < 112 days (16 weeks) and not thereafter.
  - **Persistent ADA Response**
    - Treatment-emergent positive subjects were classified as having a persistent response if they had more than 1 positive ADA sample ≥ 112 days (16 weeks) apart, or a positive ADA sample at the last time point with no further results available.
    - Treatment Boosted ADA positive subjects were classified as having a persistent response if they had more than 1 positive boosted sample ≥ 112 days (16 weeks) apart, or a positive boosted sample at the last time point with no further results available.
  - **Unclassified ADA Response**
    - Any ADA positive subject that cannot be defined as having a transient or persistent ADA response.

- **ADA-Negative Subject** – An evaluable subject without a treatment-emergent or treatment-boosted ADA-positive sample during the treatment or follow-up period.

- **ADA-Inconclusive Subject** – An evaluable subject who cannot be classified as either ADA-positive or ADA-negative (eg, assay drug tolerance issues, postdose

positive without a baseline sample, positive baseline and positive postdose sample without a titer value, etc.)

For subjects with pre- or postdose sample results, subject response level will also be summarized in categories:

- **Neutralizing ADA** - Any subject with a NAb positive sample. From the total subject population including both the evaluable and unevaluable subjects
- **ADA Prevalence** – The proportion of all ADA positive subjects, including those with pre-existing antibodies, computed as a percentage of the total number of subjects, including both the evaluable and unevaluable subjects.

7.6.3. Physical Exam

Changes in physical examinations will be described in a listing.

8. PHARMACOKINETIC ANALYSIS

All summaries and analyses of the pharmacokinetic data will be based on the Pharmacokinetic set defined in Section 4.6.

8.1. Drug Concentration

Individual pegcetacoplan concentrations, actual sampling times and deviations from nominal sampling times will be presented in a data listing for all subjects included in

the PK population. Placebo samples will also be included in the data listing if they were analyzed but will not be summarized.

PK concentrations from unscheduled visits will be listed separately. In addition, subjects undergoing early termination, and subjects starting/stopping treatment at various time points will be listed separately.

Pegcetacoplan concentrations will be summarized by treatment group at each scheduled time point using descriptive statistics (including mean, SD, coefficient of variation (CV), Median, Min, Max, Geometric Mean/%CV). The number of subjects with a BLQ concentration at each scheduled time point will also be tabulated. The handling of BLQ concentrations in the summary tables is described in Section 8.2.1. Missing values will be omitted from the calculation of descriptive statistics.

Linear and semilogarithmic individual concentration-time profiles will be generated using actual sampling times. Linear and semilogarithmic mean (± SD) and median concentration plots will be generated using nominal sampling times. The number of subjects contributing to each mean or median value at a visit will be presented above the x-axis.

8.2. Handling BLQ Values

8.2.1. Handling of BLQ Concentrations in Summary Tables

BLQ concentrations prior to first dosing (day 1): Pretreatment pegcetacoplan concentrations reported as BLQ will be taken as zero for the computation of descriptive statistics, except geometric mean. Geometric mean cannot be calculated and will be reported as “N/A” or “-”.

BLQ concentrations occurring at any time after first dosing: Pegcetacoplan concentrations reported as BLQ will be taken as half the lower limit of quantification (LLOQ/2).

8.2.2. Handling of BLQ Concentrations in Figures

BLQ concentrations prior to first dosing (day 1): Pretreatment pegcetacoplan concentrations reported as BLQ will be taken as zero for linear plots, and equal to half the lower limit of quantification (LLOQ/2) for semilogarithmic plots.

BLQ concentrations occurring at any time after first dosing: Pegcetacoplan concentrations reported as BLQ will be taken as half the lower limit of quantification (LLOQ/2) for both linear and semilogarithmic plots.

8.3. Statistical Analysis

Population pharmacokinetic and exposure-response modelling of the safety and efficacy data will be described in an APL-2 Population Pharmacokinetic/Pharmacodynamic Analysis Plan. The methods will be based on the FDA Guidance for both Exposure-Response and Population Pharmacokinetics (FDA Guidance for Industry Population Pharmacokinetics, FDA Guidance for Exposure-Response Relationships). Results of PK and exposure-response modelling may be presented in a report separate from the clinical study report.

9. PHARMACODYNAMIC ANALYSIS

9.1. Pharmacodynamic Data

9.1.1. Pharmacodynamic Endpoints and Analysis

All summaries and analyses of the pharmacodynamic (PD) data will be based on the pharmacodynamic set.

Observed values, changes from baseline and percentage changes from baseline will be summarized by treatment group at each visit using descriptive statistics for the following parameters:

- Change from baseline to week 52 and week 104 of CH50 levels
- Change from baseline to week 52 and week 104 of AH50 levels
- Change from baseline to week 52 and week 104 of C3 levels

Median profile plots will also be presented graphically by treatment group for the observed values and percentage changes from baseline. The nominal sampling time will be used on the x-axis.

Changes from baseline and percentage changes from baseline will be included in listings.

10. OTHER ANALYSES

No other analyses are planned for this study.

11. INTERIM ANALYSIS

No formal interim analysis was planned or performed.

12. DATA MONITORING COMMITTEE/REVIEW COMMITTEE

A DMC will review cumulative safety/tolerability and efficacy data. The DMC's responsibilities include conducting a thorough safety assessment at regular predefined intervals during the treatment period of the study, and recommendations for plans for study conduct, which may include continuation, modification, or termination based on the overall assessment of potential risks and benefits to the subjects.

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 was held after 20 subjects had completed visit 3 (study week 4).

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

13. DATA HANDLING CONVENTIONS

13.1. General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, standard deviation, 25th and 75th percentiles, minimum, and maximum; in addition, for variables that are log-transformed, geometric means and 95% CIs will be presented. The SE should be added to all tables containing between group statistical comparisons except where variables have been log-transformed, in which case, geometric means and 95% CIs will be presented.

Categorical and count variables will be summarized by the number of subjects (n) and the percent of subjects in each category.

Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more decimal place than the original values, and standard deviations should be printed out to 2 more decimal places than the original values. The minimum and maximum should report the same number of decimal places as the original values. Percentages will be displayed with 1 decimal place; except percentages will not be presented when the count is zero and 100% will be presented as an integer. P-values should be presented to 4 decimal places.

13.2. Definition of Relative Study Days

Unless otherwise noted, the relative study day, or analysis study day (ADAY), of an evaluation is defined as the number of days relative to the first dose date of study drug, which is designated as day 1, and the preceding day is day -1, the day before that is day -2, etc.

If the evaluation date is on or after first dose date then the relative study day is calculated as:

ADAY = Evaluation date − first dose date of study drug + 1.

If the evaluation date is before the first dose date then the relative study day is calculated as

ADAY = Evaluation date − first dose date of study drug

Relative study day takes on negative values if the evaluation date occurs prior to the first dose date and takes positive values if the evaluation date occurs on or after the first dose date of study drug.

For subjects who were randomized but not treated, the *date of randomization* will replace the *first dose date of study drug* in the above calculations.

13.3. Mapping of Visits for Clinic SVC

For the clinic-based SVC assessments, which are obtained via vendor data transfer outside the electronic data capture clinical database system, assessments will be mapped to visit numbers based on exact matches of SVC assessment dates to visit dates in the clinical database.

13.4. Definition of Visit Windows

13.4.1. All Assessments Except At-Home SVC

All assessments occurring on or before the first date of dosing (ADAY ≤ 1) will be assigned to the baseline analysis visit window.

Unless otherwise specified, the actual scheduled nominal postbaseline visit will be used for all summaries across time. Postbaseline unscheduled visits and early termination visits will be mapped to a scheduled visit and will be used in the analysis only if the nominal scheduled visit result is missing. Table 6 presents the analysis visit window mapping for unscheduled and early term visits for assessments done every 4 weeks (ALSFRS-R, EQ-5D-5L, and ZBI), and Table 7 presents these for assessments done at baseline and weeks 4, 12, 24, 36, and 52 (HHD, in-clinic SVC, ALSAQ-40, labs, and pharmacodynamics). In the case that multiple unscheduled or early termination visits are in the same analysis window, the one closest to the target date will be used. In the event that the windowed visit is mapped to an illogical sequence of visits when considering nearby scheduled visits (ie, windowed visit is higher than the subsequent visit or lower than the preceding visit), the windowed visit will be set to the logical scheduled visit.

Table 6: Postbaseline Analysis Visit Windows for Unscheduled and Early Termination Visits for Assessments Done Every 4 Weeks

Analysis visit	Target study day	Analysis window (days)
Week 4	29	2 to 43
Week 8	57	44 to 71
Week 12	85	72 to 99
Week 16	113	100 to 127
Week 20	141	128 to 155
Week 24	169	156 to 183
Week 28	197	184 to 211
Week 32	225	212 to 239
Week 36	253	240 to 267
Week 40	281	268 to 295
Week 44	309	296 to 323
Week 48	337	324 to 351
Week 52	365	• 352 to 379 for subjects who do not enter OLP • 352 to OLP RxStart for subjects who do enter OLP
Week 56	393	OLP RxStart to 407
Week 60	421	408 to 435
Week 64	449	436 to 463
Week 68	477	464 to 491
Week 72	505	492 to 519
Week 76	533	520 to 547
Week 80	561	548 to 575
Week 84	589	576 to 603

Table 6: Postbaseline Analysis Visit Windows for Unscheduled and Early Termination Visits for Assessments Done Every 4 Weeks

Analysis visit	Target study day	Analysis window (days)
Week 88	617	604 to 631
Week 92	645	632 to 659
Week 96	673	660 to 687
Week 100	701	688 to 715
Week 104	729	716 to 729
Note: OLP RxStart: date of first dose of open-label treatment.		

Table 7: Postbaseline Analysis Visit Windows for Unscheduled and Early Termination Visits for Assessments Done at Baseline and Weeks 4, 12, 24, 36, and 52

Analysis visit	Target study day	Analysis window (days)
Week 4	29	2 to 57
Week 12	85	58 to 127
Week 24	169	128 to 211
Week 36	253	212 to 309
Week 52	365	• 352 to 379 for subjects who do not enter OLP • 352 to OLP RxStart for subjects who do enter OLP

Note: OLP RxStart: date of first dose of open-label treatment.

13.4.2. At-Home SVC

The first at-home SVC assessment will be used as the baseline. All other assessments will be assigned a week value based on ADAY, which is defined relative to the study start date and is defined in Section 13.2.

All summaries over time of at-home SVC will be done by week assigned by the following formula: $Week = \lceil ADAY/7 \rceil$, for ADAY greater than the first at-home SVC assessment date, and where $\lceil x \rceil$ indicates the ceiling function.

13.5. Derived Efficacy Endpoints

13.5.1. ALSFRS-R

The ALSFRS-R includes 12 items, with each item scored on a five-point scale from 0 to 4. Individual item scores will be summed to produce a total score between 0 (worst) and 48 (best). Assessments without all 12 items completed will be excluded from analysis only at that particular time point.

Domain-specific scores (each with 3 items and a score of 0 to 12) will also be defined as follows:

- Bulbar function: speech, salivation, and swallowing
- Fine Motor: handwriting, cutting food and handling utensils, and dressing and hygiene
- Gross Motor: turning in bed and adjusting bed clothes, walking, and climbing stairs
- Respiratory: dyspnea, orthopnea, and respiratory insufficiency

13.5.2. SVC Measures

For SVC measurements, all measurements taken on the same day will be considered from the same assessment, and the maximum value (based on percent predicted SVC) will be used within a day. This will be done separately for in-clinic and at-home assessments.

13.5.3. HHD Megascore

Double trials of HHD will be performed for each subject at each visit. In the event that the 2 trials differ by 15% or more, and the evaluator believes that one of the trials was inaccurate for any reason, a third test is to be performed. All 3 values shall be recorded. The assessment used for analysis for each muscle group is determined as follows:

- If there is 1 measure (m_1) taken, use m_1
- If there are 2 measures (m_1 and m_2) taken, use max(m_1, m_2)
- If there are 3 measures (m_1, m_2, and m_3) taken:
  - If all 3 are within 15% of each other (ie, max(m_1, m_2, m_3) / min(m_1, m_2, m_3) $\leq$1.15) then use max(m_1, m_2, m_3)
  - If all 3 measures are not within 15% of each other (including cases where one or more measurements are zero) then
    - If there is a unique set of the closest 2 then use max(of closest 2 of m_1, m_2, and m_3)
    - If there is not a unique set of the closest 2 then use max(m_1, m_2, m_3)

For each subject, the megascore will be determined as following:

1. For each muscle, using the measure selected above, calculate each muscle's z-score as (muscle strength – mean of muscle strength of healthy subjects) divided by standard deviation of muscle strength of healthy subjects (see Table 8). Subjects who are "unable to test" for a given muscle (not simply 'not done') will have that muscle scored as a 0 (zero).
2. Next calculate megascore as average of overall z-scores over all muscles

In order to calculate the megascore, at least 6 of the 16 muscle groups need to be present (ie, no more than 10 of 16 can be missing).

Table 8: Mean Strength and Standard Deviation for Healthy Subjects

Muscle group	Mean (lb)	Standard deviation (lb)
Left shoulder flexion	29.71	9.27
Right shoulder flexion	30.89	9.05
Left elbow flexion	34.79	11.51
Right elbow flexion	34.99	11.77
Left elbow extension	28.23	8.74
Right elbow extension	28.20	8.33
Left wrist extension	25.02	8.72
Right wrist extension	26.49	8.75
Left knee extension	35.28	13.30
Left knee flexion	36.71	13.14
Right knee flexion	36.97	12.58
Right knee extension	35.80	14.16
Left ankle dorsiflexion	38.03	15.24
Right ankle dorsiflexion	38.46	15.49
Left first dorsal interosseous	11.18	3.83
Right first dorsal interosseous	11.79	4.34

The results are based on 228 healthy reported in Shefner et al. 2016.
If kg are used, the following conversion factor will be used: 1 lb = 0.453592 kg

13.5.4. ALSAQ-40

The ALSAQ-40 contains 40 questions with each scored from 0 (never, or best) to 4 (always, or worst), so the total possible score ranges from 0 to 160. The 40 questions represent 5 dimensions of health status:

- Physical Mobility (10 items: 1-10; possible score of 0-40) addresses problems of mobility such as difficulties of walking, standing up, going up and down stairs and falling.
- Activities of Daily Living/Independence (10 items: 11-20; possible score of 0-40) addresses a variety of limitations in ADL such as difficulties in washing oneself, dressing oneself, doing tasks around the house, as well as difficulty writing and getting dressed.
- Eating and Drinking (3 items: 21-23; possible score of 0-12): addresses problems eating solid foods, swallowing and drinking liquids.
- Communication (7 items: 24-30; possible score: 0-28) addresses a variety of problems communicating with others such as difficulties with speech such as talking slowly, stuttering whilst speaking and feeling self-conscious about speech.

- Emotional Functioning (10 items: 31-40; possible score: 0-40) addresses various emotional problems such as feeling lonely, bored, depressed, as feeling of embarrassment in social situations and feeling worried about the disease will progress in the future.

The total score and the score of each dimension will be scaled to have a range from 0 (the best health status) to 100 (the worst health status) and will be calculated as:

$$Scaled\ Score\ = \frac{sum\ of\ raw\ scores\ in\ dimension\ [\text{or total}]}{max\ possible\ sum\ of\ raw\ scores\ dimension\ [\text{or total}]} \times 100$$

13.5.5. EQ-5D-5L

The EQ5D5L contains 2 components: the VAS, which is scored between 0 and 100, and the 5 questions, each with 5 levels.

The VAS will be summarized and analyzed as a simple numeric score.

13.5.6. ZBI

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.

13.6. Repeated or Unscheduled Assessments of Safety Parameters

If a subject has repeated assessments before the start of investigational product, then the results from the final assessment made prior to the start of investigational product will be used as baseline. If end of study assessments are repeated or unscheduled, the last postbaseline assessment will be used as the end of study assessment for generating descriptive statistics. However, all postbaseline assessments will be used for PCS value determination and all assessments will be presented in the data listings.

13.7. Handling of Missing, Unused, and Spurious Data

Missing data is addressed in the relevant sections elsewhere. Spurious data will be discussed with data management and others as appropriate to address with queries to sites or vendors. In general, all data will be used as reported (and after query resolutions); any decisions to remove data would be made and documented prior to unblinding.

13.7.1. Missing Date of Investigational Product

When the date of the last dose of investigational product is missing for a subject in the safety set, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last visit date when investigational product was returned will be used in the calculation of treatment duration.

13.7.2. Missing Date Information for Prior or Concomitant Medications (Therapies/Procedures)

For prior or concomitant medications (and/or therapies/procedures), including rescue medications, incomplete (ie, partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, the start date first will be imputed first.

13.7.2.1. Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

13.7.2.1.1. Missing Day, Month, and Year

In this case, no start date will be imputed. However, the medication will be assumed to be a prior medication. If the stop date is missing or if the stop date is on or after the date of the first dose of investigational product, the medication will also be considered a concomitant medication.

13.7.2.1.2. Missing Day and Month

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.

13.7.2.1.3. Missing Month Only

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

13.7.2.1.4. Missing Day Only

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

13.7.2.2. Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of investigational product is missing, then replace it with the last visit date. If the imputed stop date is before the start date (imputed or nonimputed start date), then the imputed stop date will be equal to the start date.

13.7.2.2.1. Missing Day and Month

- If the year of the incomplete stop date is the same as the year as of the date of the last dose of investigational product, then the day and month of the date of the last dose of investigational product will be assigned to the missing fields
- If the year of the incomplete stop date is before the year of the date of the last dose of investigational product, then 31 December will be assigned to the missing fields
- If the year of the incomplete stop date is after the year of the date of the last dose of investigational product, then 01 January will be assigned to the missing fields.

13.7.2.2.2. Missing Month Only

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

13.7.2.2.3. Missing Day Only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the date of the last dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the last dose of investigational product or if both years are the same but the month is before the month of the date of the last dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the last dose of investigational product or if both years are the same but the month is after the month of the date of the last dose of investigational product, then the first day of the month will be assigned to the missing day.

13.7.3. Missing Date Information for Adverse Events

For AEs with partial start dates, nonmissing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the nonmissing date parts as to when the AE occurred relative to study drug administration, eg, AE start year and month are the same as the year and month of the first dose of investigational product, then the AE will be classified as treatment-emergent.

To facilitate categorization of AEs as treatment emergent, imputation of dates can be used. For AEs, the default is to only impute incomplete (ie, partially missing) start dates. Incomplete stop dates may also be imputed when calculation of the duration of an AE is required per the protocol. If imputation of an incomplete stop date is required, and both the start date and the stop date are incomplete for a subject, impute the start date first.

13.7.3.1. Incomplete Start Date

Follow the same rules as in Section 13.7.2.1, except in the case where the start date is completely missing (ie, missing day, month, and year):

- If the stop date is missing or is on or after the date of the first dose of investigational product, the start date will be set to the date of the first dose of investigational product.
- If the stop date is before the date of the first dose of investigational product, the start date will be set to stop date.

13.7.3.2. Incomplete Stop Date

Follow the same rules as in Section 13.7.2.2.

13.7.4. Missing Date Information for Dates of ALS Symptom Onset or Disease Diagnosis

Missing dates for ALS symptom onset and disease diagnosis will be imputed as follows:

- Missing day and month: '02-July' will be imputed for day-month
- Missing day: '15' will be imputed for day.

If these imputations result in a symptom onset date after the diagnosis date, the symptom onset date will be set equal to the diagnosis date.

13.7.5. Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of investigational product, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of investigational product, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

13.7.6. Missing Relationship to Investigational Product for Adverse Events

If the relationship to investigational product is missing for an AE starting on or after the date of the first dose of investigational product, a causality of "Related" will be assigned. The imputed values for relationship to double-blind investigational product will be used for incidence summaries, while both the actual and the imputed values will be presented in data listings.

13.7.7. Character Values of Clinical Laboratory Variables

For numeric laboratory values below an LOD (eg, reported as "<LOD"), a value of $LOD/\sqrt{2}$ will be used for descriptive statistics, shift tables and PCS values. For values above a limit of quantification, LOQ (eg, reported as ">LOQ"), a value of $LOQ + 0.0000000001$ will be used for descriptive statistics, shift tables and PCS values. However, the actual values as reported in the database will be presented in data listings.

14. ANALYSIS SOFTWARE

Statistical analyses will be performed using version 9.4 (or newer) of SAS® on a suitably qualified environment.

15. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

The following changes were made to the analyses specified in the protocol.

- The protocol stated that baseline for % predicted SVC from home spirometry was the first assessment which could be done after the first dose of study treatment. However, baseline for home SVC is required to be prior to first dose of study treatment.
- For the time to death, permanent tracheostomy, or permanent assisted ventilation endpoint, the protocol stated: “Subjects who were randomized but who not receive any treatment will be censored at the randomization date.” However, given theses analyses will be based on the ITT population, which includes all randomized subjects, any postbaseline observations will be used in the analysis.
- The MMRM models for continuous outcomes did not include the visit-by-baseline interaction term; this has been added; otherwise, if this term were not included, the effect of baseline on the outcome is assumed to be the same at all visits.

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