A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Parallel Group, Multicenter Study With an Open-Label Extension to Evaluate the Efficacy and Safety of Ravulizumab in Patients With Amyotrophic Lateral Sclerosis (ALS)

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TITLE PAGE

STATISTICAL ANALYSIS PLAN

Final Analysis of Study

Version Number: 2.0

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VERSION HISTORY

This statistical analysis plan (SAP) for study ALXN1210-ALS-308 is based on protocol amendment 6 dated 23Jun2021.

SAP Version	Version Date	Change	Rationale
1	2July2021	Not Applicable	Original version
2	18Nov2021	See Section 6.4 (Appendix 4) for detailed changes.	Due to the study meeting the pre-specified futility criterion during the first interim analysis conducted by IDMC, the scope of the analyses for this study has been revised and is reflected in this SAP amendment

APPROVAL SIGNATURES

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1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods for analyzing data for the study ALXN1210-ALS-308, "A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicenter Study With an Open-Label Extension to Evaluate the Efficacy and Safety of Ravulizumab in Patients With Amyotrophic Lateral Sclerosis (ALS)".

The scope of the analyses for this study has been revised and is reflected in this SAP amendment due to the study meeting the prespecified futility criterion. This SAP amendment will be finalized prior to the final database lock. No separate SAP will be developed for the Open-Label Extension (OLE) Period of the study.

The table, figure, and listing specifications will be provided in a separate data presentation plan document.

1.1. Objectives, Estimands and/or Endpoints

Objective	Estimand/Endpoint
Primary	
To evaluate the effect of ravulizumab compared with placebo on amyotrophic lateral sclerosis functional rating scale-revised (ALSFRS-R) score in adult patients with ALS	Estimand: Difference in mean combined assessment of function and survival (CAFS) score between ravulizumab and placebo in the eligible ALS patient population after accounting for the intercurrent event (ICE) of death into the CAFS score calculation using the composite strategy. See Section 5.3 for details.
Secondary	
To evaluate the effect of ravulizumab compared with placebo on ventilation assistance-free survival (VAFS) in adult patients with ALS	Estimand: Hazard ratio (ravulizumab versus placebo) of VAFS event in the eligible ALS patient population using treatment-policy strategy
To evaluate the effect of ravulizumab compared with placebo on respiratory function in adult patients with ALS	Estimand: Difference in mean change in slow vital capacity (SVC) percent predicted score between ravulizumab and placebo at Week 50 in the eligible ALS patient population using treatment-policy strategy
To evaluate the safety of ravulizumab compared with placebo in adult patients with ALS	Endpoint: Incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and TEAEs leading to study drug discontinuation
To evaluate the effect of ravulizumab compared with placebo on muscle strength in adult patients with ALS	Endpoint: Percent change in combined muscle megascore from Baseline at Week 50 as assessed by handheld dynamometry (HHD)
To evaluate the effect of ravulizumab compared with placebo on neurofilament light chain (NfL) concentrations in adult patients with ALS	Endpoint: NfL concentrations in serum at Week 50
To characterize the pharmacokinetics (PK) of ravulizumab in adult patients with ALS	Endpoint: Change in serum ravulizumab concentration over the study duration
To characterize the pharmacodynamics (PD) of ravulizumab in adult patients with ALS	Endpoint: Change in serum-free complement component 5 (C5) concentration over the study duration
To characterize the immunogenicity of ravulizumab in adult patients with ALS	Endpoint: Presence and titer of anti-drug antibodies (ADAs)

Objective	Estimand/Endpoint
Exploratory	
To evaluate the effect of ravulizumab compared with placebo on respiratory function in adult patients with ALS	Endpoint: Time to the first instance of SVC < 50% predicted during the 50-week Randomized Controlled Period (RCP)
To evaluate the effect of ravulizumab compared with placebo on overall health-related quality of life in adult patients with ALS	Endpoint: Change from Baseline in Short-Form Health Survey (SF-36) at Week 50; Change from Baseline in European Quality of Life Health 5-item questionnaire (EQ-5D-5L) at Week 50
To evaluate the safety of ravulizumab compared with placebo in adult patients with ALS	Endpoint: Shifts from Baseline in Columbia-Suicide Severity Rating Scale (C-SSRS) at Week 50; Change from Baseline in vital signs, electrocardiogram (ECG) parameters, and clinical laboratory assessments
To characterize biomarkers in adult patients with ALS	Endpoint: Change from Baseline in levels of biomarkers of complement dysregulation, neuroinflammation, and neurodegeneration
To evaluate the effect of ravulizumab compared with placebo on ALS-related health quality of life in adult patients with ALS	Endpoint: Change from Baseline in ALS assessment questionnaire (ALSAQ-40) score at Week 50
To characterize the effect of ravulizumab compared to placebo on disease stage in adult patients with ALS	Endpoint: Any increase from the baseline stage on the King's staging system (KSS) at Week 50
To evaluate the long-term efficacy of ravulizumab in adult patients with ALS	Endpoint: Change in ALSFRS-R total score, VAFS, SVC, HHD, and patient-reported outcome measures over time in all patients exposed to ravulizumab during the OLE Period
To evaluate the long-term safety of ravulizumab in adult patients with ALS	Endpoint: Incidence of TEAEs, TESAEs, and TEAEs leading to study drug discontinuation during the OLE Period

1.2. Study Design

Study ALXN1210-ALS-308 is a Phase 3, double-blind, randomized, placebo-controlled, parallel-group, multicenter study with an OLE to evaluate the efficacy and safety of ravulizumab in adult patients with amyotrophic lateral sclerosis (ALS). There are 3 periods in this study:

Screening Period: Patients will be screened for eligibility for up to 4 weeks during the Screening Period. Patients who are not taking or who are on a stable riluzole and/or edaravone regimen at Screening will be considered for participation.

RCP: Eligible adult ALS patients will be randomized in a 2:1 ratio to ravulizumab or placebo arm within each stratum as defined in Table 1. Approximately 354 patients will be enrolled in North America, Europe, and the Asia-Pacific region. Weight-based intravenous infusion of ravulizumab or matching placebo will be administered in a blinded fashion until Week 42 during the RCP. The primary endpoint will be evaluated at Week 50.

Table 1: Randomization Strata

Strata	ALS Muscle Weakness at the Onset	Background ALS Therapy (Riluzole or Edaravone) at Study Entry	
	(Bulbar vs. Not)	On Stable Riluzole	On Stable Edaravone
1	Not bulbar	No	Yes, No
2	Not bulbar	Yes	Yes
3	Not bulbar	Yes	No
4	Bulbar	No	Yes, No
5	Bulbar	Yes	Yes
6	Bulbar	Yes	No

[a] Stable riluzole: at least 30 days on riluzole prior to Day 1.
[b] Stable edaravone: at least 60 days on edaravone prior to Day 1.
Abbreviations: ALS = amyotrophic lateral sclerosis; vs = versus

Patients who do not enter the study on riluzole and/or edaravone will not be permitted to start treatment with either drug during the RCP.

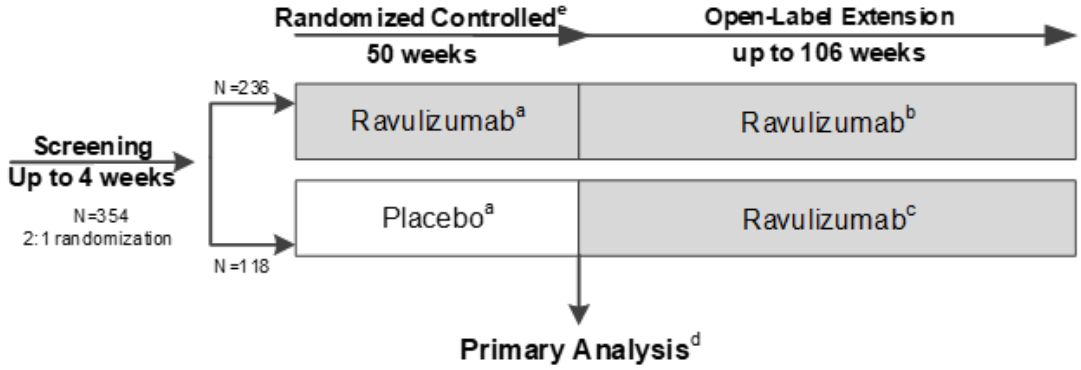
One unblinded interim analysis for futility is planned when approximately 33% of originally planned patients (N = 354) complete the Week 26 visit for the RCP. An independent data monitoring committee (IDMC) will be established to conduct this unblinded interim analysis and periodic review of accumulating data for patient safety and efficacy during the study. Details of the interim analysis methods are described in a separate interim analysis plan (IAP).

OLE Period: For each participant, the RCP ends, and the OLE Period starts, when the participant has completed the Week 50 visit assessments and received the first dose for the OLE. Regardless of the randomized assignment, all patients will receive ravulizumab during the OLE Period. Blind to the randomized treatment assignment will be maintained for patients and providers during the OLE Period until the end of the study. Initiation of riluzole and/or edaravone is permitted during the OLE Period. The first dose of the OLE Period will be administered in a blinded fashion to accommodate the loading dose for the patients originally randomized to placebo (see protocol for further details).

The OLE Period will continue for up to 2 years or until ravulizumab is approved and/or available (per country-specific regulations), whichever occurs first.

After the End of Treatment Visit or early discontinuation, patients will be followed for an additional 8 weeks after their last dose of the study drug.

Figure 1: Study Design Schematic



2. STATISTICAL HYPOTHESES

2.1. Primary Hypothesis

The primary null hypothesis is that the effect of ravulizumab is no different from placebo in functional decline measured by the change from Baseline in ALSFRS-R total score at Week 50. The alternative hypothesis is that ravulizumab will slow the disease progression by reducing the decline from Baseline in ALSFRS-R total score at Week 50 compared to placebo.

2.2. Secondary Hypotheses

The null hypotheses associated with the secondary objectives are that ravulizumab is no different from placebo for the respective endpoints; the alternative hypotheses are described below:

2.2.1. Key Secondary Hypotheses

- **Time to VAFS**: The alternative hypothesis is that treatment with ravulizumab will prolong the time to VAFS compared to placebo.
- **Change in SVC percent predicted**: The alternative hypothesis is that treatment with ravulizumab will slow the decline from Baseline in SVC at Week 50 compared to placebo.

2.2.2. Supportive Secondary Hypotheses

- **Change in muscle strength (HHD)**: The alternative hypothesis is that treatment with ravulizumab will slow the decline from Baseline in muscle strength at Week 50 compared to placebo.
- **Neurofilament concentration (NfL)**: The alternative hypothesis is that treatment with ravulizumab will reduce the NfL concentration level at Week 50 compared to placebo.

2.3. Tertiary Hypotheses

- **Change in SF-36**: The alternative hypothesis is that treatment with ravulizumab will reduce the worsening from Baseline in SF-36 physical component summary (PCS) and mental component summary (MCS) at Week 50 compared to placebo.

- **Change in EQ-5D-5L**: The alternative hypothesis is that treatment with ravulizumab will reduce the worsening from Baseline in EQ-5D-5L visual analog scale (VAS) and Health Stage Index at Week 50 compared to placebo.
- **Time to the first instance of SVC percent predicted < 50**: The alternative hypothesis is that treatment with ravulizumab will prolong the time to the first instance of SVC percent predicted < 50 compared to placebo.
- **Change in ALSAQ-40 score**: The alternative hypothesis is that treatment with ravulizumab will reduce the worsening from Baseline in ALSAQ-40 at Week 50 compared to placebo.
- **Change in KSS**: The alternative hypothesis is that treatment with ravulizumab will reduce the worsening in KSS at Week 50 compared to placebo.

3. SAMPLE SIZE DETERMINATION

The sample size calculations were based on information extracted from the PRO-ACT (Pooled Resource Open-Access ALS Clinical Trials) database consisting of clinical trials data pooled from 23 Phase 2/3 ALS clinical trials. Approximately 354 patients will be randomized to ravulizumab or placebo in a 2:1 ratio.

The mean change in ALSFRS-R total score in the placebo arm at Week 50 is estimated as −14.3 (assuming a monthly linear slope of the decline of 1.19 calculated based on the proposed study inclusion criteria). Assuming a 30% relative reduction in the monthly slope in the ravulizumab group is considered a clinically meaningful treatment effect (Castrillo-Viguera, 2010; Writing Group for Edaravone ALS Study., 2017), the mean change in ALSFRS-R total score at Week 50 is estimated as −10. A common standard deviation (SD) of 10.3 was estimated for the change from Baseline in ALSFRS-R total score. A total of 282 patients will be required to ensure at least 90% nominal power based on a 2-sided t-test (Type I error = 0.05) for detecting a non-zero treatment effect for ALSFRS-R (defined as the difference between ravulizumab and placebo in the mean change from Baseline in ALSFRS-R total score at Week 50). The total sample size is estimated as 354 after adjusting for a 20% dropout (Cudkowicz, 2013). Furthermore, assuming approximately 82% 1-year survival rate for placebo group and 50% relative reduction in the HR for mortality due to treatment with ravulizumab, this sample size will provide at least 90% nominal power based on the primary analysis (CAFS).

4. ANALYSIS SETS

Table 2: Analysis Sets

Analysis Set	Description
Screened Set	All consented participants
Randomized Set	All randomized participants grouped by randomized treatment group (for reporting disposition, demographics, and baseline characteristics)
SS	All participants who received at least 1 dose of the study drug (ravulizumab or placebo) in RCP. Participants will be compared for safety according to the treatment they actually received. For a participant to be analyzed according to the treatment they actually received and not according to the randomization schedule, they would have to receive that treatment for the entire duration of the RCP.

Table 2: Analysis Sets

Analysis Set	Description
FAS	All randomized participants who received at least 1 dose of the study drug (ravulizumab or placebo) in RCP. The primary population for efficacy assessment is the FAS. Participants will be compared for efficacy according to the treatment they were randomized to, regardless of the treatment received.
PKAS	All participants who receive at least 1 dose of the study drug and have at least 1 postdose PK sample
PDAS	All participants who receive at least 1 dose of the study drug and have at least 1 postdose PD sample
OLES	All participants who received at least 1 dose of ravulizumab starting from Week 50

Abbreviations: FAS = Full Analysis Set; OLE = Open-Label Extension; OLES = Open-Label Extension Set; PD = pharmacodynamic; PDAS = Pharmacodynamic Analysis Set; PK = pharmacokinetic; PKAS = pharmacokinetic analysis set; RCP = Randomized Controlled Period; SS = Safety Set

If the Randomized Set is identical to the Full Analysis Set (FAS), then the FAS will be used for disposition, demographics, and baseline characteristics.

5. STATISTICAL ANALYSES

5.1. General Considerations

All data collected in this study will be presented using summary tables, figures, and data listings.

- For the RCP, data summaries and inferential analyses will be presented by the treatment arms ("Ravulizumab" and "Placebo"). For certain noninferential summaries (demographics, baseline characteristics, and other prestudy information, including medical and ALS history, prior medications, and SAEs captured between screening and first infusion), a "Total" group may be formed by combining participants from both treatment arms. No "Total" group will be formed for efficacy and safety-related summaries.
- For the OLE Period, data summaries will be presented by the treatment arms ("Ravulizumab/Ravulizumab" and "Placebo/Ravulizumab"). A "Total" group may be formed by combining participants from both treatment arms.

Statistical analyses will include tabulations of summary data, inferential analyses, by-patient listings, and figures. The summary statistics for continuous variables will include, but not be limited to, the number of participants, mean, SD, minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. Inference from efficacy analyses will be based on a 2-sided Type I error (α) = 5% unless stated otherwise. The 95% confidence intervals (CI) will be produced where applicable. All p-values and CIs will be used for descriptive purposes only due to the study meeting the futility criterion.

Since the study has stopped for futility, multiplicity adjustment will not be considered.

The baseline value for analysis and reporting will be based on the last non-missing measurement on or prior to the first dose of the study drug unless stated otherwise.

Missing safety data will not be imputed.

Analyses will be performed using the SAS® software Version 9.4 or higher. Adverse events (AEs) will be coded with Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or later. Prior and concomitant medications will be coded with World Health Organization (WHO) Drug Dictionary Version 202103 or later.

5.2. Study Participants

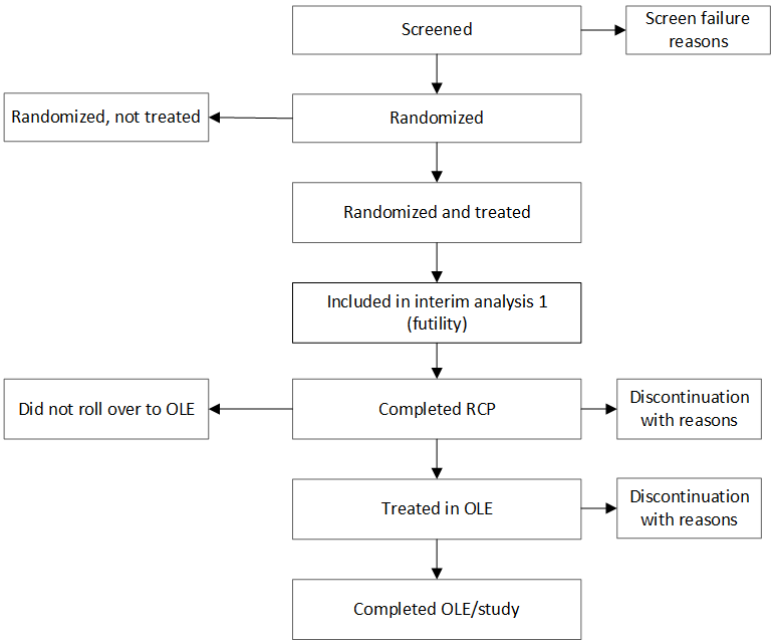
The following information will be summarized:

- The number and percentage of participants for the categories provided below (Figure 2 provides a flowchart related to the disposition)
  - Screened
  - Screen failure reasons (including coronavirus disease [COVID]-19 related screen failures)
  - Randomized
  - Treated
  - Included in the interim analysis 1
  - Completed RCP
  - Discontinuation reasons (RCP)
  - Did not roll over to OLE
  - Treated in OLE
  - Discontinuation reasons (OLE)
  - Completed OLE/study
- The number and percentage of participants randomized to placebo or ravulizumab within each of the 6 stratification levels (Table 1); the percentages will be calculated based on the total number of participants within each stratification level
  - By planned randomization strata (derived strata based on the bulbar onset and stable riluzole or edaravone use)
  - By actual randomization strata (observed stratification)
- A cross-tabulation of participants by planned and actual randomization strata for quantifying the mis-stratification
- The number and percentage of participants by protocol scheduled visits during RCP
- The number and percentage of participants in analysis datasets and reason for exclusion from specific datasets
- The number and percentage of participants who missed a study visit along with associated reasons including reasons related to COVID-19
- The number and percentage of participants who had a delayed visit along with associated reasons including reasons related to COVID-19

- The number and percentage of participants with a visit modification along with associated reasons including reasons related to COVID-19

Details will be presented in the listings.

Figure 2: Participant Disposition Flowchart



5.3. Primary Estimand and Analysis

The primary endpoint for this study is based on ALSFRS-R. It is a validated instrument for evaluating the levels of the physical functional status of patients with ALS in 4 areas, including bulbar, gross motor activity, fine motor activity, and respiratory functions. The scale includes 12 functional items, and each item is rated on a 0 to 4 scale, with a maximum total score of 48. A higher score indicates greater retention of function. The ALSFRS-R assessment schedule is provided in the Schedule of Activities in the protocol. If a participant is unable to attend the scheduled onsite visit, the ALSFRS-R can be assessed via a phone call by the Investigator or trained designee.

A joint rank analysis (referred to as CAFS) recommended in the Food and Drug Administration (FDA) guidance document on ALS, 2019, which combines deaths and ALSFRS-R, will be performed for the analysis of the primary endpoint. This analysis will be conducted based on the FAS.

5.3.1. Estimand

The 5 attributes for the primary estimand are described below:

- Treatment: ravulizumab or placebo with or without the use of stable riluzole and edaravone
- Population: adult participants with ALS as defined by the protocol inclusion/exclusion criteria

- Variable: CAFS score (defined below) based on the monthly slope in ALSFRS-R (change from Baseline in ALSFRS-R total score at last visit on or before Week 50 divided by the corresponding time [month]) and time (months) to death during RCP
- ICE: death
  - The composite strategy will be adopted to account for death in analysis for the primary endpoint (see Section 5.3.2 for details)
- Population-level summary: mean CAFS score (defined below)
  - The treatment effect will be quantified by the difference in mean between ravulizumab and the placebo arms

For participants who do not survive until Week 50, ALSFRS-R total scores will be missing, which may bias the evaluation of clinical benefit if not adequately accounted. This joint rank analysis evaluates function while accounting for missing data due to deaths in ALS by calculating a CAFS score for each participant.

CAFS scoring: For calculating the CAFS score, each participant will be compared individually to all other participants (irrespective of treatment assignment) in a pairwise fashion (Berry, 2013). For each pairwise comparison, the participant who fares better earns a point (+1), and the participant who fares worse loses a point (-1). In the case of a tie, no points (0) are added or subtracted. Each participant's summary score (CAFS score) is the sum of the comparisons (+1, 0, -1) against all other participants.

1. If both participants die, the participant surviving longer will earn a point (+1) and the participant with a shorter survival time will lose a point (-1); no points (0) are added or subtracted if the survival times are identical.
2. If only 1 participant survives, then that participant will earn a point (+1)
3. If both participants survive, the participant with the smaller decline in the slope of ALSFRS-R will earn a point (+1), the participant with the larger decline will lose a point (-1), and no points (0) are added or subtracted in the case of a tie. The slope will be calculated based on the change from Baseline in ALSFRS-R total score at the last available visit normalized by the number of months between the first study drug and the last available visit. For a participant that discontinued early without any information on death or change in ALSFRS-R, the slope will be assumed zero as it is unlikely that the ALSFRS-R score will change significantly within a short period.

Participants will be ranked based on the CAFS score, as calculated above, irrespective of the treatment assignment. The first participant who dies will have the lowest score and is ranked the lowest; the last to die is ranked above all others who die; among survivors, the participant with the greatest decline in ALSFRS-R slope is ranked immediately above the last participant who died; the surviving participant with the least decline in ALSFRS-R slope is assigned the highest rank. Participants with the same CAFS scores will be ranked with average ranks.

Section 6.2.3 provides examples of CAFS scoring.

5.3.2. Main Analytical Approach

The analysis of CAFS ranks will be based on an analysis of covariance model. The model will include the CAFS ranks as the dependent variable and the following list of independent variables: treatment indicator (0 = placebo, 1 = ravulizumab), age, sex, baseline ALSFRS-R total score, baseline SVC percent predicted, months since first muscle weakness onset at Baseline, and the stratification factors.

If the 2-sided p-value associated with the higher mean rank in the ravulizumab group compared to the placebo is less than $\alpha = 0.05$, a statistically significant treatment benefit will be established. The least squares (LS)-means and the 95% CIs of the CAFS ranks for each treatment arm and the difference between the arms will be calculated. Details will be provided in a listing.

This analysis will be conducted for sake of completion and will not support efficacy conclusion as the study met the pre-specified futility criteria.

5.3.3. Sensitivity Analysis

The following sensitivity analysis will be conducted to quantify the treatment effect magnitude.

5.3.3.1. Sensitivity Analysis: Mixed-effect Model for Repeated Measures

As the CAFS method is based on ranks and cannot quantify the magnitude of the treatment effect for ALSFRS-R, a sensitivity analysis will be performed, including all ALSFRS-R longitudinal data (either complete or partial), to estimate the treatment effect, ie, the difference in mean change from Baseline between ravulizumab and placebo.

5.3.3.1.1. Estimand

The 5 attributes for the estimand are described below:

- Treatment: ravulizumab or placebo with or without the use of stable riluzole and edaravone
- Population: adult participants with ALS as defined by the protocol inclusion/exclusion criteria
- Variable: change from Baseline in ALSFRS-R total score at the postbaseline visits during RCP up to and including Week 50.
- ICE: none
  - The treatment policy will be adopted, and all ALSFRS-R data will be used; no imputation will be performed for missing data due to death or discontinuation
- Population-level summary: mean change from Baseline in ALSFRS-R total score
  - The treatment effect will be quantified by the difference in mean between ravulizumab and the placebo arms.

5.3.3.1.2. Analytical Details for Sensitivity Analysis

The model will include the change from Baseline in ALSFRS-R total score at each study visit as the dependent variable and the following list of independent variables as fixed effects: actual time on the study (months), the interaction between time and treatment (0 = placebo, 1 = ravulizumab), age, sex, baseline ALSFRS-R total score, baseline SVC percent predicted,

months since first muscle weakness onset at Baseline, and the stratification factors. The participant-specific random slope will also be added to the model with an unstructured variance-covariance matrix to model the correlations among repeated measurements within each participant. The following covariance structures will be implemented if a convergence issue occurs in the specified order:

- Heterogeneous toeplitz (TOEPH)
- Heterogeneous autoregressive (1) (ARH (1))
- Heterogeneous compound symmetry (CSH)
- Toeplitz structure (TOEP)
- Autoregressive (1) (AR (1))
- Compound symmetry (CS)

The first covariance structure that converges will be used. The Kenward-Rogers method will be used to estimate the denominator degrees of freedom.

No imputation for the missing data will be performed after discontinuation (death or dropout) from the study, assuming the data are missing at random (MAR).

Section 6.2.9 provides details on implementing analysis windows.

A 2-sided p-value less than $\alpha = 0.05$ associated with the higher mean change in ALSFRS-R total score in the ravulizumab group compared to placebo will indicate a statistically significant treatment benefit. The LS-means and the 95% CIs of the mean change from Baseline at Week 50 for each treatment arm and the difference between the arms will be calculated. The treatment effect will be evaluated via the estimated treatment-by-visit interaction term at Week 50 (Month 11.5). Details will be provided in a listing.

5.3.4. Other Analyses

The ALSFRS-R total score and change from Baseline will be summarized descriptively by visit.

Details will be provided in a listing.

Mean score and mean change from Baseline over time, along with 95% CI, will be plotted for ALSFRS-R total score.

Table 3: Overview of Estimands, Intercurrent Events, and Analyses Related to the Primary Endpoint

Analysis	Reference Section	ICE	Estimand Strategy
Primary Analysis - CAFS	Section 5.3	Death	Composite strategy
Sensitivity Analysis	Section 5.3.3.1	None	Treatment policy strategy

Abbreviations: CAFS = combined assessment of function and survival; ICE = intercurrent event

5.4. Secondary Estimands and/or Endpoints Analysis

5.4.1. Key Secondary Estimands

5.4.1.1. Time to Ventilation Assistance Free Survival

5.4.1.1.1. Estimand

The 5 attributes for the estimand related to VAFS are described as follows:

- Treatment: ravulizumab or placebo with or without the use of stable riluzole and edaravone
- Population: adult participants with ALS as defined by the protocol inclusion/exclusion criteria
- Variable: time (months) from Day 1 (first dose of study drug in RCP) to a VAFS event during the RCP; the VAFS event is defined as the earliest of
  - Death
  - The first use of noninvasive ventilation (NIV) for ≥ 22 hours per day for ≥ 10 consecutive days
  - The first use of permanent assisted ventilation (PAV) for ≥ 22 hours per day for ≥ 7 consecutive days VAFS
- ICE: none. the treatment-policy estimand will be used
- Population-level summary: HR (ravulizumab versus placebo)

5.4.1.1.2. Main Analytical Approach

The treatment effect on the time to VAFS will be analyzed based on a Cox proportional hazards model with treatment as a fixed effect adjusting for age, sex, baseline ALSFRS-R total score, baseline SVC percent predicted, months since first muscle weakness at Baseline, and the stratification factor. A censoring indicator will be equal to 1 if the participant did not experience a VAFS event (considered "censored"), and 0 if the participant experienced an event. Censored participants will include participants who discontinue the study without a VAFS event or complete the RCP without a VAFS event.

The HR of ravulizumab versus placebo will be estimated with its associated 95% CIs. A 2-sided p-value less than $\alpha = 0.05$ associated with the HR<1 will indicate a statistically significant treatment benefit.

The components of VAFS will be analyzed separately using similar models to decompose the contribution of each component to VAFS, ie, using the first event of the 3 components. The total number of participants experiencing the first event will be equal to the total number of participants experiencing the VAFS event. Given the composite nature of VAFS, the p-value associated with each component (death, NIV, and PAV) need not be significant.

5.4.1.1.3. Other Analyses Related to VAFS and Components of VAFS (NIV, PAV and Mortality)

An analysis for time (months) to NIV, PAV, and death will be performed separately with a Cox proportional hazards model similarly to that described in Section 5.4.1.1.2. However, these

analyses are different from the analyses of the VAFS components; for example, a participant may experience an event of NIV followed by death; hence, NIV will contribute to VAFS, but death will not. Hence the total number of participants experiencing any of these events may be greater than the total number of participants experiencing the VAFS event.

For VAFS and its components, the Kaplan-Meier curves by treatment group will be produced. Estimated survival probabilities at Week 50 (Month 11.5) will be provided for both treatment groups. The number and percentage of participants experiencing a VAFS event and its components will be provided. In addition, the number and percentage of deaths will be summarized by the associated reasons.

The number and percentage of participants with ventilator use (regardless of the number of hours) at least once during RCP, NIV, and PAV will be summarized. Details will be provided in listings.

5.4.1.2. Slow Vital Capacity Percent Predicted

5.4.1.2.1. Estimand

The 5 attributes for the estimand related to SVC percent predicted are described as follows:

- Treatment: ravulizumab or placebo with or without the use of stable riluzole and edaravonee
- Population: adult participants with ALS as defined by the protocol inclusion/exclusion criteria and included in the FAS
- Variable: change from Baseline in SVC percent predicted at Week 50 based on the in-clinic assessment or the at-home assessment when in-clinic assessment is not available
- ICE: none. The treatment-policy strategy will be adopted.
- Population-level summary: mean change from Baseline in SVC percent predicted at Week 50; the treatment effect will be quantified by the difference in mean between ravulizumab and the placebo arms.

5.4.1.2.2. Main Analytical Approach

The treatment effect on SVC percent predicted will be evaluated based on a mixed-effect model repeated measure with the change from Baseline in SVC percent predicted as the dependent variable and the following list of independent variables as fixed effects: actual time on study (months), time and treatment interaction, age, sex, baseline ALSFRS-R total score, baseline SVC, disease duration, and the stratification factor. In addition, the participant-specific random slope will be added to the model with an unstructured variance-covariance matrix. The strategy for selecting other covariance structures outlined in Section 5.3.3.1.2 will be used if a convergence issue occurs. The Kenward-Rogers method will be used to estimate the denominator degrees of freedom. No imputation for the missing data will be performed after death or discontinuation, assuming the data are MAR.

A 2-sided p-value less than $\alpha = 0.05$ associated with the higher mean change in SVC percent predicted in the ravulizumab group compared to placebo will indicate a statistically significant treatment benefit. The LS-means and the 95% CIs of the mean change from Baseline at Week 50

(month 11.5) for each treatment arm and the difference between the arms will be calculated. Details will be provided in a listing.

5.4.1.3. Other Analyses for Slow Vital Capacity

The absolute values and changes from Baseline will be summarized by visits for the SVC data. Figures of the mean values and the changes from Baseline over time will be provided, along with 95% CIs. Details will be provided in listings.

5.4.2. Supportive Secondary Endpoints and Analysis

5.4.2.1. Muscle Strength Measured by Handheld Dynamometry

The absolute values and changes from Baseline will be summarized by visits for the HHD data. Figures of the mean values and the changes from Baseline over time will be provided along with 95% CIs. Details will be provided in listings. See Section 6.2.6 for additional details.

5.4.2.2. Neurofilament Light Chain (NfL) Concentration

The absolute values and the log-transformed values will be summarized by visits. Figures of the geometric means over time will be provided along with 95% CIs. Details will be provided in listings.

5.5. Tertiary/Exploratory Endpoints and Analyses

No analyses and no any summary tables or listings will be done for any tertiary/exploratory endpoints.

5.6. Safety Analyses

The safety analyses will be descriptive in nature and will include the following:

- Exposure to IP
- AEs
- Laboratory data
- Vital signs
- ECG
- Physical examination
- Neurological examination
- C-SSRS
- Exposure to COVID-19

All safety analyses for the RCP and OLE Period will be conducted based on the Safety Set (SS) and OLE Set.

5.6.1. Extent of Exposure

Descriptive statistics will be generated for the variables described in Table 4.

Table 4: Variables for Study Duration, Exposure, and Treatment Compliance

Variable (Unit)	Study Period (Population)	Definition	Calculation
Duration			
Duration of RCP participation (days)	RCP (SS)	Number of days from informed consent to last day in RCP. Note: The last day in RCP is defined as the latest of RCP completion, discontinuation date, date of death, or date of the follow-up visit from RCP.	Date of last day in RCP -date of informed consent + 1
Duration of study participation (days)	RCP and Study (SS)	Number of days from informed consent to last day in study. Note: The last day in the study is defined as the latest of study completion or discontinuation date or date of death or date of the follow-up visit from the study	Date of last day in the study - date of informed consent + 1
Treatment duration (days) - RCP	RCP (SS)	Number of days on study treatment from first study drug infusion until the last study drug infusion during RCP. Note: Week 50 dosing will not be included in this calculation.	Last study drug infusion date in RCP - first RCP study drug infusion date + 1
Treatment duration (days) – OLE	OLE (OLES)	Number of days on study treatment from first OLE study drug infusion until the last study drug infusion during OLE.	Last study drug infusion date in OLE - first OLE study drug infusion date + 1
Duration of RCP (days)	RCP (SS)	Number of days from first study drug infusion to last day in RCP.	Date of last day in RCP - date of the first infusion in RCP + 1
Total patient-years (years) – RCP	RCP (SS)	Total RCP duration (years) for all participants.	Sum of RCP duration (days) / 365.25 for all participants
Duration of OLE (days)	OLE (OLES)	Number of days from first OLE study drug infusion to last day in OLE.	Date of last day in OLE - date of the first infusion in OLE + 1
Total patient-years (years) – OLE	OLE (OLES)	Total OLE duration (years) for all participants.	Sum of OLE duration (days) / 365.25 for all participants
Exposure			
Total number of infusions	RCP (SS)	Total number of infusions in RCP Note: Infusions with an interruption at the same visit will be counted once.	The total number of infusions in RCP.
Total number of loading dose infusions	RCP (SS)	Total number of loading dose infusions	The total number of loading dose infusions in RCP.
Total number of maintenance dose infusions	RCP (SS)	Total number of maintenance dose infusions	The total number of maintenance dose infusions in RCP.
Total dose administered (mg)	RCP (SS)	Total dose administered	Sum of all doses in RCP. Note: Placebo kits will contribute to zero doses.
	OLE (OLES)	Total dose administered	Sum of all doses in OLE. Note: Placebo kits will contribute to zero doses.
Total infusion volume (mL)	RCP (SS)	Total infusion volume	Sum of all infusion volume in RCP.
	OLE (OLES)	Total infusion volume	Sum of all infusion volume in OLE.

Table 4: Variables for Study Duration, Exposure, and Treatment Compliance

Variable (Unit)	Study Period (Population)	Definition	Calculation
Treatment Compliance			
Number of participants with an infusion interruption for any reason	RCP (SS)	Number of participants with an infusion interruption at any time (for any reason) during loading dose or maintenance dose infusion in RCP.	Count of participants with an infusion interruption (for any reason) at any time during loading dose or maintenance dose infusion in RCP.
Number of interrupted infusions for any reason per participant	RCP (SS)	Total number of interrupted infusions (for any reason) per participant at any time during loading dose or maintenance dose infusion in RCP.	Sum of all instances of infusion interruption (for any reason) in RCP.
Number of participants with an infusion interruption for AEs	RCP (SS)	Number of participants with an infusion interruption at any time (for AEs) during loading dose or maintenance dose infusion in RCP.	Count of participants with an infusion interruption (for AEs) at any time during loading dose or maintenance dose infusion in RCP
Number of interrupted infusions for AEs per participant	RCP (SS)	Total number of interrupted infusions (for AEs) per participant at any time during loading dose or maintenance dose infusion in RCP.	Sum of all instances of infusion interruption (for AEs) in RCP
Percent compliance	RCP (SS)	Percentage of the total number of infusions administered out of the total number of expected infusions during RCP.	100 × (Total number of infusions administered in RCP) / (Total number of expected infusions in RCP)
Percent compliance category	RCP (SS)	Percent compliance categories range from 100% to 0% by decrements of 10% per category.	100%, 90% to < 100%, 80% to < 90%, etc.

Abbreviations: AE = adverse event; OLE = Open-Label Extension; OLES = Open-Label Extension Set; RCP = Randomized Controlled Period; SS = Safety Set

5.6.2. Adverse Events

AEs will be coded to the corresponding system organ class (SOC) and preferred term (PT) using the latest available version of the MedDRA.

The definitions of TEAE provided in Table 5 will be used to analyze AEs for different study periods. The TEAE (RCP) and TEAE (OLE) represent TEAEs during RCP and OLE, respectively. For handling missing dates of onset, refer to Section 6.2.1. AEs with onset prior to the first administration of study drug will be summarized as pretreatment AEs.

Table 5: Definition of TEAEs

TEAE (RCP)	TEAE (OLE)
For RCP participants entering the OLE, a TEAE will be defined as any AE with onset on or after the first dose of IP in the RCP up to and including the day prior to the first OLE dose.	A TEAE will be defined as any AE with onset on or after first dose of OLE.
For RCP participants not entering the OLE, TEAE will be defined as an AE with onset on or after the first RCP dose of IP.	

If the time of the AE onset is available, it will be used to determine the treatment emergence by comparing with the time of the first study drug infusion, ie, if the AE onset time is prior to the time of infusion, it will not be considered as treatment-emergent.

Abbreviations: AE = adverse event; IP = investigational product; OLE = Open-Label Extension; RCP = Randomized Controlled Period; TEAE = treatment-emergent adverse event

The incidence, toxicity, and relationship to IP will be summarized by the treatment group. Specific AEs will be counted once for each participant for calculating percentages (e.g., overall, SOC, PT). In addition, if the same AE occurs multiple times for a participant, the highest severity and relationship to IP observed will be reported. All TEAEs will be summarized overall and categorized by MedDRA SOC and PT. The ordering of SOC will be alphabetical, and the ordering for PT will be most prevalent (using percentage) PT within each SOC based on the ravulizumab (RCP analysis) or total column (OLE). PTs with the same number of participants (eg, to break ties) will be further sorted by the number of events and then alphabetically.

Table 6 provides an overview of the tabular summaries of AEs for different periods, underlying analysis sets, and treatment group display convention. An "X" in the table represents that an analysis will be performed for the period. For incidence tables, the number of participants and percentage will be tabulated; percentages will be based on the number of participants in the respective treatment groups. For event-rate tables, the rate per 100 patient-years will be calculated as follows (see Table 4 for the definition of patient-years):

$$= 100 \times \frac{\text{Total number of TEAEs for specific reporting period}}{\text{Total Person years for specific reporting period}}$$

The following participant-level listings will be generated for AE data:

- All AEs
- All SAEs
- AEs leading to study drug discontinuation
- AEs leading to death
- AEs of special interest
- Infusion reaction related AEs
- COVID-19 AEs

Table 6: Overview of Adverse Event Analysis by Study Period

Type of Analysis	Period Analysis Set Treatment Group Display Convention			Additional Notes
	Screening SS Ravulizumab, Placebo, Total	RCP SS Ravulizumab, Placebo	OLE OLES Ravulizumab/Ravulizumab, Placebo/Ravulizumab, Total	
Overall summary of TEAEs		X	X	
TEAEs by SOC and PT		X	X	
TESAEs by SOC and PT		X	X	
Nonserious TEAEs by SOC and PT		X	X	
TEAEs leading to study drug withdrawal by SOC and PT		X	X	
TEAEs leading to death by SOC and PT		X	X	
TEAEs by SOC and PT by highest relationship to IP		X		Relationship to IP: related, not related
TEAEs by SOC, PT, and highest severity		X		Severity: Grade 1, 2, 3, 4, and 5
TEAEs (IP-related) by SOC, PT, and highest severity		X		
TEAEs (IP-related) by SOC and PT		X		
TESAEs (IP-related) by SOC and PT		X		
TESAEs by SOC, PT, and highest relationship to IP		X		Relationship to IP: related, not related
TEAEs (≥ 1%) by SOC and PT		X		≥ 1% in all participants
TEAEs by SOC sorted by decreasing frequency		X		Decreasing frequency by ravulizumab arm (RCP), all participants (OLE)
TEAEs by PT sorted by decreasing frequency		X		
TESAEs by PT sorted by decreasing frequency		X		

Table 6: Overview of Adverse Event Analysis by Study Period

Type of Analysis	Period Analysis Set Treatment Group Display Convention			Additional Notes
	Screening SS Ravulizumab, Placebo, Total	RCP SS Ravulizumab, Placebo	OLE OLES Ravulizumab/Ravulizumab, Placebo/Ravulizumab, Total	
TEAEs (IP-related) by PT sorted by decreasing frequency		X		
AESI by SOC and PT		X		AESI: Meningococcal infection
Infusion reaction related TEAEs by SOC and PT		X		
Infusion reaction related TESAEs by SOC and PT		X		
Infusion reaction related TEAEs (IP related) by SOC and PT		X		
Overall Summary of COVID-19 related TEAEs		X		
COVID-19 related TEAEs by SOC and PT		X		
COVID-19 related TESAEs by SOC and PT		X		
AEs during Screening Period by SOC and PT	X			

Abbreviations: AE = adverse event; AESI = adverse event of special interest; IP = investigational product; OLE = Open-Label Extension; OLES = Open-Label Extension Set; PT = preferred term; RCP = Randomized Controlled Period; SOC = system organ class; SS = Safety Set; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

5.6.3. Laboratory Tests

The analysis of central laboratory parameters (hematology, clinical chemistry, and urinalysis) will be summarized descriptively. Laboratory results based upon standardized units will be used for analyses. The last record will be used if there are multiple records of laboratory measurements at Baseline or post-Baseline Visits. The following analyses will be performed:

- Actual laboratory results, baseline values, and changes from Baseline will be summarized using descriptive statistics (mean, SD, etc.) for each scheduled study visit and for the last visit within each period for the respective laboratory parameter.
- Shift analyses will be conducted by calculating the number and percentage of participants in the low, normal, and high category combinations at both Baseline and post-Baseline Visits; the total number of participants with nonmissing values at both Baseline and post-Baseline Visits will be used as the denominator for the percentage calculation.
- The number (%) of participants meeting the criteria in Table 7 for the liver function-related laboratory values (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and total bilirubin [TBL]) will be provided.

Table 7: Abnormality Criteria for Liver Function Laboratory Values and Analysis Timepoints

Criteria	Analysis Timepoints
ALT • > 3 × ULN • > 5 × ULN • > 10 × ULN • > 20 × ULN	• By scheduled visit • Any post-Baseline value
AST • > 3 × ULN • > 5 × ULN • > 10 × ULN • > 20 × ULN	• By scheduled visit • Any post-Baseline value
ALT > 3 × ULN and TBL > 2 × ULN	• By scheduled visit
ALT > 3 × ULN and ALP < 2 × ULN and TBL ≥ 2 × ULN	• By scheduled visit

Criteria involving multiple laboratory analytes should be evaluated concurrently, ie, based on the same sample.
For any post-Baseline value, a participant can contribute to multiple categories.
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal

Table 8 provides an overview of the laboratory data analyses for different periods, underlying analysis sets, treatment group display convention, the definition of baseline values, and laboratory data analyses. An "X" in the table represents that an analysis will be performed for the period.

Table 8: Overview of Analysis of Laboratory Data for RCP (SS)

Type of Analysis	Assessment Performed	Additional Notes
Actual value and change from Baseline	X	
Abnormal laboratory values (with respect to normal range)	X	
Shift analysis of abnormality compared to Baseline	X	
Liver function abnormality	X	
Box plots	X	ALT, AST, creatinine, glucose, hematocrit, hemoglobin, lymphocytes neutrophils, leukocytes, and platelets

The treatment group display convention is "Ravulizumab, Placebo", and the definition of baseline values is "Last nonmissing value prior to first RCP study drug infusion."
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; RCP = Randomized Controlled Period; SS = Safety Set

5.6.4. Vital Signs

The analysis of the following vital signs will be summarized descriptively: systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (beats/min), respiratory rate (breaths/min), weight (kg), and temperature (°C).

If there are multiple records of vital sign measurements at Baseline or post-Baseline Visits, the last record will be used. The following analyses will be performed:

- Actual vital sign measurements, baseline values, and changes from Baseline will be summarized using descriptive statistics (mean, SD, etc.) for each scheduled study visit.
- The number (%) of participants meeting the potentially clinically significant abnormality criteria (Table 9) at least once during the RCP will be provided.

Table 9: Potentially Clinically Significant Abnormality Criteria for the Vital Signs

Vital Sign Measurement	Criteria
Systolic blood pressure	< 90, > 140, > 160
Diastolic blood pressure	< 50, > 90, > 100
Heart rate	< 60, > 100
Respiratory rate	< 12, > 20
Weight	Decrease of ≥ 7% from Baseline; increase of ≥ 7% from Baseline
Temperature	> 38.0, < 36.0

Table 10 provides an overview of the analyses of the vital sign data for different periods, underlying analysis sets, treatment group display convention, the definition of baseline values, and analyses of the vital sign data. An "X" in the table represents that an analysis will be performed for the period.

Table 10: Overview of Analysis of Vital Sign Data for RCP (SS)

Type of Analysis	Assessment Performed
Actual value and change from Baseline	X
Potentially clinically significant abnormality criteria	X

The treatment group display convention is "Ravulizumab, Placebo", and the definition of baseline values is "Last nonmissing value prior to first RCP study drug infusion."
Abbreviations: RCP = Randomized Controlled Period; SS = Safety Set

5.6.5. Electrocardiogram

The analysis of the following ECG measurements will be summarized descriptively: heart rate (beats/min), PR interval (msec), QRS duration (msec), RR interval (msec), QT interval (msec), corrected QT interval by Fridericia (QTcF; msec), and overall interpretation.

If there are multiple records of ECG measurements at Baseline or post-Baseline Visits, the last record will be used. The following analyses will be performed:

- Actual ECG measurements, baseline values, and changes from Baseline will be summarized using descriptive statistics (mean, SD, etc.) for each scheduled study visit
- The number (%) of participants with abnormal ECG findings (normal, abnormal – not clinically significant, and abnormal – clinically significant).
- The number (%) of participants meeting the potentially clinically significant abnormality criteria (Table 11) for QT and QTcF at least once during the RCP will be provided.

Table 11: Potentially Clinically Significant Abnormality Criteria for QT and QTcF

ECG Measurement	Criteria
QT, QTcF absolute value	> 450, > 480, > 500
QT, QTcF absolute value	> 450 to ≤ 480, > 480 to ≤ 500, > 500
QT, QTcF change from Baseline	> 30, > 60
QT, QTcF change from Baseline	> 0 to ≤ 30, > 30 to ≤ 60, > 60

Note: Maximum post-Baseline value or maximum change from Baseline will be used for these evaluations.

Table 12 provides an overview of the different periods, underlying analysis sets, treatment group display convention, the definition of baseline values, and analyses of ECG data. An "X" in the table represents that an analysis will be performed for the period.

Table 12: Overview of Analysis of ECG Data for RCP (SS)

Type of Analysis	Assessment Performed
Actual value and change from Baseline	X
Abnormal ECG findings	X
Potentially clinically significant abnormality criteria for QT and QTcF	X

The treatment group display convention is "Ravulizumab, Placebo", and the definition of baseline values is "Last nonmissing value prior to first RCP study drug infusion."
Abbreviations: ECG = electrocardiogram; QTcF = corrected QT interval by Fridericia; RCP = Randomized Controlled Period; SS = Safety Set

5.6.6. Physical Examination

Details will be provided in a listing.

5.6.7. Neurological Examination

Details will be provided in a listing.

5.6.8. Columbia-Suicide Severity Rating Scale

The following C-SSRS categories with a yes/no binary response have been re-ordered from the actual scale to facilitate the definitions of the composite and comparative endpoints and enable clarity in presenting the results.

Table 13: C-SSRS Categories for Reporting

Category No.	Category
1	Wish to be Dead
2	Nonspecific Active Suicidal Thoughts
3	Active Suicidal Ideation With Any Methods (Not Plan) Without Intent to Act
4	Active Suicidal Ideation With Some Intent to Act, Without Specific Plan
5	Active Suicidal Ideation With Specific Plan and Intent
6	Preparatory Acts or Behavior
7	Aborted Attempt
8	Interrupted Attempt
9	Actual Attempt (Nonfatal)
10	Completed Suicide

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale; No. = number

In addition, the response to the "Self-injurious behavior without suicidal intent (not suicide-related)" question will also be summarized.

Table 14 provides the definitions for the composite endpoints based on the categories provided in Table 13.

Table 14: Composite Endpoints Based on C-SSRS

Endpoint	Description
Suicidal ideation	A "yes" answer to any of the 5 suicidal ideation questions (Categories 1-5) on the C-SSRS.
Suicidal behavior	A "yes" answer to any of the 5 suicidal behavior questions (Categories 6-10) on the C-SSRS.
Suicidal ideation or behavior	A "yes" answer to any 1 of the 10 suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.

The following analyses will be performed:

- The number and percentage of participants who experience an event at Baseline ("Lifetime" and "past 12 months," separately) and at least once during the treatment period will be summarized by the treatment group for
  - Each of the 3 composite endpoints in Table 14
  - The self-injurious behavior without suicidal intent
- A shift tabulation from Baseline ("Lifetime" and "past 12 months," separately) will be produced by treatment group during the RCP against the 3 composite endpoints for each of the 3 following groupings:
  - No suicidal ideation or behavior,
  - Composite endpoint of suicidal ideation, and
  - Composite endpoint of suicidal behavior. Each participant is counted once in 1 cell only for each of the 2 tabulations. Participants with both suicidal ideation and suicidal behavior are included in the suicidal behavior category for the shift analysis.

5.6.9. Coronavirus Disease 2019 Exposure

Details will be provided in a listing.

5.7. Other Analyses

5.7.1. Pharmacokinetic Analyses

Individual serum concentration data for all participants in PKAS will be summarized descriptively. Descriptive statistics (mean, SD, coefficient of variation [CV], median, minimum, maximum, geometric mean, and geometric %CV) will be calculated for serum concentration data at each sampling time, as appropriate. Graphs of mean serum concentration-time profiles will be constructed. Graphs of serum concentration-time profiles for individual participants may also be provided.

5.7.2. Pharmacodynamic Analyses

PD analyses will be performed for all participants in PDAS. Descriptive statistics will be presented for all ravulizumab PD endpoints at each sampling time. The PD effects of ravulizumab will be evaluated by assessing the absolute values, changes, and percentage changes from Baseline in free C5 serum concentrations over time, as appropriate.

Assessments of ravulizumab PK/PD relationships may be explored using data from this study or in combination with data from other studies.

5.7.3. Biomarker Assessments

Analysis of Neurofilament Light Chain (NfL) concentration can be found in Section 5.4.2.2. All other biomarkers may be analyzed by treatment and visits.

5.7.4. Immunogenicity

The number and percentage of participants developing confirmed positive ADAs and anti-drug neutralizing antibodies, where applicable, will be summarized by treatment group and visit. ADA titer values will be listed.

5.7.5. Subgroup Analyses

5.7.5.1. Subgroup Analyses for Adverse Events

The TEAEs during the RCP will be summarized for the following subgroups (no p-value will be produced for these subgroup analyses):

- Sex
- Race
- Region
- Age category (< median, ≥ median)
- Baseline weight category (< median, ≥ median)

5.7.5.2. Subgroup Analyses for Laboratory Data

The abnormality criteria for liver function laboratory values (Table 7) will be summarized for the following subgroups; no p-value will be produced for these subgroup analyses:

- Stable use of riluzole at baseline (yes, no)
- Stable use of edaravone at baseline (yes, no)

5.8. Interim Analyses

An unblinded interim analysis is planned to assess futility when approximately 33% of planned 354 participants complete Week 26. The interim analysis will be conducted by an IDMC. Details have been described in a separate IAP document.

5.8.1. Data Monitoring Committee

The safety and efficacy data of this study will be monitored by an IDMC composed of external physicians and a statistician who have expertise in both the field of ALS and clinical trial conduct and with no direct relationship to the study. An independent statistical center will perform all statistical analyses presented to the IDMC. The IDMC will independently evaluate safety and efficacy data from the study periodically and at prespecified enrollment-dependent time points. The IDMC will make recommendations regarding study modification or continuation based on their review and in accordance with the agreed-upon IDMC charter. To maintain study integrity and prevent the potential introduction of bias, all study team members

will remain blinded until the final analysis of the RCP is conducted. Details of this process are documented in the IDMC charter.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1: Demographics, Baseline Characteristics, Inclusion/Exclusion Criteria, Protocol Deviations, Medical/Surgical History, Prior/Concomitant Medication

6.1.1. Demographics and Other Baseline Characteristics

The following demographics and baseline characteristics (including ALS disease history) will be summarized using the FAS by treatment group and overall. No statistical test will be performed for homogeneity among treatment groups. The continuous data will be summarized with descriptive statistics (number of participants with nonmissing data [n], mean, SD, minimum, and maximum), and the categorical data will be summarized with the number of participants with non-missing data (n) and percentages (%) for each category. The denominator will not include the missing data for percentage calculation.

6.1.1.1. Demographics

- Sex (male, female, undifferentiated, unknown) – n (%)
- Race – n (%) (as characterized in Section IV of the FDA guidance titled, "Collection of Race and Ethnicity Data in Clinical Trials"); Table 15 provides both the primary and the detailed categories with mapping per the FDA guidance. The primary race category will be used for subgroup analysis.
- Ethnicity – n (%) (as characterized in Section IV of the FDA guidance titled, "Collection of Race and Ethnicity Data in Clinical Trials"); Table 16 provides both the primary and the detailed categories with mapping per the FDA guidance.
- Age (years) at screening – descriptive statistics
- Age category (< 45, 45 to < 65, ≥ 65 years) – n (%)
- Weight (kg) – descriptive statistics
- Weight category (< 40, ≥ 40 to < 60, ≥ 60 to < 100, ≥ 100 kg) – n (%)
- Height (cm) measured at screening – descriptive statistics
- Body mass index (BMI) (kg/m^2) – descriptive statistics
- BMI categories (<18.5, ≥ 18.5 to < 25, ≥ 25 to < 30, ≥ 30) – n (%)

Table 15: Race Categories

Primary (section IV.D of FDA guidance document)	Detailed (section IV.E of FDA guidance document and as recorded on the case report form)
American Indian or Alaska Native	American Indian or Alaska Native
Asian	Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, Other Asian
Black or African American	Black or African American

Table 15: Race Categories

Primary (section IV.D of FDA guidance document)	Detailed (section IV.E of FDA guidance document and as recorded on the case report form)
Native Hawaiian or Other Pacific Islander	Native Hawaiian, Guamanian or Chamorro, Samoan, Other Pacific Islander
White	White

Table 16: Ethnicity Categories

Primary (section IV.D of FDA guidance document)	Detailed (section IV.E of FDA guidance document and as recorded on the case report form)
Hispanic or Latino	• Mexican, Mexican American, Chicano/a • Puerto Rican • Cuban • Another Hispanic, Latino/a or Spanish origin
Not Hispanic or Latino	Not of Hispanic, Latino/a, or Spanish origin
Not reported	Not reported
Unknown	Unknown

Age, weight, and BMI will be reported based on the most recent data on or before Day 1 (the first study drug infusion).

6.1.1.2. Baseline Characteristics

Table 17 provides the list of baseline characteristics to summarize along with the type of summary.

Table 17: Baseline Characteristics

Baseline Characteristics	Definition
Time (months) since first muscle weakness at Screening – descriptive statistics	12 × [date of informed consent – date of first muscle weakness] / 365.25 (rounded to nearest 1)
Time (months) since first muscle weakness at Baseline – descriptive statistics	12 × [date of Day 1 – date of first muscle weakness] / 365.25 (rounded to nearest 1)
Time since first muscle weakness at Baseline category – n (%)	< 12, 12 to ≤ 24, > 24 months
Time (months) since initial diagnosis of ALS at Baseline	12 × [date of Day 1 – date of diagnosis] / 365.25 (rounded to nearest 1)
Time (months) since first muscle weakness to the initial diagnosis of ALS – descriptive statistics	12 × [date of diagnosis – date of first muscle weakness] / 365.25 (rounded to nearest 1)
Site of muscle weakness onset – n (%)	Bulbar, other
El Escorial Diagnostic Criteria – n (%)	Possible; Probable; Probable, Laboratory-supported; Definite
Type of ALS disease – n (%)	Sporadic, Familial
ALS gene mutation – n (%)	C9ORF72, SOD1, TDP43, FUS, No known mutation, Other

Table 17: Baseline Characteristics

Baseline Characteristics	Definition
Ventilation use at Screening – n (%)	• PAV use • PAV use for ≥ 22 hours for ≥ 7 consecutive days • NIV use • NIV use for ≥ 22 hours for ≥ 10 consecutive days
King's ALS Clinical Staging at Baseline – n (%)	Stage 1, Stage 2, Stage 3, Stage 4
King's ALS Clinical Staging assessment, region affected – n (%)	Bulbar, Upper extremity, Lower extremity
King's ALS Clinical Staging assessment, nutritional status – n (%)	• Lost > 10% from predisease weight • Feeding tube needed
King's ALS Clinical Staging assessment, evidence of respiratory failure – n (%)	NIV use, SVC < 50% predicted, SVC 50% to < 80% predicted with respiratory symptoms, None of the above
Dependence on mechanical ventilation – n (%)	Yes, No
Type of dependence on ventilation – n (%)	• Unable to lie flat (supine) without it • Unable to sleep without it • Daytime use > 6 hours per day for > 3 days per week
Stable riluzole or edaravone at Screening – n (%)	• Riluzole • Edaravone • Riluzole, not edaravone • Edaravone, not riluzole • Both riluzole and edaravone • No riluzole or edaravone
Stable riluzole or edaravone at any time prior to Screening – n (%)	• Riluzole • Edaravone • Riluzole, not edaravone • Edaravone, not riluzole • Both riluzole and edaravone • No riluzole or edaravone
Time (months) since the first use of riluzole at baseline – descriptive statistics	12 × [date of Day 1 – date of first riluzole use] / 365.25 (rounded to nearest 1)
Time (months) since the first use of edaravone at Baseline – descriptive statistics	12 × [date of Day 1 – date of first edaravone use] / 365.25 (rounded to nearest 1)
ALSFRS-R total score at Screening and Baseline – descriptive statistics	
ALSFRS-R total score at Screening categories – n (%)	< 34, 34 to 38, > 38 to 40, > 40
ALSFRS-R total score at Baseline categories – n (%)	< 34, 34 to 38, > 38 to 40, > 40
Prestudy monthly ALSFRS-R progression rate at Screening – descriptive statistics	As collected on the case report form
Prestudy monthly ALSFRS-R progression rate at Day 1 – descriptive statistics	[48-ALSFRS-R total score at Day 1] / Time (months) since first muscle weakness at Day 1 – descriptive statistics
Progression rate of ALSFRS-R at Screening categories – n (%)	< −1, −1 to < −0.7, −0.7 to < −0.5, −0.5 to −0.3, > −0.3
Progression rate of ALSFRS-R at Baseline categories – n (%)	< −1, −1 to < −0.7, −0.7 to < −0.5, −0.5 to −0.3, > −0.3

Table 17: Baseline Characteristics

Baseline Characteristics	Definition
SVC volume (L) at Screening and Baseline – descriptive statistics	
SVC percent predicted at Screening and Baseline – descriptive statistics	
Baseline SVC percent predicted categories – n (%)	< 50, 50 to < 65, 65 to < 75, 75 to < 85, >=85
Premorbid weight (kg) – descriptive statistics	

Abbreviations: ASL = amyotrophic lateral sclerosis; ALSFRS-R = amyotrophic lateral sclerosis functional rating scale revised; NIV = noninvasive ventilation; PAV = permanent assisted ventilation; SVC = slow vital capacity

6.1.2. Inclusion/Exclusion Criteria

The number and percentage of participants not meeting specific inclusion or exclusion criteria will be summarized.

6.1.3. Protocol Deviations

All protocol deviations will be listed for all randomized participants. The number and percentage of participants with important protocol deviations for the categories provided in Table 18 will be summarized by treatment group and overall.

Table 18: Protocol Deviation Categories

1. Eligibility and entry criteria 2. Investigational product 3. Concomitant medication 4. Informed consent 5. Laboratory assessment	6. Visit schedule 7. Study procedure/tests 8. Randomization 9. Safety reporting 10. Source document 11. Other

The following protocol deviations will be determined programmatically:

1. Participants who did not take at least 80% of the required treatment doses in RCP
2. Participants who were incorrectly stratified

6.1.4. Medical and Surgical History

The medical and surgical history will be summarized by SOC and PT using MedDRA using the latest version in use at the time of analysis. The number and percentage of participants for each category will be reported by treatment group and overall for the FAS.

6.1.5. Prior and Concomitant Medications / Therapies

Prior medications are defined as medications with a start date occurring before the first study dose of the RCP. Concomitant medications (RCP) are defined as medications taken during RCP, i.e., either with a stop date after the first study dose of RCP or ongoing during RCP. Concomitant medications (OLE) are defined as medications taken during OLE, i.e., either with a stop date after the first study dose of OLE or ongoing during OLE.

Medications will be coded using the WHODrug Dictionary version in use at the time of the analysis. The number (%) of participants using prior and concomitant medications will be summarized based on the WHO Anatomical Therapeutic Chemical Level 3 Class code and

generic name for FAS. All meningococcal vaccinations and prophylactic antibiotic medications after receiving meningococcal vaccine for subjects who initiated study drug will be listed separately as well.

Nonpharmacologic therapies and procedures will be reported by treatment group and overall for the SS using SOC and PT.

6.1.5.1. Stable Riluzole or Edaravone Use

The number and percentage of participants will be summarized for the following categories during RCP

- Riluzole use (discontinued versus stable)
- Edaravone use (discontinued versus stable)

Participants will be considered "stable" on the respective medications if not discontinued.

6.2. Appendix 2: Technical Specifications for Derived Variables

6.2.1. Derivation of Treatment-emergent Adverse Events for Missing or Incomplete Date of Onset

If both start and end dates of AEs are completely missing, no imputation will be performed, and those AEs will be considered treatment-emergent.

<u>If the start date is partial:</u>

1. If only the day is missing:
   1.1. If the month/year of the start date is the same as those of the first study drug administration date, then the missing day will be imputed as the smaller non-missing value of (day of first study drug administration, day of the AE end date).
   1.2. Otherwise, impute the missing day as "01".
2. If both day and month are missing:
   2.1. If the year of the AE start date coincides with the year of the first study drug administration date, the partial start date will be set as the first study drug date. If this leads to a date after the AE end date, then the missing day and month of the AE start date will be imputed as the day and month of the AE end date.
   2.2. If the year of the AE start date is different from the year of the first study drug administration date, the missing day and month of the AE start date will be imputed as the "01" and "01".

<u>If the stop date is partial:</u>

1. If only the day is missing:
   1.1. The missing day will be imputed as the last of the month, adjusting for the leap year.
2. If both day and month are missing:
   2.1. If the year of the AE end date coincides with the maximum of (the year of first study drug administration date or the year of the last study drug administration), then the missing month will be imputed as the month of the corresponding study drug

administration date (first or last) and the missing day will be imputed as the last of the month adjusting for the leap year.

2.2. Otherwise, the missing day and month of the AE stop date will be imputed as the "31" and "12".

6.2.2. Derivation of Prior and Concomitant Medication for Missing or Incomplete Dates

If both start and end dates of medications are completely missing, no imputation will be performed, and those medications will be considered both prior and concomitant medications.

<u>If the end date is partial:</u>

1. If only the day is missing
   1.1. If the year and month coincide with those of the last study drug administration date, then the end of medication will be set to the last study drug administration date.
   1.2. If the year and month do not coincide with those of the last study drug administration date, then the missing day will be imputed as the last day of the month considering leap year and month in consideration.
2. If both day and month are missing
   2.1. If the year coincides with that of the last study drug administration date, then missing month and day will be imputed as the month and day of the last study drug administration.
   2.2. If the year does not coincide with that of the last study drug administration date, then the missing month and day will be imputed as "12" and "31", respectively.

<u>If the start date is partial:</u>

1. If only the day is missing
   1.1. If the year coincides with that of the first study drug administration date, then do the following:
   1.2. If the month does not coincide with that of the first study drug administration date, then impute the missing day as "01".
   1.3. If the month coincides with that of the first study drug administration date
      1.3.1. If the end date is greater than the first study drug administration date, then impute the missing day as the day of the first study drug administration date
      1.3.2. If the end date is less than or equal to the first study drug administration date, then impute the missing day as the day of the end date of medication.
   1.4. If the year and the month do not coincide with those of the first dose date, then impute the missing day as "01".
2. If both day and month are missing:
   2.1. If the year does not coincide with that of the first study drug administration date, then impute missing month as "01" and missing day as "01".
   2.2. If the year coincides with that of the first study drug administration date
      2.2.1. If the end date is greater than the first study drug administration date, then impute the missing day and month as those of the first study drug administration.

2.2.2. If the end date is less than or equal to the first study drug administration date, then impute the missing day and month as those of the end date of the medication.

2.3. If the start date is completely missing, the missing start date will be set as the earlier of the first study drug administration date and end of the medication date.

For meningococcal vaccination, the missing end date will not be imputed.

6.2.3. Combined Assessment of Function and Survival Scoring Example

Table 19 provides an example of the CAFS scoring technique and associated ranking. For each of the 9 participants (3 in the placebo arm and 6 in the ravulizumab arm), the ALSFRS-R change from Baseline, the death or study withdrawal information is provided. Each participant is followed for a maximum of 12 months. Participants PPD died at Months PPD and PPD respectively, with the last available ALSFRS-R change scores being –12 and –7. Participant PPD dropped out at Month 1, with the last ALSFRS-R change score being 3 (showing improvement). For the rest of the participants that completed 12 months of follow-up, the last ALSFRS-R change from Baseline scores are shown in the fifth column. The ALSFRS-R slopes are calculated based on the ratio of change from Baseline score and the time on study; for example, for Participant PPD the slope is calculated as –17/12 = –1.41. Columns c1 to c9 provide the points (–1, 0, 1) based on the pairwise comparison for each participant with the rest of the 8 participants. Columns c2 and c9 are shaded for ease of identification, as both these participants died. Note, a point of 0 is assigned to each participant against himself by default.

Let us first consider the nondeaths for which the points will be awarded solely based on the ALSFRS-R slopes. Participant PPD slope = 0.0) gets a positive point (+1) when PPD slope is compared with the slopes for Participants PPD as each of those participants has declined at a higher rate (corresponding slopes being –1.41, –0.33, –0.25 and –1.0, respectively). When compared with Participants PPD Participant PPD eceives a negative point (–1), as those participants declined at a lower rate (in fact, improved) with corresponding slopes being 0.16 and 3.0, respectively). Lastly, when compared with the 2 participants who died, Participant PPD automatically receives a positive point (+1) because of PPD survival until the end of the study. By summing all of these points, the total CAFS score for Participant PPD ecomes 4. Participant PPD receives a positive point (+1) when compared with the rest of the participants because of PPD highest positive change (least decline) and survival; the CAFS score for Participant PPD becomes 8. The scores for the remaining nondeath participants can be derived similarly, as shown in the 16th column.

Let us now consider the participants who died. For example, Participant PPD ets a negative point (–1) for all pairwise comparisons; the negative point is awarded as all participants (except Participan PPD survived. When compared with Participant PPD a negative point (–1) is awarded to Participant PPD because Participan PPD survived longer than Participan PPD Hence, the CAFS score for Participant PPD becomes –8.

The CAFS scores are ranked irrespective of the treatment groups, with the lowest score receiving Rank 1 and the highest score receiving Rank 9.

Table 19: Example of CAFS Scoring and Ranking

Treatment	Participant	Time-to-death (months)	Time on study (months)	ALSFRS-R		Pairwise scores for CAFS calculation									CAFS	
				Change from baseline	Slope	c1	c2	c3	c4	c5	c6	c7	c8	c9	Score	Rank
Placebo	PPD	.	12	0	0.0	0	1	1	-1	-1	1	1	1	1	4	7
		PPD	.	-12	.	-1	0	-1	-1	-1	-1	-1	-1	-1	-8	1
		.	12	-17	-1.41	-1	1	0	-1	-1	-1	-1	-1	1	-4	3
Ravulizumab		.	12	2	0.16	1	1	1	0	-1	1	1	1	1	6	8
		.	1	3	3.0	1	1	1	1	0	1	1	1	1	8	9
		.	12	-4	-0.33	-1	1	1	-1	-1	0	-1	1	1	0	5
		.	12	-3	-0.25	-1	1	1	-1	-1	1	0	1	1	2	6
		.	12	-12	-1.0	-1	1	1	-1	-1	-1	-1	0	1	-2	4
		PPD	.	-7	.	-1	1	-1	-1	-1	-1	-1	-1	0	-6	2

6.2.4. Short-Form Health Survey

The 8 different dimensions of SF-36, PCS and MCS, will be calculated based on the software developed by Optum.

6.2.5. Amyotrophic Lateral Sclerosis Assessment Questionnaire

The 5 ALSAQ-40 subscores will be derived per Table 20.

Table 20: Algorithms for ALSAQ-40 Subscore Calculation

Domain	Formula
Physical mobility	$100 \times \frac{\text{Sum(Item 1 to Item 10)}}{40}$
Activities of daily living/independence	$100 \times \frac{\text{Sum(Item 11 to Item 20)}}{40}$
Eating and drinking	$100 \times \frac{\text{Sum(Item 21 to Item 23)}}{12}$
Communication	$100 \times \frac{\text{Sum(Item 24 to Item 30)}}{28}$
Emotional functioning	$100 \times \frac{\text{Sum(Item 31 to Item 40)}}{40}$

6.2.6. Handheld Dynamometry

The HHD megascores will be derived as follows for Baseline and post-Baseline visits:

- For each muscle, calculate the ratio over baseline as 100 × (visit raw value/Baseline raw value)
- Three megascores (ie, upper, lower, and total) are defined as the average of the nonmissing ratios for the muscles involved (upper limb, lower limb, total).
- Megascore is always 100 at Baseline when HHD assessment is available.

If both Baseline and post-Baseline raw values are 0, then the ratio will be defined as 100. If the Baseline raw value is 0, but the post-Baseline value > 0, then the ratio will be set to missing.

6.2.7. Treatment Satisfaction Questionnaire for Medicine

Scores for each domain are computed by adding the TSQM items in each domain and then transforming the composite score into a value ranging from 0 to 100. Of note, a score can be computed for a domain only if no more than 1 item is missing from that domain. The calculations specific to each domain are presented in detail below.

Table 21: Algorithms for TSQM-9 Domain Score Calculation

Domain	Item Missingness	Formula
Effectiveness (Items 1 to 3)	If items 1, 2, and 3 are nonmissing	$100 \times \frac{[\text{Sum(Item 1 to Item 3)} - 3]}{18}$
	If 1 item is missing	$100 \times \frac{[\text{Sum(the two completed items)} - 2]}{12}$
Convenience (Items 4 to 6)	If items 4, 5, and 6 are nonmissing	$100 \times \frac{[\text{Sum(Item 4 to Item 6)} - 3]}{18}$

Table 21: Algorithms for TSQM-9 Domain Score Calculation

Domain	Item Missingness	Formula
	If 1 item is missing	$100 \times \frac{[\text{Sum(the two completed items)} - 2]}{12}$
Global Satisfaction (Items 7 to 9)	If items 7, 8, and 9 are nonmissing	$100 \times \frac{[\text{Sum(Item 7 to Item 9)} - 3]}{14}$
	If either Item 7 or Item 8 is missing	$100 \times \frac{[\text{Sum(the two completed items)} - 2]}{10}$
	If Item 9 is missing	$100 \times \frac{[\text{Sum(item 7 and item 8)} - 2]}{8}$

Abbreviation: TSQM-9 = Treatment Satisfaction Questionnaire for Medication

6.2.8. European Quality of Life Health 5-item Questionnaire Health State Index Calculations

The responses to the 5 EQ-5D-5L dimensions can be converted into a single number called an index value. The index value can be calculated by subtracting the appropriate weights listed in Table 22 for each dimension level of health state from 1. The weight for this study is provided by the US composite time trade-off (cTTO) method. The calculation is illustrated in Table 22.

Table 22: EQ-5D-5L US Composite Time Trade-off Value Set

US TTO		Example: the value for health state 21354
Full health (11111)		Full health = 1
Mobility		
Mobility level 2	–0.096	–0.096
Mobility level 3	–0.122	
Mobility level 4	–0.237	
Mobility level 5	–0.322	
Self-care		
Self-care level 2	–0.089	0
Self-care level 3	–0.107	
Self-care level 4	–0.220	
Self-care level 5	–0.261	
Usual activity		
Usual activity level 2	–0.068	
Usual activity level 3	–0.101	–0.101
Usual activity level 4	–0.255	
Usual activity level 5	–0.255	
Pain/discomfort		
Pain/discomfort level 2	–0.06	
Pain/discomfort level 3	–0.098	
Pain/discomfort level 4	–0.318	
Pain/discomfort level 5	–0.414	–0.414
Anxiety/depression		
Anxiety/depression level 2	–0.057	
Anxiety/depression level 3	–0.123	
Anxiety/depression level 4	–0.299	–0.299
Anxiety/depression level 5	–0.321	

Table 22: EQ-5D-5L US Composite Time Trade-off Value Set

US TTO		Example: the value for health state 21354
Health State Index Score		= 1 - 0.096 + 0-0.101 - 0.414 - 0.299 = 0.090

Abbreviations: EQ-5D-5L = European Quality of Life Health 5-item questionnaire; TTO = time trade-off; US = United States

6.2.9. Analysis Windows

Since the actual study visits for a participant may not exactly coincide with their targeted visit date, the actual visit date will be mapped to the analysis visits as described below.

The analysis visits for the RCP will be derived using prespecified windows around the number of days during the study since the first dose of the study drug (called Day 1). The lower and the upper limits of the analysis windows are described in Table 23 .

Table 23: Analysis Windows for Randomized Controlled Period

Analysis Visit	Target Day	Low	High
Week 2	15	2	29
Week 6	43	30	57
Week 10	71	58	85
Week 14	99	86	113
Week 18	127	114	141
Week 22	155	142	169
Week 26	183	170	211
Week 34	239	212	267
Week 42	295	268	323
Week 50	351	324	For participants entering OLE, the day of first dose in OLE; the last day in the study for other participants

The analysis visits for the OLE Period will be derived using prespecified windows around the number of days during the study since the first dose of the OLE Period. The lower and the upper limits of the analysis windows are described in Table 24.

Table 24: Analysis Windows for Open-Label Extension Period

Analysis Visit	Target Day	Low	High
Week 2	15	2	43
Week 10	71	44	99
Week 18	127	100	155
Week 26	183	156	211
Week 34	239	212	267
Week 42	295	268	323
Week 50	351	324	379
Week 58	407	380	435
Week 66	463	436	491
Week 74	519	492	547

Table 24: Analysis Windows for Open-Label Extension Period

Analysis Visit	Target Day	Low	High
Week 82	575	548	603
Week 90	631	604	659
Week 98	687	660	715
Week 106	743	716	-

6.2.9.1. Rules for Selecting the Analysis Records

Only 1 record per analysis window will be selected for analysis. The following defines the selection rule.

1. Only scheduled visits of the specific endpoint will be selected and summarized in the tables and figures. If the earlier versions of the protocol and the final version of the protocol have different assessment schedules, then both scheduled visits will be used for the descriptive summary, as appropriate. Only the scheduled visits in the latest protocol will be selected for inferential analysis.
    a. For example, an unscheduled SVC assessment may fall into the Week 22 analysis window. However, because Week 22 is not a scheduled visit for SVC, this record will not be flagged for descriptive and inferential analysis.
2. If there are multiple non-missing records within the same analysis window, the record closest to the target day will be selected.
3. If there are records with equal distance from the target day, the later record will be selected.
4. For CAFS analysis, only the last nonmissing record of ALSFRS-R will be selected.

Similar visit windows will be implemented for the OLE Period.

6.3. Appendix 3: List of Abbreviations

The following abbreviations are used in this SAP.

Table 25: Abbreviations

Abbreviation	Definition
ADA	Antidrug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALS	Amyotrophic lateral sclerosis
ALSAQ-40	ALS assessment questionnaire
ALSFRS-R	Amyotrophic lateral sclerosis functional rating scale revised
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CAFS	Combined assessment of function and survival
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of variation

Table 25: Abbreviations

Abbreviation	Definition
ECG	Electrocardiogram
ED	Early discontinuation
EQ-5D-5L	European Quality of Life Health 5-item questionnaire
FAS	Full Analysis Set
FDA	Food and Drug Administration
HHD	Handheld dynamometry
HR	Hazard ratio
IAP	Interim analysis plan
ICE	Intercurrent Event
IDMC	Independent data monitoring committee
IP	Investigational product
IV	Intravenous
KSS	King's staging system
LS	Least squares
MAR	Missing at random
MCS	Mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects model repeated measures
NfL	Neurofilament
NIV	Noninvasive ventilation
OLE	Open-Label Extension
OLES	Open-Label Extension Set
PAV	Permanent assisted ventilation
PCS	Physical component summary
PD	Pharmacodynamics
PDAS	Pharmacodynamic Analysis Set
PK	Pharmacokinetics
PKAS	Pharmacokinetic Analysis Set
PRO-ACT	Pooled Resource Open-Access ALS Clinical Trials
PT	Preferred term
PTAEs	Pre-Treatment Adverse Events
RCP	Randomized-controlled period
SAP	Statistical analysis plan
SD	Standard deviation
SF-36	Short-Form Health Survey
SoA	Schedule of activities
SOC	System organ class
SS	Safety Set
SVC	Slow vital capacity
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TSQM-9	Treatment Satisfaction Questionnaire for Medication
ULN	Upper limit of normal
VAFS	Ventilation assistance-free survival
VAS	Visual analog scale
WHO	World health organization

6.4. Appendix 4: Changes to Protocol-planned Analyses

The following table summarizes the changes in the planned analyses compared to the SAP version 1.0.

Section # and Name	Description of Changes	Brief Rationale
1.INTRODUCTION	The following texts have been deleted: *The scope of this analysis plan includes all efficacy, safety, pharmacokinetics, pharmacodynamics, and immunogenicity data collected during the randomized-controlled period. It will also include select analyses for the open-label extension period data available at the time of database lock for submission to the regulatory agencies. A separate analysis plan will be created to describe the planned analysis methods for the open-label extension period before the final database lock (study closeout).* *The table, figure, and listing specifications will be provided in a separate Data Presentation Plan document.* The following texts have been added: *The scope of the analyses for this study has been revised and is reflected in this SAP amendment due to the study meeting the pre-specified futility criterion. The amendment will be finalized prior to the final database lock and randomization code release. No separate SAP will be developed for the open-label extension period of the study.*	Describe the reason for the SAP amendment and some corresponding plan.
4.ANALYSIS Table 25: Analysis Sets	Per-Protocol Set (PPS) and Ravulizumab Exposure Set (RTS) have been deleted from Table 2.	The PPS analyses are not meaningful as the study stopped due to futility. Given a small amount of data for the open-label extension period, the analyses based on RTS will be redundant.
5.1 General Consideration	The following texts have been added: *All p-values and confidence intervals will be used for descriptive purposes only due to the study meeting the futility criterion.*	To explain how the p-values and confidence intervals will be interpreted.
5.2 Study Participants	Deleted the randomized by region information	Reduced scope for the abbreviated CSR.
5.3.3 Alternate Primary Estimand and Analysis	Deleted this section	Not meaningful given the futility decision.
5.3.4 Other Analyses	Deleted the ALSFRS-R subscore summaries.	Reduced scope for the abbreviated CSR.
5.3.4.2 -5.3.4.8 Sensitivity Analysis 2-8	Deleted	Not meaningful given the futility decision.
5.3.5 Supplementary Analyses	Deleted	Not meaningful given the futility decision.

5.3.6 Other Analyses	Deleted the following sentence: *In addition, longitudinal changes in ALSFRS-R subscores will be modeled using the analytical approach described in Section 5.3.4.1*	Not meaningful given the futility decision.
5.4.1.1.3 Sensitivity Analysis of VAFS	Deleted	Not meaningful given the futility decision.
5.4.1.1.4 Other Analyses Related to VAFS and Components of VAFS (NIV, PAV and Mortality)	Deleted the following sentences: *The log-rank tests will also be performed for these endpoints.* *The Vonesh Shared Parameter model described in Section 5.3.4.3 will be used for joint estimation of treatment effect on mortality and ALSFRS-R.*	Not meaningful given the futility decision.
5.4.1.3 Sensitivity Analysis: Slow Vital Capacity Percent Predicted	Deleted	Not meaningful given the futility decision.
5.4.1.4 Other Analyses for Slow Vital Capacity	Deleted the following: *An analysis of the change from baseline in slow vital capacity volume (Liter) will be conducted similar to the method described in Section 5.4.1.2.2.*	Not meaningful given the futility decision.
5.4.2 Supportive Secondary Endpoints and Analysis	Deleted the MMRM analyses for HHD and NfL.	Not meaningful given the futility decision.
5.5 Tertiary/Exploratory Endpoints and Analyses	Deleted all the analyses for tertiary/exploratory endpoints	Reduced scope for the abbreviated CSR.
5.6 Safety Analyses	Deleted all analyses related to Ravulizumab Exposure Set. Deleted all summary analyses for OLE except the first 6 TEAE tables in Table 6. For RCP, added the following in Table 6: *-TEAEs (IP related) by SOC and PT;* *-TESAEs by SOC and PT and by Highest Relationship to IP;* Changed the following in Table 6: *-TESAEs (IP related) by SOC, PT and by Highest Severity* to *-TESAEs (IP related) by SOC and PT* Added the following listings and tables: Lisitngs: *-Infusion reaction related AEs* *-COVID-19 AEs* Tables: *- Infusion reaction related AEs by SOC and PT* *-Infusion reaction related SAEs by SOC and PT* *- Infusion reaction related AEs (IP-related) by SOC and PT* *- Overall Summary of COVID-19 related AEs* *- COVID-19 related AEs by SOC and PT* *- COVID-19 related SAEs by SOC and PT*	Given a small amount of data for the open-label extension period, the analyses based on RTS or OLES will be redundant or not not meaningful. Additional output to support safety evaluation of ravulizumab.

5.6.1 Extent of Exposure	Deleted the worst post baseline value analyses	
5.6.3 Laboratory Tests	Deleted the following variables from Table 4: *Ravulizumab Treatment Duration(days)* *Total Patient-years (years) Ravulizumab exposure* *Total number of ravulizumab infusions*	RTS was dropped.
5.6.6 Physical Examination	Deleted the following: *The number and percentage of participants with normal and abnormal findings for each physical examination category will be reported by visit for the RCP and the OLE. Participants reporting 'not done' will not be included in the denominator for the percentage calculation.*	Reduced scope for the abbreviated CSR.
5.6.7 Neurological Examination	Deleted the following: *The number and percentage of participants with different findings for each neurological examination category will be reported by visit for the RCP and the OLE.*	Not meaningful given the futility decision. Reduced scope for the abbreviated CSR.
5.6.9 COVID-19 Exposure	Deleted the following: *The number and percentage of participants with COVID-19 exposure will be summarized*.	Small amount of COVID-19 Exposure data.
5.7.2 Pharmacodynamics	Deleted the following: *Details for PK/PD analyses and potential exposure-response analyses will be described in a separate PK/PD analysis plan.*	Not meaningful given the futility decision.
5.7.3 Biomarker Assessments	The exploratory biomarker analyses may be instead of will be performed.	Reduced scope for the abbreviated CSR.
5.7.5 Healthcare Resource Utilization	Deleted	Reduced scope for the abbreviated CSR.
5.7.6.1 Subgroup Analyses for Efficacy	Deleted	Not meaningful given the futility decision.
6.1.5 Prior and Concomitant Medications/Therapies	Added the following listing: *Prophylactic antibiotic medications after receiving meningococcal vaccine for subjects who initiated study drug*	Reduced scope for the abbreviated CSR.
6.2.9. Analysis Windows	Added the following: *Table 24. Analysis Windows for Open Label Extension*	Incorporating OLE in this SAP.
6.3 Appendix 3. Additional details on Statistical Methods	Deleted	Not needed anymore after analyses updates.
6.4 Appendix 4. Changes to Protocol-planned Analyses	Section renumbered.	Section renumbered.
7. References	Deleted the following reference: *5.Vonesh EF, Greene T, Schluchter MD. Shared parameter models for the joint analysis of longitudinal data and event times. Stat Med. 2006;25(1):143-163. doi:10.1002/sim.2249*	Not needed anymore after analyses updates.

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