STATISTICAL ANALYSIS PLAN

VERSION: 1.0
DATE OF PLAN: 14-DEC-2018

STUDY DRUG: RELDESEMTIV (CK-2127107)

PROTOCOL NUMBER: CY 5022

STUDY TITLE:

A PHASE 2, MULTI-CENTER, DOUBLE-BLIND, RANDOMIZED, DOSE-RANGING, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF CK-2127107 IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS)

BASED ON:

Protocol Amendment 03 dated April 18, 2018

SPONSOR:

Cytokinetics, Inc.
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South San Francisco, CA 94080

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

SIGNATURE PAGE

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TECHNICAL SUMMARY REPORT (TSR)

Name of Sponsor/Company Cytokinetics Inc.	**Individual Study Table Referring to Part of the Dossier:** **Volume:**	***(For National Authority Use Only)*:**
Name of Finished Product: No generic or trade name	**Page:**	
Name of Active Ingredient: Reldesemtiv (CK-2127107)		
Title of Study: A PHASE 2, MULTI-CENTER, DOUBLE-BLIND, RANDOMIZED, DOSE-RANGING, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF CK-2127107 IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS)		
Investigators: Study Center(s):		
Studied period (years): 2017-2018	**Phase of development: Phase 2**	
Objectives: Primary: • To assess the effect of reldesemtiv versus placebo on respiratory function in patients with ALS. Secondary: • To assess the effect of reldesemtiv versus placebo on measures of skeletal muscle function • To assess the effect of reldesemtiv versus placebo on global function • To evaluate the safety and tolerability of reldesemtiv administered orally to patients with ALS • To evaluate the exposure of reldesemtiv and its metabolites, when administered orally in tablet form to patients with ALS in the fed state		
Methodology: This study is a Phase 2, double-blind, randomized, placebo-controlled, dose ranging study of reldesemtiv in patients with ALS. Approximately 445 eligible ALS patients will be randomized (1:1:1:1) to receive the following doses of reldesemtiv or placebo: • 150 mg reldesemtiv twice a day for a 300 mg total daily dose (TDD) • 300 mg reldesemtiv twice a day for a 600 mg TDD • 450 mg reldesemtiv twice a day for a 900 mg TDD • Placebo twice a day. Randomization will be stratified by riluzole and/or edaravone use (yes/no) at baseline.		
Number of Subjects (planned and analyzed): Approximately 445 eligible ALS patients will be enrolled and approximately 400 patients are expected to complete 12 weeks of double-blind treatment.		
Criteria for inclusion and exclusion: Inclusion criteria: 1. Able to comprehend and willing to sign an Informed Consent Form (ICF) 2. Males or females between the ages of 18 and 80 years of age, inclusive		

3. Diagnosis of familial or sporadic ALS (defined as meeting the possible, laboratory-supported probable, probable, or definite criteria for a diagnosis of ALS according to the World Federation of Neurology El Escorial criteria published in 2000) ≤ 24 months prior to screening
4. Upright Slow Vital Capacity (SVC) ≥ 60% of predicted for age, height and sex at screening
5. Able to swallow tablets
6. A caregiver (if one is needed)
7. Able to perform reproducible pulmonary function tests
8. Pre-study clinical laboratory findings within the normal range or, if outside the normal range, deemed not clinically significant by the Investigator
11. Patients must be either on riluzole for at least 30 days prior to screening or have not taken riluzole for at least 30 days prior to screening and not planning to start riluzole during the course of the study.
12. Patients on edaravone must have completed at least 2 cycles of dosing with edaravone at the time of screening or have not taken edaravone for at least 30 days prior to screening and not planning to start edaravone during the course of the study. Two cycles of dosing are defined as having completed Cycle 1 infusion, which is 14 consecutive days of intravenous (IV) edaravone followed by 14 days off edaravone, and Cycle 2, which is 10 out of 14 days of IV edaravone.

Exclusion criteria:

1. At the time of screening, any use of non-invasive ventilation (NIV), eg, continuous positive airway pressure [CPAP], noninvasive bi-level positive airway pressure [NPPV] or noninvasive volume ventilation [NVV]for any portion of the day, or mechanical ventilation via tracheostomy, or on any form of oxygen supplementation
2. Neurological impairment due to a condition other than ALS
3. Presence at screening of any medically significant cardiac, pulmonary, GI, musculoskeletal, or psychiatric illness that might interfere with the patient's ability to comply with study procedures or that might confound the interpretation of clinical safety or efficacy data, including, but not limited to:
   a. A pulse <40 or >100 bpm; mean systolic blood pressure >180 mm Hg; mean diastolic blood pressure >100 mm Hg (based on measurements taken after rest for 3 minutes) that persist on 3 successive measurements taken at least 2 minutes apart
   b. Clinically significant ECG abnormalities that require medical attention (ie, persistent atrioventricular conduction block >first degree, or acute myocardial ischemic changes)
   c. New York Heart Association Class II or greater congestive heart failure
   d. Chronic obstructive pulmonary disease or asthma requiring daily use of bronchodilator medications
   e. Gastrointestinal disorder that is likely to impair absorption of study drug from the gastrointestinal tract
   f. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than or equal to 3-times the upper limit of normal (ULN) or has total bilirubin greater than or equal to 2-times the ULN at screening. These assessments may be repeated at the Investigator's discretion (within the screening window)
   g. Poorly controlled or brittle diabetes mellitus
   h. Amputation of a limb
   i. Cognitive impairment, related to ALS or otherwise, sufficient to impair the patient's ability to understand and/or comply with study procedures and provide informed consent
   j. Cancer with metastatic potential (other than basal cell carcinoma, carcinoma in situ of the cervix, or squamous cell carcinoma of the skin excised with clean margins) diagnosed and treated within the last five years
   k. Any other condition, impairment or social circumstance that, in the opinion of the Investigator, would render the patient not suitable to participate in the study

l. Patient judged to be actively suicidal or a suicide risk by the Investigator
m. Patient has estimated glomerular filtration rate (eGFR) less than 40 mL/min/1.73 m^2 calculated by the CKD-EPI cystatin equation based on a cystatin C measurement at baseline

4. Has taken any investigational study drug within 30 days or five half-lives of the prior agent, whichever is longer, prior to dosing
5. Known to have received reldesemtiv or tirasemtiv in any previous clinical trial
6. Has received or is considering receiving during the course of the study any form of stem cell therapy for the treatment of ALS
7. Has received or is considering receiving during the course of the study any form of gene therapy for the treatment of ALS
8. Has received or is considering obtaining during the course of the study a diaphragmatic pacing system
9. History of substance abuse within the past 2 years
10. Use of a strong cytochrome P450 (CYP) 3A4 inhibitor within 7 days prior to first dose of study drug or a strong CYP3A4 inducer within 14 days prior to first dose of study drug
11. Use of a medication that is an OCT1/OCT2 substrate within 7 days prior to first dose of study drug(see Appendix B of study protocol)

Test product, dose and mode of administration:

Reldesemtiv study drug will be supplied as tablets at a dose strength of 150 mg of reldesemtiv per tablet, and administered orally twice a day for a daily dose of 300, 600 or 900 mg if patients are assigned to reldesemtiv dose groups.

Duration of treatment:

12 weeks.

Reference therapy, dose and mode of administration:

Placebo tablet will be provided and administered orally twice a day for 12 weeks.

Criteria for evaluation;

Primary Efficacy Endpoint:

Change from baseline to Week 12 in percent predicted slow vital capacity (SVC)

Secondary Efficacy Endpoint:

- Slope from baseline to Week 12 in muscle strength mega score measured by hand held dynamometry and handgrip dynamometry
- Change from baseline to Week 12 in ALS Functional Rating Scale – Revised (ALSFRS-R).

Other Secondary Endpoints:

- The incidence and severity of treatment-emergent adverse events (TEAEs)
- Plasma concentrations of reldesemtiv at the sampled time points during the study

Statistical methods:

Unless otherwise specified, descriptive statistics for continuous data will be presented using the number of patients with data to be summarized (n), mean, standard deviation (SD), median, minimum (min) and maximum (max). Least square (LS) means, standard error (SE), and two-sided 95% confidence interval (CI) of LS means (where an applicable statistical model is used) will be presented. All categorical/qualitative data will be presented using frequency counts and percentages. Two-sided 95% CIs will be presented, where applicable. Change from baseline to Week 12 in percent predicted SVC will be analyzed using a MMRM with the contrast (-5, -1, 3, 3) to reflect the assumed relationship for the placebo, 300 mg/day, 600 mg/day and 900 mg/day dose groups. The response variable in the model will be the change in the percent predicted SVC from baseline to each post baseline visit. The model will include the terms of treatment, baseline value, pooled sites, visit, riluzole and edaravone use, as well as treatment-by-visit and baseline-by-visit interactions. An unstructured variance-covariance matrix will be used to model within-patient errors.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

The following abbreviations are used in this analysis plan.

Abbreviation	Term
AE	adverse event
ALSAQ-5	ALS Assessment Questionnaire Short Form
ALS	amyotrophic lateral sclerosis
ALSFRS-R	ALS Functional Rating Scale - Revised
ALT	alanine aminotransferase (alanine transaminase)
AST	aspartate aminotransferase (aspartate transaminase)
AUC	area under the plasma concentration-time curve
BDI	Beck Depression Inventory
BMI	body mass index
CI	confidence interval
C_{max}	maximum observed plasma concentration
C_{trough}	pre-dose plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FAS	full analysis set
HHD	hand-held dynamometry
ICF	informed consent form
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
NCI	National Cancer Institute
PCS	potentially clinically significant
PD	pharmacodynamic
PK	pharmacokinetic
PKS	pharmacokinetics analysis set
QTc	corrected QT interval
SAE	serious adverse event
SAS	safety analysis set
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
SVC	slow vital capacity
TDD	total daily dose
TEAE	treatment emergent adverse event
t_{max}	time where maximum concentration is reached
ULN	upper limit of normal

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide a technical elaboration of the planned analyses and detailed data displays to be included in the Clinical Study Report (CSR) for CY 5022.

This SAP was developed in accordance with ICH E9 guideline. All decisions regarding final analysis, as defined in this SAP document, will be made prior to the database lock (unblinding) of the study data. Further study information can be found in the protocol.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of this study is to assess the effect of reldesemtiv versus placebo on respiratory function in patients with amyotrophic lateral sclerosis (ALS).

2.1.2. Secondary Objectives

The secondary objectives of this study are:

- To assess the effect of reldesemtiv versus placebo on measures of skeletal muscle function
- To assess the effect of reldesemtiv versus placebo on global function
- To evaluate the safety and tolerability of reldesemtiv administered orally to patients with ALS
- To evaluate the exposure of reldesemtiv and its metabolites, when administered orally in tablet form to patients with ALS in the fed state

2.1.3. Exploratory Objectives

The exploratory objectives of this study are:

- To assess the effect of reldesemtiv versus placebo on respiratory function self-assessments made at home by patients with help as needed by caregivers
- To assess the effect of reldesemtiv versus placebo on disease progression through measurement of speech production characteristics over time
- To assess the effect of reldesemtiv versus placebo on disease progression through measurement of handwriting abilities over time
- To assess the change from baseline to Visit Week 12 in quality of life (as measured by the ALS Assessment Questionnaire Short Form [ALSAQ-5]) and muscle strength in patients on reldesemtiv compared to placebo

- To assess the change in the slope of decline of measures of function in patients on reldesemtiv compared to placebo

2.1.4. Pharmacokinetic / Pharmacodynamic Objectives

The pharmacokinetic (PK) / pharmacodynamic (PD) objectives of this study are to characterize the pharmacokinetics of reldesemtiv following multiple doses in the fed state at three dose levels in ALS patients as well as to evaluate possible relationships between both dose and exposure of reldesemtiv and its pharmacodynamic effects following multiple oral doses in patients with ALS.

2.2. Study Endpoints

2.2.1. Efficacy Endpoints

2.2.2. Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline to Visit Week 12 in percent predicted slow vital capacity (SVC).

2.2.3. Secondary Efficacy Endpoints

- Slope from baseline to Visit Week 12 in the muscle strength mega score measured by hand held dynamometry (HHD) and handgrip dynamometry
- Change from baseline to Visit Week 12 in the ALS Functional Rating Scale – Revised (ALSFRS-R)

2.2.4. Exploratory Efficacy Endpoints

Endpoints assessed as a change from baseline include:

- Change from baseline to Visit Week 12 in the percent predicted SVC measured at home
- Change from baseline to Visit Week 12 in the components of voice analysis
- Change from baseline to Visit Week 12 in the components of handwriting analysis
- Percent change in the strength of the muscle groups from baseline to Visit Week 12 that contribute to the Mega score at Visit Week 12
- Change from baseline to Visit Week 12 in the ALSAQ-5

Endpoints assessed as a change in slope include:

- Slope of change from baseline to Visit Week 12 in the percent predicted SVC
- Slope of change from baseline to Visit Week 12 in the ALSFRS-R
- Slope of change from baseline to Visit Week 12 in percent predicted SVC measured at home
- Slope of change from baseline to Visit Week 12 in the components of voice analysis

- Slope of change from baseline to Visit Week 12 in the components of handwriting analysis
- Slope of change from baseline to Visit Week 12 in the ALSAQ-5

2.2.5. Safety Endpoints

The safety endpoints are listed in the following:

- Incidence and severity of treatment-emergent adverse events (TEAEs)
- Clinically important changes in safety assessment results [including, as appropriate, vital signs, clinical laboratory tests, ECGs, Ashworth score, falls assessment, physical and neurological examinations, beck depression inventory and suicidality assessment]

2.2.6. Pharmacokinetic Measurements

- The plasma concentrations of reldesemtiv and possible metabolites will be measured at the sampled time points during the study.

3. STUDY DESIGN

3.1. Summary of Study Design

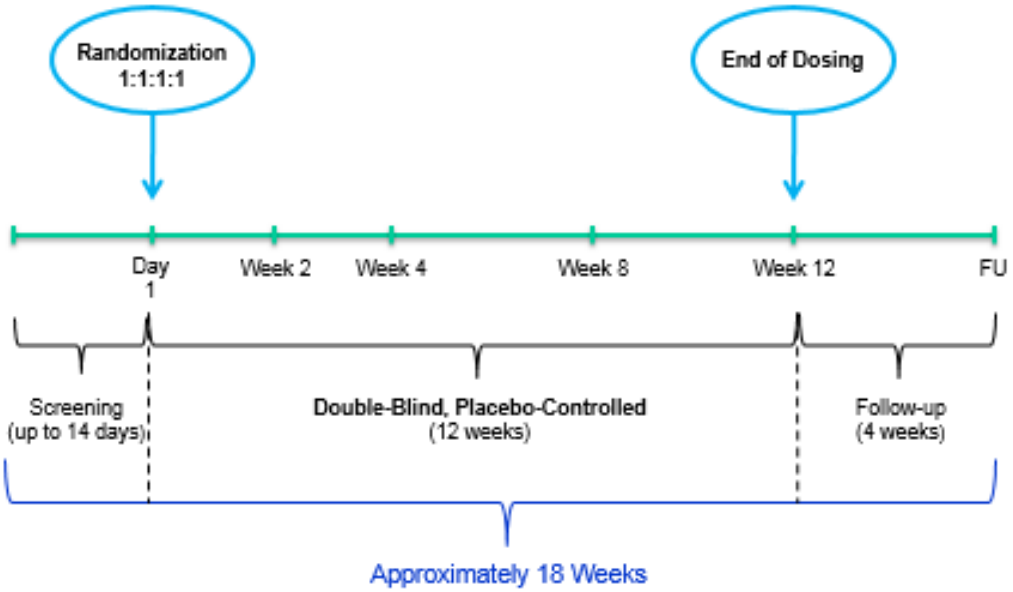
This is a Phase 2, double-blind, randomized, placebo-controlled, dose ranging study of reldesemtiv in patients with ALS. An overview of the randomized treatment groups is provided in Table 1:

Table 1: CY 5022 Randomized, Double-Blind Treatment Groups

CK-2127107			Placebo
300 mg TDD 1 tablet (150 mg) of reldesemtiv and 2 placebo tablets twice daily for 12 weeks	600 mg TDD 2 tablets (150 mg) of reldesemtiv and 1 placebo tablet twice daily for 12 weeks	900 mg TDD 3 tablets (150 mg) of reldesemtiv twice daily for 12 weeks	3 placebo tablets twice daily for 12 weeks

The screening and qualification period for the study will be no more than 14 days in duration. Once patients have completed screening and are considered eligible for the study, they will be randomized as described above and stratified by riluzole and edaravone use status.

Figure 1: Patient Visit Diagram



PD measures, vital signs, ECGs, and clinical laboratory evaluations will be performed at Screening and at specified times during the study. Patients will be evaluated at each study visit for signs and symptoms of intolerance to study drug.

3.2. Description of Study Drug

Reldesemtiv is a small molecule activator of the fast skeletal muscle troponin complex, a sarcomere-directed therapy intended to improve skeletal muscle function in conditions associated with muscle weakness and/or fatigue. Reldesemtiv is supplied as immediate release, white to off-white, modified capsule-shaped tablets. Active reldesemtiv tablets contain 150 mg of reldesemtiv per tablet plus excipients. Placebo tablets contain excipients only. Reldesemtiv and matching placebo tablets will be supplied to the clinical site in blister strips inside labeled wallets. Patients will receive one or more wallets of study drug, reldesemtiv or matching placebo at the appropriate visit. Each wallet is sufficient for one week of dosing, plus overage. Double-blind wallets will be labeled with a unique random kit number.

3.3. Sample Size Consideration

3.3.1. Sample Size Justification

Approximately 445 patients will be randomized. The dropout rate at Visit Week 12 is estimated to be 10%, thus approximately 400 patients are expected to complete 12 weeks of double-blind treatment. The effect of reldesemtiv on the change from baseline to Week 12 in percent predicted SVC will be analyzed using a mixed model for repeated measures (MMRM) with the contrast (-5, -1, 3, 3) to reflect the assumed relationship for the placebo, 300 mg/day, 600 mg/day and 900 mg/day dose groups. The sample size is estimated to provide 90% power to detect 2.75, 5.5 and 5.5 percentage points advantage over placebo in the change from baseline to Visit Week 12 of

percent predicted SVC for the 300 mg/day, 600 mg/day and 900 mg/day reldesemtiv dose groups, respectively. This calculation is based on a two-sided test with alpha set at 0.05 and a common standard deviation (SD) of 14 percentage points.

3.4. Randomization

Patients will be randomized to receive either one of the three reldesemtiv doses (300 mg/day, 600 mg/day and 900 mg/day TDD) or matching placebo tablets in a ratio of 1:1:1:1. Randomization will be stratified by riluzole and edaravone use status at baseline.

3.5. Clinical Assessments

Clinical assessments of all visits are listed in Schedule of Events in Appendix A.

4. PLANNED ANALYSES

4.1. Safety Monitoring

An independent data monitoring committee (DMC) will meet after approximately 30% of patients complete 2 weeks of dosing to review the accumulated safety data (potentially unblinded) for this trial. This committee will make a recommendation as to the continuation of this study based on safety data analysis reports provided at the meeting. The DMC will also provide recommendation(s) on the study conduct.

The DMC will be informed of all initial suspected unexpected serious adverse reactions (SUSARs) within 15 days from the time Cytokinetics is first made aware of it. The DMC will further receive the final case versions of all SUSARs within 15 days after the case closure. DMC will also receive monthly summaries and listings of all serious adverse events and early termination of study treatment.

The DMC may review additional data for safety monitoring purpose. The DMC or Cytokinetics can require an ad hoc DMC meeting at any time. No study activities will be suspended during the safety review.

4.2. Interim Analyses

Not applicable.

4.3. Final Analyses

The final analysis will be conducted after all patients have either completed all the scheduled study visits or have early terminated from the study. At that time, the database will be cleaned and locked and the study treatment will be unblinded. All endpoints will be analyzed based on the final data after the database is locked.

5. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

5.1. General Summary Table and Individual Patient Data Listing Considerations

Summary tables will present descriptive statistics such as number of patients, mean, median, standard deviation, minimum and maximum for continuous variables, and number of patients and the percentage for categorical variables, by dose level in the planned analysis sets. For model based analysis, least square mean, difference of least square means among various dose levels, their standard errors and 95% confidence intervals, and two-sided p-values for the relative statistical inferences will be presented. For survival analyses, time to event will be summarized by median, 95% CI of median, and 1st and 3rd quartiles. Number and percentage will be presented for patients with events and patients whose data are censored. Hazard ratio between dose levels and the corresponding 95% CI and p-value will also be presented.

Listings will include patient ID, demographics, dose level assigned and other relevant items, and sorted by treatment assignment, patient ID and date of assessment.

5.2. Data Management

Data will be entered into the clinical database with programmed edit checks and manual data review to insure integrity. Adverse events, Concomitant Medications and Medical History will be coded automatically by imbedded program in the clinical database with manual review of unique terms. Clinical safety laboratory, pharmacokinetic, handwriting, and voice recording data will be provided from external laboratory(s) or research organization(s) in the pre-specified format.

5.3. Data Presentation Conventions

The following conventions are applied to all data presentations and summaries.

- For continuous variables, all mean and median values are formatted to one more decimal place than the measured value. Standard deviation values are formatted to two more decimal places than the measured value. Minimum and maximum values are presented with the same number of decimal places as the measured value.
- For categorical variables, the number and percentage of responses are presented in the form XX (XX.X%) where the percentage is in the parentheses.
- Date variables are formatted as DDMMMYYYY for presentation. Time is formatted in military time as HH:MM for presentation.
- P-values, if applicable, will be presented to 4 decimal places. If the p-value is less than 0.0001 then it will be presented as <0.0001. If the rounded result is a value of 1.000, it will be displayed as >0.9999.
- Unless otherwise stated, any statistical tests performed will use 2-sided tests at the 5% significance level.

The table, figure and listing shells and table of contents provide the expected layout and titles of the produced outputs of tables, figures and listings. Only differences in the analysis methods or data handling will necessitate a SAP revision.

5.4. Analysis Sets

5.4.1. Full Analysis Set

The Full Analysis Set (FAS) will consist of all randomized patients who received any amount of study drug and have a baseline and at least one post baseline efficacy assessment during the double-blind treatment.

5.4.2. Safety Analysis Set

The Safety Analysis Set (SAS) will consist of all randomized patients who received at least one dose or portion of a dose of study drug.

5.4.3. Pharmacokinetics Analysis Set

The Pharmacokinetics Analysis Set (PKS) will consist of all randomized patients who have at least one evaluable plasma concentration of reldesemtiv, provided they have no major protocol violations that could affect the PK results of reldesemtiv.

5.4.4. Use of Analysis Sets in Different Analyses and Summary Level

The analysis datasets to be used are described in Table 2.

Table 2: Analysis Set and Summary Level

Analyses	Analysis Set
Patients Disposition (Section 6.1)	Randomized Patients, FAS
Study Population (Section 6) except for Patients Disposition (Section 6.1) and Screen Failures (Section 6.2)	SAS, FAS
Efficacy Analyses (Section 7)	FAS
Safety and Tolerability (Section 8)	SAS
PK/PD Analyses (Section 9)	PKS

5.5. Definitions

5.5.1. Baseline Assessments

Baseline assessments are defined as the last non-missing measurement prior to administration of the first dose of study drug.

5.5.2. Change from Baseline

Change from baseline is calculated as (post baseline result – baseline result).

Percent change from baseline is calculated as (change from baseline/baseline result) x 100%.

If either the baseline or the post baseline result is missing, the change from baseline and/or percentage change from baseline will be set to missing.

5.5.3. Study Day

If the date of interest occurs on or after the first dose date, then study day will be calculated as (date of interest – date of first dose) + 1. If the date of interest occurs prior to the first dose date, then study day will be calculated as (date of interest – date of first dose). There is no study day 0.

5.5.4. Analysis Visit Windows

Since study visits do not always take place exactly as scheduled in the protocol, it is necessary to assign the actual observation dates to visit windows for analysis purposes.

For measurement taken prior to the first dose of study treatment, the visit window is defined as the interval of time prior to the first dose of study treatment. Measurements taken on or after the first dose of study treatment will be assigned to the next scheduled visit window.

For data collected at a scheduled post baseline visit, the visit window is assigned based on the scheduled study day of the nominal visit as collected on the electronic case report form (eCRF).

For unscheduled or early discontinuation post baseline visits, measurements taken on or after the first dose of study treatment will be assigned to a visit window using defined lower and upper bounds for each visit window. Measurements assigned in a visit window will have study day greater than or equal to the lower bound but no greater than the upper bound of the visit window. The lower bound and the upper bound for the visit windows are defined as the midpoints of the scheduled visits for all assessments (see Appendix B).

Visits are identified as the nominal visits according to the eCRFs. Each visit will be identified with the visit descriptor (eg, “Week 12”). If a patient has two or more study visits in one visit window, one record will be flagged as the “analyzed record” for that visit window.

5.5.5. Determining “Analyzed Record” for Each Analysis Visit Window

Once visit windows are assigned, a patient’s individual visit window could potentially contain more than one visit. Records from all visits, including scheduled, unscheduled and early discontinuation visits could be flagged as the “analyzed record” within the visit window, although the records from scheduled visit will take priority.

For measurement taken prior to the first dose of study treatment, in the event of multiple visits falling within the visit window, the following rule will be used to determine the “analyzed record”:

- The record closest to, but prior to the first dose of study treatment should be selected as the baseline “analyzed record.” This could include scheduled visits and other screening visits.

For post baseline visits, in the event of multiple visits falling within a visit window, the following rules will be used in sequence to determine the “analyzed record” for the visit window:

- If a scheduled visit occurred during the visit window, then the measurement taken from the scheduled visit will be used.

- If no scheduled visit occurred during the visit window, the measurement taken closest to the scheduled day will be used as the "analyzed record."
- If no scheduled visit occurred during the visit window and there is a tie between visits in the number of days before and after the scheduled day, measurements from the later visit will be used as the "analyzed record."

For all analyses, only the "analyzed record" within each visit window will be summarized in a table. If there are other visit records within the visit window, they will only be included in data listings. In addition, composite scores (eg, ALSFRS-R total score or muscle strength mega score) will be calculated based on the "analyzed record."

5.5.6. Pooled Sites

The "study site" will be used as a fixed effect in the efficacy analysis models. For analysis purpose, study sites that have few patients enrolled (eg, less than 10% of patients among all enrolled) may be pooled to ensure sufficient number of patients from each site and approximately equal number of patients among the sites. For study sites with few patients enrolled, the sites within a country will be pooled by geographic proximity into groups with appropriate number of patients in each group. If an entire country has less patients enrolled compared to other study sites, all sites within the country will be pooled into one group, and the group will further be pooled across countries as appropriate. See Appendix C for regional site pooling for FAS.

5.5.7. Calculated Rate of Pre-Study Disease Progression

Change in ALSFRS-R total score will be used to represent the status of ALS disease progression. The pre-study rate of disease progression evaluated at baseline will be calculated as the change in ALSFRS-R total score between the date of ALS symptom onset and the date at baseline. Assuming a patient has a ALSFRS-R total score of 48 at the time of ALS symptom onset, the rate of disease progression per month evaluated at baseline can be calculated as follows: (48 – ALSFRS-R total score at baseline) / months (30.25 days) since ALS symptom onset.

5.5.8. Efficacy Assessments

This section describes the efficacy assessments including how scores are calculated.

5.5.8.1. Percent Predicted Slow Vital Capacity

SVC is used to evaluate pulmonary status. It is the maximum volume of air that can be exhaled slowly after slow maximum inhalation. The percent predicted SVC presents the test result as a percent of the predicted values for patients based on sex, age, height, and race. It is calculated as: Percent Predicted SVC = (Trial SVC / Predicted SVC) x 100 (%)

The predicted SVC is calculated using the Quanjer GLI-2012 Regression Equation (Quanjer 2012) that factor the characteristics of sex, age, height and race into the prediction.

For male,

Predicted SVC = exp [–11.2281 + 2.4135 x ln(Height)(cm) + 0.0865 x ln(Age)(yrs)

– 0.1684 x AfrAm – 0.0405 x NEAsia – 0.1177 x SEAsia

– 0.0825 x Other + Mspline]

For female,

Predicted SVC = exp [–10.403 + 2.2633 x ln(Height)(cm) + 0.0234 x ln(Age)(yrs)

– 0.1555 x AfrAm – 0.0262 x NEAsia – 0.1516 x SEAsia

– 0.0833 x Other + Mspline]

where

ln( ) = natural log transformation

AfrAm = 1 if a patient is African American, otherwise = 0

NEAsia = 1 if a patient is from North East Asia, otherwise = 0

SEAsia = 1 if a patient is from South East Asia, otherwise = 0

Other = 1 if a patient belongs to other ethnic group or has mixed ethnicity, otherwise = 0

Mspline is determined by age and sex as shown in Appendix D.

For each clinical visit, a patient's SVC was evaluated in triplicate. The highest result among the evaluable measurements confirmed by the central read of an independent pulmonologist will be used for analysis (ie, measurements not confirmed as evaluable by the central read will be excluded from analysis). For SVCs measured at home, the highest result among the evaluable measurements collected during a day will be used for analysis, where 'evaluable' is defined as a measurement of SVC is not smaller than 0.5 times and not greater than 1.5 times of the highest evaluable SVC measured in clinic during the same week.

The percent predicted SVC declines over time in patients with ALS. The change from baseline in percent predicted SVC will be calculated as the post baseline value minus the baseline value, so that a negative number for change from baseline indicates respiratory function decline relative to baseline, and a positive treatment difference (reldesemtiv minus placebo) favors reldesemtiv.

5.5.8.2. Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised

The ALSFRS-R is a validated rating instrument for monitoring the progression of disability in patients with ALS (Cedarbaum 1999). The assessment is based on 12 clinical ratings that are categorized in four domains: bulbar (speech, salivation, swallowing), fine motor skills (handwriting, cutting food and handling utensils, dressing hygiene), gross motor skills (turning in bed and adjusting bedclothes, walking, climbing stairs) and respiratory function (dyspnea, orthopnea, respiratory insufficiency). Each clinical rating is assessed using an ordinal scale that ranges from 0 to 4, with a score of 4 representing normal function and lower scores indicating worse function.

The ALSFRS-R total score is calculated as the sum of the 12 ratings. The score of each of the four domains (bulbar, fine motor skill, gross motor skill, and respiratory function) is calculated as the sum of the three ratings within each domain, and can range from 0 to 12. If a single rating is missing, the score of the corresponding domain and the ALSFRS-R total score will be set to missing.

The ALSFRS-R total scores can range from 0 to 48, with higher scores indicating less functional impairment. The score change from baseline will be calculated as the post baseline score minus the baseline score, so that a negative number for change from baseline indicates greater impairment relative to baseline. A positive treatment difference in the change from baseline (reldesemtiv minus placebo) favors reldesemtiv.

5.5.8.3. Muscle Strength Mega Score

Patients' muscle strength was measured bilaterally using HHD and hand grip dynamometry. The HHD measures muscle strength of the six muscle groups: elbow flexion, wrist extension, first dorsal interosseous, knee extension, ankle dorsiflexion, and hip flexor. The hand grip dynamometry measures maximum hand grip strength. In each clinical visit, a patient's muscle strength was evaluated in triplicate for those measured by HHD. The maximum result among the three measurements will be used for analysis.

The muscle strength was recorded as 0 (pounds) on the eCRF for the following situations:

- A patient was able to assume the correct position but unable to exert any force.
- A patient was unable to assume the correct position, and the evaluator is able to determine the cause as muscle weakness or contracture.
- A patient was too weak to perform the test.

The muscle strength of each measured body location is transformed as a percent change from baseline using the equation: [(post baseline value – baseline value) / baseline value] x 100. The transformed muscle strength will be set to missing if the baseline value is zero.

The mega score is a composite score that averages strength across muscle groups. It is calculated as the mean of the non-missing transformed muscle strength scores among the 14 measured body locations, including the six muscle groups measured bilaterally by the HHD, and the hand grip strength measured bilaterally by hand grip dynamometry.

A greater muscle strength mega score indicates less muscle strength loss, and a positive treatment difference (reldesemtiv minus placebo) favors reldesemtiv.

5.5.8.4. Ashworth Score

Ashworth score measures resistance during passive soft-tissue stretching and is used as a simple measure of spasticity (Bohannon 1987). Ashworth score will be assessed for elbow and knee bilaterally in this study. For analysis purpose, the average of non-missing measurements from all assessed body location will be calculated as the Ashworth total score.

5.5.8.5. Components of Voice Analysis

To evaluate speech change associated with neuro-degeneration in patients with ALS, speech samples for voice analysis will be collected periodically using mobile app and analyzed using a computational model for speech production. The parameters of speech-based outcome can be classified in 3 domains (precision in speaking, vocal control, and speaking rate). Each parameter within the domains were summarized by Aural Analytics as follows:

Precision in Speaking

- **Articulation Entropy**: An aggregated measure of how 'typical' speech sounds are. For example, the score for the word more is a combination of the typicality of pronunciation for 'm', 'o' and 'r'. All articulation entropy raw values are negative. Normal speech has articulation entropy close to 0. Articulation Entropy is more negative in imprecise speech, as is typical in advanced ALS patients.
- **Vowel Space Area**: A measure of how distinct vowel sounds are from each other. Typical speech has a large, positive vowel space area. Vowel Space Area decreases toward 0 as vowel sounds become less differentiated, as is typical in advanced ALS patients.
- **Low-Frequency Energy Distribution**: A measure of how much speech sounds are 'nasalized', sounding like 'm' or 'n'. All values are negative; values closer to 0 are more nasalized, as often occurs in advanced ALS patients.
- **Low-Frequency/High Frequency Ratio**: Another measure of how much speech sounds are 'nasalized', sounding like 'm' or 'n'. All values are negative; values closer to 0 are more nasalized, as often occurs in advanced ALS patients.

Vocal Control

- **Perceptual Loudness Decay**: Measures how quickly the voice loses energy when holding out the sound 'aaaaahhh.' Normal voices lose energy slowly and have decay values that are near 0. Values can be positive or negative. Larger negative values are associated with an inability to sustain speech, as occurs in advanced ALS patients.
- **Flutter**: A measure of involuntary movement (rapid tremor) in the vocal folds. Normal speech has 0 flutter. Greater than 0 flutter is associated with the type of vocal fold vibration that occurs in advanced ALS patients.
- **Phonatory Duration**: Measures how long a patient can hold out the sound 'aaaaahhh.' Longer, positive hold times are associated with normal voices; as the ability to hold out the vowel sound is lost, phonatory duration decreases toward 0.
- **Fundamental Frequency**: A measure of voice pitch. Low fundamental frequency indicates low pitch. Fundamental frequency is always greater than 0.
- **Fundamental Frequency Variability**: A measure of variability in voice pitch. Steadier voices have variability near 0; larger positive variability values indicate a more widely varying voice pitch.

Speaking Rate

- **Articulation Rate**: A measure of how quickly individual sounds in a word are spoken. Articulation rate is always greater than 0. Articulation rate closer to 0 indicates slower speech and is associated with more advanced ALS patients.
- **Articulation Rate Variability**: A measure of change in articulation rate over the course of a clinical session. Articulation rate variability can be positive or negative; more negative values indicate fatigue of muscles involved in speech.

- **Speaking Rate**: A measure of how quickly syllables in a word are spoken. Speaking rate is always greater than 0. Speaking rate closer to 0 indicates slower speech and is associated with more advanced ALS patients.
- **Speaking Rate Variability**: A measure of change in speaking rate over the course of a clinical session. Speaking rate variability can be positive or negative; more negative values indicate fatigue of muscles involved in speech.
- **Pause Rate**: A measure of how often patients need to pause for breath while speaking. Pause Rate is always greater than 0. A higher pause rate indicates that a speaker needs to pause for breath often, as is the case in advanced ALS patients.
- **Pause Rate Variability**: A measure of control over respiration, derived from the change in pause rate over the course of a clinical session. Pause rate can be positive or negative; more positive values indicate loss of respiratory control.

The speech-based outcome will be tracked within session and at each study visit over time. For each parameter, the longitudinal outcome collected at each study visit will first be normalized to adjust for background differences for individual patient, and be transformed as a percent change from baseline using the equation: [(post baseline value – baseline value) / baseline value] x 100. For a domain, the outcome for analysis will be the average of the percent changes from baseline from all parameters within the domain.

5.5.8.6. Components of Handwriting Analysis

Fine motor assessments, including handwriting and figure tracing, will be performed using a stylus and mobile app. The parameters used in the handwriting analysis can be classified into 2 domains (fine motor precision and fine motor fatigue) and were summarized by Aural Analytics as follows:

Fine Motor Precision

- **Tracing Error**: Measure of deviation from traced line. All values are positive. Lines that closely match the trace will have low tracing error; lines that do not closely match the trace will have high tracing error.

Fine Motor Fatigue

- **Average Pressure**: Measure of pen pressure on writing surface. Pressure is always positive. The larger the value, the more pressure the user is applying to the surface of the iPad.
- **Average Pressure Decay**: A measure of the decay in pressure over time. A negative value indicates reduced pressure over time; this means that the user is applying less and less pressure over the duration of the task.
- **Average Speed**: Measure of pen speed over writing surface. Larger values indicate faster pen motion.
- **Average Speed Decay**: A measure of the decay in speed over time. A negative value indicates greater reduction in speed over time; this means that the user is becoming slower and slower over the duration of the task.

- **Average Acceleration**: Measure of pen acceleration on the writing surface. Larger values indicate higher pen acceleration.
- **Average Acceleration Decay**: A measure of the decay in acceleration over time. A negative value indicates greater reduction in acceleration over time. This means that the user's acceleration is changing less and less over the duration of the task.
- **Average Tracking Jerk**: A measure of change in the pen's acceleration over the duration of the tasks. This captures 'jerking' behavior where the pen doesn't glide smoothly across the tablet surface but rather exhibits 'stop-go' behavior.

The fine motor assessments will be performed at all study visits. For analysis, the longitudinal data collected from each patient will be transformed as a percent change from baseline using the equation: [(post baseline value – baseline value) / baseline value] x 100. For a domain, the outcome for analysis will be the average of the percent changes from baseline from all parameters within the domain.

5.5.8.7. ALS Assessment Questionnaire Short Form

The ALSAQ-5 is a subjective health measure designed to assess the health-related quality of life in patients with ALS (Jenkinson 2001). It is a short form of ALSAQ derived from ALSAQ-40 that includes 40 items evaluating 5 dimensions of health status that are affected by the disease: physical mobility (10 items), activities of daily living and independence (10 items), eating and drinking (3 items), communication (7 items), and emotional reactions (10 items).

The ALSAQ-5 includes five selected items with one item representing each dimension. It produces results closely resembled those of the five dimension scores of the ALSAQ-40. The dimensions and the corresponding items for ALSAQ-5 are shown in Table 3.

Patients are asked to select one of the five options according to the frequency of each event experienced during the last two weeks, and a score is assigned for each option: 0=never, 1=rarely, 2=sometimes, 3=often, 4=always or cannot do at all.

Table 3: Dimensions and Items of ALSAQ-5

Dimension	Item (Question) for ALSAQ-5
physical mobility	Q1: I have found it difficult to stand up.
activities of daily living and independence	Q2: I have had difficulty using my arms and hands.
eating and drinking	Q3: I have had difficulty eating solid food.
communication	Q4: I have felt that my speech has not been easy to understand.
emotional functioning	Q5: I have felt hopeless about the future.

The score of item for each dimension is then transformed on a scale of 0 to 100 using the equation: (score of each dimension/4) x 100, with 0 indicating perfect health and 100 indicating worst possible health status. The interpretation of the score is shown in Table 4.

Table 4: Interpretation of Score Ranges for Dimensions on ALSAQ-5

Score range	Interpretation
0 –19	No problems
20-39	Problems rarely
40-59	Problems Sometimes
60-79	Problems Often
80-100	Problems always/ nearly always or unable to do at all

Source: Jenkinson 2001

The ALSAQ-5 total score is calculated as sum of the score from the 5 individual items, and the total score will be set to missing if any of the score among the 5 items is missing.

5.5.9. Health Economic Outcome Measures

If a patient is prescribed and agrees to receive any of the following during the course of the study, the date of prescription will be recorded:

- Non-invasive ventilation
- Gastrostomy tube
- Manual wheelchair
- Power wheelchair
- Augmentative and alternative communication

5.5.10. Safety and Related Data

5.5.10.1. Exposure and Compliance

Information of whether a patient received a scheduled dose will be recorded.

5.5.10.2. Adverse Event

AE Duration

The duration (in days) of an adverse event (AE) is calculated as AE stop date - AE start date + 1. If the event is ongoing, the final database lock date will be used as the stop date in duration calculations.

AE Severity

The severity of an AE is based on the Common Terminology Criteria for Adverse Events (CTCAE) grades collected on the CRF:

Grade 1 = Mild

Grade 2 = Moderate

Grade 3 = Severe

Grade 4 = Life threatening

Grade 5 = Fatal

For summary purposes, missing severity will be counted as severe.

AE Relatedness

All AEs classified as treatment related by the investigator on the CRF are considered treatment related. For summary purposes, missing relatedness will be counted as related.

TEAE and Serious TEAE

An AE or serious AE (SAE) will be regarded as treatment emergent if it starts or worsens (eg, increases in severity or frequency) during or after the first dose of study drug.

Death

Date and reason of death will be recorded and presented.

5.5.10.3. Clinically Relevant Abnormalities in Vital Signs, Weight, and ECG

The criteria used to identify clinically significant abnormalities in vital signs are given in Table 6. The criteria used to identify clinically significant abnormalities in ECG are given in Table 7.

5.5.10.4. Prior and Concomitant Medications

The prior and concomitant flags for medications other than study treatment will be derived. Medications with a stop date prior to the first dose of study drug will be considered prior medications. Medications with a stop date on or after the first dose of study drug will be considered concomitant medications.

5.5.10.5. Beck Depression Inventory

The Beck Depression Inventory (BDI®) ─ Fast Screen (BDI-FS) is a shortened version of the BDI-II that evaluates key symptoms of depression. It was developed to factor out co-occurring depression symptomatology that may be related to a medical condition (Steer 1999), and concentrate on factors of depression that relate solely to depression. The BDI-FS contains 7 self-reported items that evaluate major depressive symptoms over the past 2 weeks, including sadness, pessimism, past failure, loss of pleasure, self-dislike, self-criticalness, and suicidal ideations (Beck 2000, Steer 1999). Individual scale items are scored on a 4-point continuum (0=least, 3=most), with a total summed score range of 0–21. Higher scores indicate greater depressive severity. Patient's depression level will be classified using the BDI total score as shown in Table 5. The BDI total score will be set to missing if an answer to any of the 7 items is missing.

Table 5: Depression Level Classification by BDI Total Score

Depression Level	BDI Total Score
Minimal Depression	0 - 3
Mild Depression	4 - 6
Moderate Depression	7 - 9
Severe Depression	10 - 21

5.5.11. Pharmacokinetics Parameters

The PK parameters are defined as follows:

Parameter	Definition
AUC_{0-t}	Area under the concentration-time curve from time zero to the last measurable concentration, also called AUC_{last}.
$AUC_{0-\tau}$	Area under the concentration-time curve from time zero to time τ (eg, hours). It is calculated by using the trapezoid rule if all concentrations are above quantitation limit before time τ, and by using extrapolation if concentration drops below quantitation limit before time τ.
C_{max}	The maximum (or peak) concentration that a drug achieves in tested area after the drug has been administrated and prior to the administration of next dose.
C_{trough}	The minimum concentration between dose time and dose time + τ (at T_{trough}).
t_{max}	The time that C_{max} was observed.

The parameters C_{max}, AUC and t_{max} will be derived using the following rules:

- For calculation of C_{max}, pre-dose value will not be included in the determinations.
- Analyses will be based on actual sampling time converted to elapse time defined as time from dosing.
- Any concentration below the lower limit of quantitation (LLOQ) will be reported as 0.00 for summaries by each time point.
- For AUC calculations, samples with values below the LLOQ prior to the first measurable concentration will be set to zero. Samples with below the LLOQ result after the first measurable concentration will be treated as missing and the calculation of AUC will proceed by fitting a trapezoid between the surrounding, non-missing values.
- t_{max} will be calculated only for patients who have at least two samples collected after dosing.

At Weeks 2 and 12 PK samples will be collected at pre-dose, and 1, 3 and 6 hours post-dose. For AUC_{12} calculation, the pre-dose concentration will be used to approximate the concentration value at 12 hours.

5.5.12. Reldesemtiv Concentration Bin

The average C_{trough} value from Weeks 2, 4, 8 and 12 as well as the average C_{max} value from Weeks 2 and 12 will be calculated for each patient who received reldesemtiv, and the averaged C_{trough} or C_{max} values will then be used to assign patients to one of the reldesemtiv concentration bins that are classified by selected ranges of percentiles. For example, a set of the concentration bins can be defined using the quartiles of averaged C_{trough} values as follows:

- Bin A: averaged $C_{trough} \leq Q1$
- Bin B: $Q1 <$ averaged $C_{trough} \leq Q2$
- Bin C: $Q2 <$ averaged $C_{trough} \leq Q3$
- Bin D: averaged $C_{trough} > Q3$

where Q1, Q2 and Q3 represent the 1st, 2nd and 3rd quartiles of the averaged C_{trough} values, respectively. Approximately equal number of patients will be assigned to each reldesemtiv concentration bin.

5.6. Handling of Missing Data

5.6.1. Missing Efficacy Endpoints

The efficacy analysis will be performed using mixed effect model as specified. The model will provide unbiased results without imputation assuming that the missing patterns are missing at random (MAR). If the percentage of missing values in the primary efficacy endpoint is > 20%, sensitivity analyses assuming different missing data pattern will be conducted. Multiple imputation within the dose group of each missing data pattern will be performed using Markov chain Monte Carlo method.

5.6.2. Missing Start and Stop Dates for Prior and Concomitant Medication

Imputation of missing/partial dates will not be performed. The available year or year and month in a partial date will be used and will be compared to first dosing year, month and day to determine whether to include the medication in the medication history or as a concomitant medication. If the available data do not give sufficient information to classify the medication, the medication will be classified as concomitant medication.

5.6.3. Missing Dates of ALS Symptom Onset and Diagnosis

Imputation of missing/partial dates will not be performed. The available year or year and month in a partial date will be used to calculate the time from ALS symptom onset and the time from ALS diagnosis (in months). The following derivation rules will be used in sequence in the calculation:

- If the duration in days can be derived based on the available date information, the duration in months will be calculated as

Duration in month = Duration in day / 30.4375

- If the duration in months can be derived but not the duration in days, the derived duration in months will be used for data summary.
- If the duration in years can be derived but not the duration in days and months, the duration in months will be calculated as

Duration in month = Duration in year x 12

5.6.4. Missing Onset and Stop Dates for Adverse Events

For AEs with incomplete date information recorded in the eCRF, the imputation will follow the following algorithm:

1. For missing AE onset Day and Time:
   - If an AE onset Day is missing and the Month of AE onset is known, then the first day of the month of AE onset will be imputed as the AE onset date.
   - If AE onset information is not available, then the first dosing date will be imputed as the AE onset date.
2. For missing AE end Day and Time:
   - If the AE end Day is missing and the AE end Month is earlier or later than that of the Follow-Up Visit, then the last day of the AE end month will be the imputed as the AE end date.
   - If the AE end Day is missing and the AE end Month is the same as that of the Follow-Up Visit, then the date of the Follow-Up Visit will be the imputed as the AE end date.
   - If no AE end information is available, then
     – For patients who discontinued early from study drug, the imputed AE end date will be on the later of the last dosing date + 28 days or the last visit or contact date.
     – For patients who completed the study, the imputed AE end date and time will be the date of the Follow-Up Visit.
     – If the stop date is missing and the event is ongoing, the event will be noted as ongoing” in the stop date column in data listings.

6. STUDY POPULATION

6.1. Patient Disposition

Number of patients in each analysis set will be summarized. The number and percentage of patients who were randomized, who received at least one dose of study drug, who completed the study treatment, and who prematurely discontinued from the study treatment and/or from the study, will be presented by each dose level and overall, as well as by baseline riluzole and

edaravone use status. Reasons for premature discontinuation as recorded on the termination page of the eCRF will be summarized as well.

All enrolled patients will be listed with their date of screening, date of last visit, dates of first and last dose, demographic information including age, sex, race, last contact date, and reasons for discontinuation from the study treatment and/or from the study.

6.2. Screen Failures

Number and percentage of screen failures will be summarized by reasons of screening failure. A listing will also be provided.

6.3. Protocol Deviations

Protocol deviation is any divergence from the protocol that impacts a patient's safety, rights, or welfare or materially reduces the quality or completeness of the data. Number and percentage of patients meeting any protocol deviation criteria will be summarized by type of deviation (major, minor), dose level and overall. A listing of protocol deviations will be provided.

6.4. Demographic and Baseline Characteristics

Demographic and baseline characteristics which include age, sex, race, ethnicity, height, weight, BMI, tobacco and alcohol use, etc. will be summarized overall, by dose level and by riluzole and edaravone use status at baseline. Patient listings will be provided.

6.5. Listing of Patient Inclusion and Exclusion Criteria

A listing of randomized patients who violate the inclusion and exclusion criteria will be provided.

6.6. Medical History and Medical Conditions Present at Entry

Medical history will be summarized by dose level and overall for the safety population. The number and percentage of patients within each medical history item will be summarized by system organ class and preferred term. Patient listings with start date, stop date, system organ class, and preferred term will be provided.

Medical history of ALS will be summarized by dose level and overall for the safety population. The number and percentage of patients with or without family history, onset site of ALS, and the descriptive statistics of time since first symptom onset and time since first diagnosis will be provided. Patient listing containing symptom onset date, and diagnosis date will be provided.

6.7. Prior Medication History and Medications Present at Entry

Prior medication history and medication present at entry will be coded using WHO Drug Dictionary Enhanced with Herbal, June 2015 to classify medications by therapeutic class (ATC Class 3) and preferred name. If ATC Class 3 is not available, ATC Class 2 will be used in the summary. See Section 5.5.10.4 for the definition of prior medications.

6.8. Baseline Physical Examination

Clinically significant physical examination findings will be summarized as medical history or AEs, as appropriate.

6.9. Baseline Vital Signs

Baseline vital signs such as heart rate, blood pressure, respiratory rate and BMI will be summarized and listed along with post baseline vital signs.

6.10. Baseline Laboratory Data

Baseline laboratory data of hematology, serum chemistry and urinalysis will be summarized and provided in the table along with post baseline laboratory data. The laboratory parameters to be included for analysis are given in appendices of the protocol.

6.11. Baseline Primary and Secondary Efficacy Evaluations

Baseline primary and secondary efficacy evaluation will be summarized and listed along with post baseline efficacy evaluation.

7. EFFICACY

Inferential statistical tests will be two-sided and will be performed at alpha levels of 0.05 to declare the significance of effects.

7.1. Testing Statistical Assumptions

Assumptions for statistical models will be evaluated graphically. If assumptions are substantially violated, additional analysis methods will be performed.

7.2. Statement of the Null and Alternate Hypotheses

The statistical null hypothesis is that there is no treatment difference between the two high dose groups combined and placebo group plus low dose group (ie, 600 mg/day and 900 mg/day dose groups combined vs. placebo and 300 mg/day dose groups combined) with the assumed dose-response relationship in percent predicted SVC change from baseline to Week 12. The statistical alternative hypothesis is that there is a positive treatment difference (reldesemtiv minus placebo) in change from baseline to Week 12 in the percent predicted SVC.

Suppose the means of the efficacy endpoint for the placebo, 300 mg/day, 600 mg/day and 900 mg/day dose groups are $\mu_{placebo}$, $\mu_{300\ mg/day}$, $\mu_{600\ mg/day}$ and $\mu_{900\ mg/day\ 300\ mg/day}$, respectively. With the assumed dose-response relationship for the means among the placebo, 300 mg/day, 600 mg/day and 900 mg/day dose groups, the null and alternative hypotheses can be expressed as follows:

- H_0: $-5 \times \mu_{placebo} - 1 \times \mu_{300\ mg/day} + 3 \times \mu_{600\ mg/day} + 3 \times \mu_{900\ mg/day} = 0$
- H_A: $-5 \times \mu_{placebo} - 1 \times \mu_{300\ mg/day} + 3 \times \mu_{600\ mg/day} + 3 \times \mu_{900\ mg/day} \neq 0$

7.3. Subgroup Analyses

To examine the consistency of the observed treatment effect and to gain insight into the effectiveness of reldesemtiv in subpopulations, subgroup analyses will be performed. Analyses of the primary endpoint (percent predicted SVC change from baseline to Week 12) and the secondary endpoints (slope of muscle strength mega score through Week 12, and ALSFRS-R score change from baseline to Week 12) will be conducted for the following subgroups if the sample size in each category of a subgroup is sufficient for statistical modeling convergence and sound interpretation of analysis results:

- Sex (male, female)
- Age group (< 65, ≥ 65 years old)
- Race (white, non-white)
- BMI at baseline (< 25 kg/m^2, ≥ 25 kg/m^2)
- Riluzole and edaravone use status at baseline (use both, use riluzole only, use edaravone only, use neither)
- Percent predicted SVC at baseline (< 80%, ≥ 80%)
- ALSFRS-R total score at baseline (< 38, ≥ 38)
- ALSAQ-5 total score at baseline (< 150, ≥ 150)
- Geographic region (North America, Europe, Australia)
- Anatomic site of disease onset (limb, bulbar, cognitive, respiratory)
- Time since ALS symptom onset (< 2 years, ≥ 2 years)
- Time since ALS diagnosis (< 1 year, ≥ 1 year)
- Time since ALS diagnosis (< 6 months, ≥ 6 months)
- Pre-study rate of disease progression (1^{st} tertile, 2^{nd} tertile, and 3^{rd} tertile)

7.4. Multiple Comparisons and Multiplicity

The null hypothesis for the primary and secondary efficacy endpoints will be tested in a prespecified order using a closed testing procedure. This procedure will maintain the family-wise error rate at two-sided significance level of 0.05 for all primary and secondary hypotheses tested in a confirmatory sense.

Step 1. The null hypothesis H_{01} is that there is no treatment difference in the primary efficacy endpoint, percent predicted SVC change from baseline to Week 12, in the FAS. The hypothesis will be tested at the two-sided significance level of 0.05. If this hypothesis is rejected, testing will proceed to Step 2; otherwise testing will stop.

Step 2. The null hypotheses H_{02} is that there is no treatment difference in the secondary efficacy endpoint, slope of muscle strength mega score through Week 12, in the FAS.

The hypotheses will be tested at the two-sided significance level of 0.05. If this hypothesis is rejected, testing will proceed to Step 3; otherwise testing will stop.

Step 3. The null hypotheses H_{03} is that there is no treatment difference in the secondary efficacy endpoint, ALSFRS-R total score change from baseline to Week 12, in the FAS. The hypotheses will be tested at the two-sided significance level of 0.05.

No further hypothesis testing will be carried out in this closed testing procedure.

7.5. Analysis of the Primary Efficacy Endpoints

7.5.1. Primary Efficacy Analysis

The primary efficacy endpoint (change from baseline to Visit Week 12 in percent predicted SVC) will be analyzed for the FAS based on the percent predicted SVCs collected in clinic and were confirmed evaluable by the central read of an independent pulmonologist. A MMRM with the contrast (-5, -1, 3, 3) will be used for the analysis to reflect the assumed relationship for the placebo, 300 mg/day, 600 mg/day and 900 mg/day dose groups. The response variable will be the change from baseline to each post baseline visit up to Week 12. The model will include the following covariates:

- Treatment (reldesemtiv 300 mg/day, 600 mg/day and 900 mg/day, and placebo)
- Baseline (baseline value of the response variable)
- Pooled site (Center)
- Visit (scheduled, a categorical variable)
- Riluzole and edaravone use status at baseline
- Treatment-by-visit interaction
- Baseline-by-visit interaction

An unstructured variance-covariance structure will be used to model the within-subject errors. If a model fails to converge, other covariance matrix structures (eg, compound symmetry) may be used instead of the unstructured covariance matrix. Least square means and the corresponding standard errors, 95% CIs and p-values will be presented.

7.5.2. Sensitivity Analyses of the Primary Efficacy Results

Sensitivity analysis under the assumption of missing not at random (MNAR) will be conducted using control-based pattern imputation approach (Ratitch 2011) for the primary efficacy endpoint (change from baseline to Visit Week 12 in percent predicted SVC). A model for imputing missing observations of percent predicted SVC in both reldesemtiv and placebo groups will be constructed using the observed data in the placebo group. The sensitivity analysis will include all observed and the aforementioned imputed data in the analysis model for the primary efficacy endpoint.

7.6. Analysis of the Secondary Efficacy Endpoints

Slope of muscle strength mega score over time through Week 12 will be analyzed for the FAS. The response variable will be muscle strength mega score at each post baseline visit up to Week 12. The model will include the following covariates:

- Treatment (reldesemtiv 300 mg/day, 600 mg/day and 900 mg/day, and placebo)
- Pooled site (Center)
- Time (time from the first dose, a continuous variable)
- Riluzole and edaravone use status at baseline
- Treatment-by-riluzole use status interaction
- Treatment-by-edaravone use status interaction
- Treatment-by-time interaction

The time will be set as a random effect and the intercept will be set to zero.

The Change from baseline to Visit Week 12 in ALSFRS-R will be analyzed using the same model as for the primary efficacy endpoint, except for the response variable.

7.7. Analysis of the Exploratory Efficacy Endpoints

Analyses for the exploratory endpoints specified in Section 2.2.4 will be performed for the FAS.

The endpoints of change from baseline will be analyzed using the same model as described for the primary efficacy endpoint, except for the response variable.

The endpoint of percent change from baseline or muscle strength mega score (calculated as percent change in muscle strength from baseline) will be analyzed using the same model as described for the primary efficacy endpoint, except that the terms “baseline” and “baseline-by-visit interaction” will be excluded from the model.

The endpoints of slope of the change from baseline will be analyzed using a MMRM. The response variable will be the change from baseline to each post baseline visit up to Week 12. The model will include the following covariates:

- Treatment (reldesemtiv 300 mg/day, 600 mg/day and 900 mg/day, and placebo)
- Baseline (baseline value of the response variable)
- Pooled site (Center)
- Time (time from the first dose, a continuous variable)
- Riluzole and edaravone use status at baseline
- Treatment-by-baseline
- Treatment-by-time interaction

The time will be set as a random effect and the intercept will be set to zero.

The endpoints of slope of percent change from baseline, including slope of percent change in parameters of handwriting and voice recording, will be analyzed using the same model as for the slope of muscle strength mega score over time described in Section 7.6.

7.8. Summary of Reasons for Efficacy Non-Evaluability/Exclusion from Efficacy Analyses

Reasons for excluding individual patients from the FAS will be summarized and listed.

7.9. Exploratory Analyses

7.9.1. Joint Rank Test

Joint rank analyses using the combined assessment of function and survival (CAFS) (Berry 2013) will be conducted to account for survival time in the analyses of change in the percent predicted SVC and ALSFRS-R total score at Week 12, individually.

Each patient will be compared with all others in the analysis population in a pairwise manner on their survival status and the functional measurements, ie, changes from baseline in the percent predicted SVC or ALSFRS-R total score. A score of +1 or -1 will be assigned if one has better or worse outcome than the other, respectively. The following rule will be used:

- Patients who died are ranked worse than those who survived.
- Among patients who died, patients who died first are ranked worse.
- For patients who discontinued treatment early but were alive, comparison is based on the last time-point measurements that are both available for the patients in pairs. A patient is ranked worse if the patient discontinued treatment early and did not have functional measurement collected before the discontinuation.
- Among patients who completed, patients with greater decline from baseline in the functional measurement are ranked worse.
- If it is not possible to assign either patient as having the better outcome, then the score assigned to the pair is 0.

For each patient, the assigned scores from the pairwise comparisons with all others will first be summed, and all patients in the analysis population will be ranked according to their summated scores to create a rank score from 1 for the lowest summated score to N (total number of patients in the analysis population) for the highest summated score. If ties occur, each of the tied summated scores will be assigned the average of the ranks the tied summated scores would have if there were no ties.

The rank scores will be analyzed using the generalized Gehan-Wilcoxon test. In addition, the rank scores will be analyzed using an ANCOVA model that adjusts for baseline variables (baseline functional measurement, time from symptom onset, site of disease onset and riluzole or edaravone use). The rank scores between the reldesemtiv and placebo groups will be compared, and the least square mean difference as well as the p-value will be presented.

7.9.2. Time-To-Event Analysis for Muscle Strength

Time-to-event analysis will be performed for muscles that had a measurable muscle strength at baseline. The muscle strength measured by HHD will be analyzed using proportional hazard Cox regression model. The event is defined as muscle strength as measured by HHD equals 0 from any muscle in the evaluated muscle groups. For patients who had the event, the date of muscle strength reached 0 will be used as the event date. For patients who did not have the event, data will be censored at their last date of study visit. Kaplan-Meier method will be used to summarize the time to event, and median, 95% CIs of the median, Q1, Q3, and range will be provided.

7.9.3. Evaluation of SVC Measured at Home Using SVC Measured in Clinic as the Standard

In addition to performing SVC assessments in clinic, GoSpiro home spirometer was given to patients for collecting their SVC data weekly from home. However, the usage of the spirometer varies among patients due to different reasons (eg, patients forgot to take the assessments or had technical difficulties, etc.). Hence it is of interest to evaluate consistency of the SVCs measured at home vs. the SVCs measured in clinic. Also, there may be potential learning effect due to more frequent use of the spirometer that may resulting in higher SVC assessed later on. The analyses to be used for the evaluations are described in the following sections.

7.9.3.1. Correlation Between at Home and in Clinic Assessments of SVC

The test-retest reliability of SVC measured at home will be assessed using the measures in clinic as the standard for each patient. Each measure at home will be paired with a measure in the clinic within a seven-day of window. Correlation between at home and in clinic SVC assessments overall and by visit will be evaluated using Pearson correlation coefficient and paired t-test.

7.9.3.2. Change from Baseline to Week 12 in Percent Predicted SVC Assessed at Home and in Clinic

The SVC assessed at home and in clinic will be combined for a supportive analysis of change from baseline to Week 12 in percent predicted SVC. A MMRM will be used for the analysis. The response variable will be the change from baseline to each post baseline visit up to Week 12. The model will include the following covariates:

- Treatment (reldesemtiv 300 mg/day, 600 mg/day and 900 mg/day, and placebo)
- Location of SVC collection (at home or in clinic)
- Baseline (baseline value of the response variable)
- Pooled site
- Time (time from the first dose, a continuous variable)
- Riluzole and edaravone use status at baseline
- Baseline-by-time interaction
- Treatment-by-time interaction

An unstructured variance-covariance structure will be used to model the within-subject errors. If a model fails to converge, other covariance matrix structures (eg, compound symmetry) may be used instead of the unstructured covariance matrix. Least square means and the corresponding standard errors, 95% CIs and p-values will be presented.

7.9.3.3. Time to Event Analysis of Percent Predicted SVC Decline to Less Than 50%

To evaluate consistency of the SVCs measured at home vs. that measured in clinic, percent predicted SVC collected during clinic visits and at home will be analyzed using a proportional hazard Cox regression model. The event is defined as percent predicted SVC decline to less than 50% during the 12 weeks of the study. For patients who had the event, the first date of SVC less than 50% will be used as the event date. For patients who did not have the event, data will be censored at their date of study visit or Week 12 visit, whichever is earlier. Kaplan-Meier method will be used to summarize the time to event for percent predicted SVC measured in clinic and at home, separately. The median of the time to event, 95% CIs of the median, Q1, Q3, and range will be provided.

7.9.3.4. Comparing Percent Predicted SVC Between Patients Who Used a Home Spirometer for SVC Assessments and Those who Never Used

To evaluate the potential learning effect of using a spirometer and its impact on the percent predicted SVC measured in clinic, the use of the spirometer will be added as a covariate in the MMRM for a supportive analysis of change from baseline to Week 12 in percent predicted SVC and be evaluated for if it's a significant factor in predicting the outcome. The rates of decline (ie, slope) in percent predicted SVC assessed in clinic will also be compared between patients who performed SVC assessments using the home spirometer and those who did not use. In addition, since SVC will be assessed 3 times in each clinic visit, the variation among the 3 measurements collected at each visit will be compared between patients who used the home spirometer for SVC assessments and those who did not use.

8. SAFETY AND TOLERABILITY

8.1. Adverse Event Preferred Term and Body/Organ System Summary Tables

TEAEs and serious TEAE will be summarized. See Section 5.5.10.2 for the definitions of TEAEs and serious TEAEs.

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to classify AEs by system organ class and preferred term. The severity of adverse events will be evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0. Coding will be performed using version 20.0 of the MedDRA coding dictionary.

8.1.1. Summaries of Adverse Event Incidence Rates for All Patients

The number and percentage of patients with TEAEs will be summarized by system organ class, preferred term, dose level and overall, riluzole and edaravone use status at baseline, and will be further tabulated by CTCAE grade or relationship to study drug. For a patient with a particular

TEAE that were reported more than once within a particular system organ class or preferred term, the patient will be counted only once in that category using the most severe occurrence or closest relationship to the study drug. Listings of all AEs by patient will also be presented.

8.1.2. Summaries of Adverse Incidence Rates for Serious Adverse Events, Adverse Event Dropouts, and Death

SAEs and AEs leading to treatment discontinuation or death will also be summarized by system organ class, preferred term, dose level and overall, and riluzole and edaravone use status at baseline. Listings will be presented for patients who died and/or experienced serious AEs and for patients who discontinued due to TEAEs.

8.2. Total Duration of Therapy, Average Daily Dose, Maximum Daily Dose, Final Daily Dose of Study Medication, and Compliance

The duration and exposure of study drug will be summarized by dose level and overall, and riluzole and edaravone use status at baseline for the safety analysis set. The duration will be calculated as the difference between the study day of the first dose and the last dose plus one day. The exposure will be calculated as the total dosage in mg. Patient listing with date, day and time of dose, actual/average daily dose, reason for incorrect dose and dose interruption will be presented.

8.3. Concomitant and Other Medications

Concomitant medications reported on the eCRF will be summarized for the safety analysis set. See Section 5.5.10.4 for the definition of concomitant medications. Medications with a start date that is 28 days after the last dose of the study drug will be excluded from the summary. The World Health Organization Drug dictionary will be used to classify medications by therapeutic class (ATC Class 3) and preferred name. If ATC Class 3 is not available, ATC Class 2 will be used in the summary. Coding will be performed using WHO Drug Dictionary Enhanced with Herbal Dictionary, B2, March 2017.

The number and percentage of patients who received concomitant medication will be summarized by dose level, therapeutic class and preferred term (using ATC Class Level III). Multiple drug usage by a patient will be counted only once in each category.

CYP3A4 strong inhibitors that should be avoided from 7 days before the start of dosing through the last day of dosing. CYP3A4 strong inducers that should be avoided from 14 days before the start of dosing through the last day of dosing. OCT1/OCT2 substrates that should be avoided from 7 days before the start of dosing or should be used with caution during the trial. Patients who take CYP3A4 strong inhibitors, CYP3A4 strong inducers, or OCT1/OCT2 substrates prior or during the study treatment will be listed.

In addition, a listing of concomitant medication with start/stop date, days relative to the start of therapy, dose / unit / route / frequency, indication and purpose of all medications taken from screening through the end of study will be provided.

8.4. Routine Laboratory Data

Clinical laboratory evaluations, including hematology, serum chemistry, and urinalysis as detailed in the protocol, will be collected at the Screening, Day 1, Week 2, Week 4, Week 12 and Follow-Up Visits. Descriptive statistics of assessment value and change from baseline of laboratory parameters will be presented at each assessment time point by dose level and overall.

The number and percentage of patients who had normal or missing laboratory values at baseline and abnormal laboratory values post baseline will be presented by dose level and overall. The lower limit of normal (LLN) and upper limit of normal (ULN) provided by the laboratories will be used as the criteria for abnormality. For each parameter, the denominator of the percentage will include patients with normal or missing assessments at baseline, and with at least one assessment post baseline. The numerator of the percentage will include patients who had at least one abnormal assessment post baseline among the patients that were counted in the denominator. Assessment collected at an unscheduled visit or the Follow-up Visit will also be included in the summary.

Shift of clinical laboratory results in NCI-CTCAE grade from baseline grade to the maximum post baseline grade will be presented for selected laboratory parameters. Clinical laboratory values will be also listed. Values outside the Laboratory's normal ranges and potentially clinically significant abnormal values will be flagged.

Hy's law (Temple 2006) will be used to evaluate drug induced liver injury (DILI); patients with ALT or AST elevations > 3 x ULN and total bilirubin elevations > 2 x ULN will be marked on a scatter plot. Elevations of ALT or AST to 5 x, 10 x or 20 x ULN will also be plotted.

Clinical laboratory results from patients with eGFR decline of 1) greater than 25%, 2) below 60, 3) greater than 25% and below 60, and 4) greater than 25% or below 60 will be summarized and listed. Time-to-event analysis will be performed for eGFR decline of greater than 25% using proportional hazard Cox regression model with the following model terms: riluzole and edaravone use status at baseline, age, sex, BMI and baseline eGRF values. Kaplan-Meier method will be used to summarize the time to eGFR decline of greater than 25% where the median of the time to event, 95% CIs of the median, Q1, Q3, and range will be provided. In addition, the correlation between eGFR level change from baseline and C_{trough} of reldesemtiv and its metabolites will be examined. Similar method as described in Section 9.2 will be used for the analysis.

8.5. Vital Signs

Vital signs, which include blood pressure, heart rate and respiratory rate (measured after the patient has been resting for at least 3 minutes), height, weight and BMI will be obtained at the Screening, Day 1, Week 2, Week 4, Week 8, Week 12 and Follow-Up Visits. Descriptive statistics of absolute values and changes from baseline of vital sign parameters will be presented at each assessment time point by dose level and overall.

The number and percentage of patients who had normal or missing values at baseline and Potentially Clinically Significant (PCS) values post baseline will be presented by dose level and overall. The PCS criteria are specified in Table 6. For each parameter, the denominator of the percentage will include patients with non-PCS or missing assessments at baseline, and with at

least one assessment post baseline. The numerator of the percentage will include patients who had at least one PCS assessment post baseline among the patients that were counted in the denominator. Assessment collected at an unscheduled visit or the Follow-up Visit will also be included in the summary.

Oral temperature will be taken at Screening and will be presented in a listing. Individual vital signs will be listed with dose level, patient ID, and assessment time. Values outside the normal ranges will be flagged.

Table 6: Criteria of Potentially Clinically Significant (PCS) Vital Signs

Vital Sign Parameter	Flag	Criteria
Systolic Blood Pressure (mmHg)	High	≥160 mmHg
	Low	≤80 mmHg
Diastolic Blood Pressure (mmHg)	High	≥100 mmHg
	Low	≤ 50 mmHg
Respiration Rate (Breaths per minute)	High	>18 bpm
	Low	<8 bpm
Pulse (bpm)	High	≥120 bpm
	Low	≤50 bpm
Weight (kg)	Clinically Significant	≥5% reduction from baseline
Temperature (°C)	High	≥ 38 °C
	Low	< 35 °C

8.6. Electrocardiogram

A 12-lead ECG, including ECG parameters of RR, PR, QRS, and QT intervals as well as significant findings will be obtained at Screening, Week 4 and Follow-Up Visits. Descriptive statistics of absolute value and change from baseline of ECG parameters (PR interval, RR interval, QRS duration, QT interval, QTc interval [Bazett's and Fridericia's], Ventricular Heart Rate) will be presented at each assessment time point by dose level and overall.

The number and percentage of patients who had normal or missing values at baseline and PCS values post baseline will be presented by dose level and overall. ECG parameters are regarded as PCS if the value meets the criterion shown in Table 7. For each parameter, the denominator of the percentage will include patients with non-PCS or missing assessments at baseline, and with at least one assessment post baseline. The numerator of the percentage will include patients who had at least one PCS assessment post baseline among the patients that were counted in the denominator. Assessment collected at an unscheduled visit or the Follow-up Visit will also be included in the summary.

Twelve-lead ECG parameters (PR interval, QRS duration, QT interval, QTc interval [Bazett's and Fridericia's], Ventricular Heart Rate, and RR interval), will be listed with dose level, patient ID, visit and assessment date and time. PCS ECG values will be flagged. ECG findings and interpretations will be listed as well.

Table 7: Criteria of Abnormal and PCS ECG Values

ECG Variable	Units	Upper Limit of Normal	PCS High Values
QRS Interval	msec	80	≥120
PR Interval	msec	200	≥240
QTcB Interval	msec	Males: 450 Females: 460	>500
QTcF Interval	msec	Males: 450 Females: 460	>500
QT Interval	msec	—	> 500
Ventricular Heart Rate	bpm	—	>100

8.7. Physical Examination

A routine physical examination will be performed at Screening and Follow-Up Visits. Abnormal and clinically significant findings in physical examinations will be reported and summarized as Medical History or Adverse Events, as appropriate.

8.8. Neurological Examinations

A neurological examination will be administered at Screening and Follow-Up Visits. Neurological examination findings will be summarized for eye movements, facial sensations, motor function strength, sensory, reflexes, plantar response, cerebellar function / coordination by

visit, dose level and overall. Neurological examination findings shift from baseline visit to post-baseline visit will also be tabulated.

Individual neurological examination findings will be listed for each test chronologically by patient ID, visit, and the actual assessment date and time.

8.9. Ashworth Score

Ashworth score will be assessed at all study visits. Summary statistics of the Ashworth total score at each study visit will be tabulated. A list will be provided with the actual assessment date and answers to all the questions.

8.10. Beck Depression Inventory Fast Screen Version

The BDI-FS will be assessed at all study visits. Summary statistics of the BDI total score will be provided for each assessment time point by dose level and overall. A list will be provided with the actual assessment date and answers to all questions.

8.11. Fall Assessment

The fall assessment will be conducted at all study visits except Screening. The number and percent of patients with one, two, three, four or more falls, with answers to the activities engaged at the time of fall, physical symptoms immediately preceding the fall, and whether resulting injury will be tabulated. A list will be provided with the actual assessment date, and answers to all questions.

8.12. Study Termination Status

Number and percentage of patients who completed or prematurely discontinued planned study dosing, and reasons of prematurely discontinuation will be tabulated. For patients who discontinued prematurely, the date and reason of premature discontinuation will be listed.

9. PHARMACOKINETIC AND PHARMACODYNAMIC /PHARMACODYNAMIC ANALYSES

9.1. Pharmacokinetic Analyses

PK analysis will be performed based on the PKS. All of the PK samples collected, including those obtained at Hours 0, 1, 3 on Day 1 as well as Hours 0, 1, 3 and 6 at Week 2 and Week 12 from patients enrolled prior to Amendment 03, will be used for PK analyses. Descriptive statistics in terms of mean, SD, geometric mean, coefficient of variation (CV), geometric CV, median, and range will be provided for concentrations at all planned sampling time points. Geometric mean concentrations over time will be graphically displayed.

For each patient enrolled prior to Amendment 03, the PK parameters t_{max}, C_{max} and AUC_{12} at Week 2 and Week 12 will be calculated based on the plasma concentrations of reldesemtiv, its metabolites and riluzole using non-compartmental PK methods. The PK parameters t_{max}, C_{max} on Day 1 for patients enrolled prior to Amendment 03, and C_{trough} at Week 2 and Week 12 for all

patients will be calculated based on the plasma concentrations of reldesemtiv, its metabolites and riluzole. The PK parameters listed above will also be summarized by dose level.

Dose proportionality will be examined using the power model approach based on C_{trough}. The relationship between the PK parameter, C_{trough} and dose can be described by the following power model:

$$ln\ (C_{trough}) = \alpha + \beta \times ln\ (\text{dose}) + \varepsilon$$

where α and β are the intercept and slope of the modeling equation, and ε represents the error term. A tentative conclusion of dose-proportionality will be made if the 90% CI for the slope includes 1.

The attainment of steady-state of reldesemtiv following multiple doses will be verified using a linear regression model for log-transformed trough concentrations on sample collection time by dose group. Since the first post baseline PK sample is collected at Week 2, the trough concentrations starting from Week 2 and beyond will be included in the model. If the 90% confidence interval (CI) of the slope from the model contains zero, steady state will be concluded as attained at no later than Week 2.

Selected PK parameters (eg, AUC_{12}, C_{max} and C_{trough} at Week 12) between patients who took reldesemtiv alone and those who took reldesemtiv plus edaravone will be compared. The natural log-transformed least square mean difference and the associated 90% CI will be calculated using a linear regression model that includes model terms of dose level, edaravone use status at baseline, and interaction of dose level by edaravone use status. An unstructured covariance matrix will be used for the model. Back-transformation will provide point estimates and 90% CIs for the geometric mean ratio that indicates the magnitude of drug interaction. Summaries of selected PK parameters will be presented graphically by dose level, as appropriate.

9.2. Pharmacokinetic/Pharmacodynamic Analyses

PD analyses may be performed to explore the PK/PD relationship based on the PKS. PD measures will include, but not limited to, the following assessments:

- Percent predicted SVC
- Muscle strength mega score
- ALSFRS-R
- ALSAQ-5

The change from baseline analyses will use the same model as for analysis of the primary efficacy endpoint, except that the model term ‘Treatment’ will be replaced by ‘Concentration’ (a continuous variable, plasma concentration of reldesemtiv) or “Concentration Bin” (a categorical variable that includes placebo group and approximately equal number of patients in each classified reldesemtiv concentration bin).

10. HEALTH ECONOMIC OUTCOMES ANALYSIS

The prescription of non-invasive ventilation, gastrostomy tube, Manual wheelchair, power wheelchair, or augmentative and alternative communication will be analyzed. For patients who were prescribed and agree to receive the items above, the event will be set as 1, and the date of prescription will be used as the event date. For patients who were not prescribed or agreed to receive the items above, the event will be set as 0, and data will be censored at their last date of study visit. Time to event will be summarized by each dose group for patients with an event, and the differences of time to event between each reldesemtiv dose group vs. placebo will be tested using the log-rank test. In addition, the hazard ratios of each reldesemtiv dose group vs. placebo as well as the hazard for the assumed dose response trend (-5, -1, 3, 3) will be calculated using the proportional hazard Cox regression model.

11. COMPUTER METHODS

Statistical analyses will be performed using Version 9.4 (or newer) of SAS®. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc. in USA and other countries.

12. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

Not available.

13. STATISTICAL CODES

The following code will be used as the prototype of the codes that will be used for the final analysis of the study. The final version of the statistical codes to be used will be determined prior to the database lock and will be documented in the specification document for the statistical report of the study.

1. The SAS code to produce the estimates of the dose response relationship among treatment groups:

For continuous variables:

```
PROC MIXED data = work METHOD = REML;
class <Patient> <Pooled Site> <Visit> <Treatment> <Riluzole Use> <Edaravone Use>;
model <Continuous Variable> = <Pooled Site> <Visit> <Treatment> <Baseline Value> <Riluzole Use> <Edaravone Use>
      <Interaction between Visit and Treatment> <Interaction between Visit and Baseline Value> / ddfm = kenwardroger; repeated
<Visit> / subject = <Patient> type = un;
lsmeans <Visit>*<Treatment> / pdiff cl;
lsmestimate <Visit>*<Treatment> '300mg and 450mg - placebo at week 2' [-1,1 1] [0,1 2] [0.5,1 3] [0.5,1 4] / cl;
lsmestimate <Visit>*<Treatment> '300mg and 450mg - placebo at week 4' [-1,2 1] [0,2 2] [0.5,2 3] [0.5,2 4] / cl;
lsmestimate <Visit>*<Treatment> '300mg and 450mg - placebo at week 8' [-1,3 1] [0,3 2] [0.5,3 3] [0.5,3 4] / cl;
lsmestimate <Visit>*<Treatment> '300mg and 450mg - placebo at week 12' [-1,4 1] [0,4 2] [0.5,4 3] [0.5,4 4] / cl;
lsmestimate <Visit>*<Treatment> 'Contrast at week 2' [-0.83333,1 1] [-0.16666,1 2] [0.5,1 3] [0.5,1 4] / cl;
lsmestimate <Visit>*<Treatment> 'Contrast at week 4' [-0.83333,2 1] [-0.16666,2 2] [0.5,2 3] [0.5,2 4] / cl;
lsmestimate <Visit>*<Treatment> 'Contrast at week 8' [-0.83333,3 1] [-0.16666,3 2] [0.5,3 3] [0.5,3 4] / cl;
lsmestimate <Visit>*<Treatment> 'Contrast at week 12' [-0.83333,4 1] [-0.16666,4 2] [0.5,4 3] [0.5,4 4] / cl;
ods output LSMeans = lsm Diffs = diff LSMEstimates = lsmest;
run;

Note: Include outcome measurements collected at Weeks 2, 4, 8 and 12. For the endpoints of percent change from baseline (e.g.,
muscle strength mega score), the term "baseline value" and the interaction term <Interaction between Visit and Baseline Value>
will be excluded from the model.
```

2. The SAS code to produce estimates of slope:

```
PROC MIXED data = work METHOD = REML;
class <Patient> <Pooled Site> <Treatment> <Riluzole Use> <Edaravone Use>;
model <Continuous Variable> = <Pooled Site> < Days from First Dose> <Treatment> <Baseline Value> <Riluzole Use>
      <Edaravone Use> <Interaction between Treatment and Day> <Interaction between Treatment and Baseline Value> / ddfm =
kenwardroger noint;
random <Day> / subject = <Patient>;

estimate 'slope for placebo' <Day> 1 <Interaction between Day and Treatment> 1 0 0 0 / cl;
estimate 'slope for 150mg'<Day> 1 <Interaction between Day and Treatment> 0 1 0 0 / cl;
estimate 'slope for 300mg' <Day> 1 <Interaction between Day and Treatment> 0 0 1 0 / cl;
estimate 'slope for 450mg' <Day> 1 <Interaction between Day and Treatment> 0 0 0 1 / cl;
estimate 'slope for 300 & 450mg' <Day> 1 <Interaction between Day and Treatment> 0 0 0.5 0.5 / cl;
estimate 'slope 150mg - placebo' <Interaction between Day and Treatment> -1 1 0 0 / cl;
estimate 'slope for 300mg - placebo' <Interaction between Day and Treatment> -1 0 1 0 / cl;
estimate 'slope for 450mg - placebo' <Interaction between Day and Treatment> -1 0 0 1 / cl;
estimate 'slope for 300mg & 450mg combined - placebo' <Interaction between Day and Treatment> -1 0 0.5 0.5 / cl;
estimate 'slope for contrast' <Interaction between Day and Treatment> -0.83333 -0.1666 0.5 0.5 / cl;

ods output Estimates = est SolutionF = sf;
run;
```

- Note: The variable 'Day'= days from the 1st dose. Include outcome measurements collected at baseline, Weeks 2, 4, 8, 12. For the endpoints of slope of percent change from baseline (e.g., slope of muscle strength mega score), the terms "baseline value" and "interaction between Treatment and Baseline" will be excluded from the model, and the interaction terms "Treatment-by-Riluzole use status" and "Treatment-by-Edaravone use status" will be added to the model.

3. The SAS code to produce time to event analysis results among treatment groups:

```
PROC LIFETEST data = work;
time <Event Variable><Censor Variable(1)>;
strata <Treatment>;
ods output CensoredSummary=sum Quartiles=quart HomTests=test;
run;

PROC PHREG data = work;
class <Pooled Site> <Riluzole Use> <Edaravone Use>;
model <Event Variable> <Censor Variable(1)> = <Treatment> <Baseline Value>;
strata <Pooled Site> <Riluzole Use> <Edaravone Use>;
Contrast '150 mg - placebo' <Treatment> -1 1 0 0 / Estimate=exp;
```

```
Contrast '300 mg - placebo' <Treatment> -1 0 1 0 / Estimate=exp;
Contrast '450 mg - placebo' <Treatment> -1 0 0 1 / Estimate=exp;
Contrast '300 and 450 mg - placebo' <Treatment> -1 0 0.5 0.5 / Estimate=exp;
Contrast 'Contrast' <Treatment> -0.83333 -0.1666 0.5 0.5 / Estimate=exp;
ods output ContrastEstimate=est;
run;
```

Note: Include outcome measurements collected at baseline, Weeks 2, 4, 8, 12. For the endpoints of slope of percent change from baseline (e.g., slope of muscle strength mega score), the term "baseline value" will be excluded from the model.

4. The SAS code to produce estimates of slope for concentration effect PK/PD analyses:

Slope 1:

```
PROC MIXED data = work METHOD = REML;
class <Patient> <Pooled Site> <Riluzole Use> <Edaravone Use>;
model <Efficacy Continuous Variable> = <Day> <Pooled Site> <Concentration> <Baseline Value> <Riluzole Use> <Edaravone Use> /
       ddfm=kenwardroger s;
random <Day> / subject = <Patient>;
ods output SolutionF = sf;
run;
```

Slope 2:

```
PROC MIXED data = work METHOD = REML;
class <Patient> <Pooled Site> <Visit> <Riluzole Use> <Edaravone Use>;
model <Continuous Variable> = <Pooled Site> <Visit> <Concentration> <Baseline Value> <Riluzole Use> <Edaravone Use>
      <Interaction between Concentration and Visit> <Interaction between Concentration and Baseline Value>/ ddfm=kenwardroger
s;
estimate 'slope of concentration at Week 2' <Concentration> 1 <Interaction between Visit and Concentration> 1 0 0 0/ cl;
estimate 'slope of concentration at Week 4' <Concentration> 1 <Interaction between Visit and Concentration> 0 1 0 0/ cl;
estimate 'slope of concentration at Week 8' <Concentration> 1 <Interaction between Visit and Concentration> 0 0 1 0/ cl;
estimate 'slope of concentration at Week 12'<Concentration> 1 <Interaction between Visit and Concentration> 0 0 0 1/ cl;

ods output SolutionF = sf estimates = est;
run;
```

Note: The variable 'Day'= days from the 1st dose. Include outcome measurements collected at Weeks 2, 4, 8, 12. For the endpoints of percent change from baseline (e.g., muscle strength mega score), the terms "baseline value" and "Interaction between Visit and Baseline Value" will be excluded from the model.

5. The SAS code to produce the estimates of concentration bin effect PK/PD analyses:

For continuous PD parameters:

```
PROC MIXED data = work METHOD = REML;
class <Patient> <Pooled Site> <Visit> <Riluzole Use> <Edaravone Use> <Concentration Bin>;
model <Continuous Variable> = <Pooled Site> <Visit> <Concentration Bin> <Baseline Value> <Riluzole Use> <Edaravone Use>
      <Interaction between Visit and Concentration Bin> <Interaction between Concentration Bin and Baseline Value> /
ddfm=kenwardroger s;
repeated <Visit> / subject = <Patient> type = un;
lsmeans <Visit>*<Concentration Bin> / pdiff cl;
ods output lsmeans = lsm diffs = diff;
run;
```

Note: For the endpoints of percent change from baseline (e.g., muscle strength mega score), the terms "baseline value" and "Interaction between Visit and Baseline Value" will be excluded from the model.

14. REFERENCES

Beck, A. T., Steer, R. A. and Brown, G. K. (2000). "BDI-fast screen for medical patients manual." Psychological Corporation, San Antonio, TX.

Berry, J. D., Miller, R., Moore, D. H., Cudkowicz, M. E., Van Den Berg, L. H., Kerr, D. A., et al. (2013). "The Combined Assessment of Function and Survival (CAFS): a new endpoint for ALS clinical trials." Amyotrophic lateral sclerosis and frontotemporal degeneration **14**(3): 162-168.

Bohannon, R. W. and Smith, M. B. (1987). "Interrater Reliability of a Modified Ashworth Scale of Muscle Spasticity." Physical Therapy **67**(2): 206-207.

Cedarbaum, J. M., Stambler, N., Malta, E., Fuller, C., Hilt, D., Thurmond, B., et al. (1999). "The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function." Journal of the Neurological Sciences **169**(1): 13-21.

Jenkinson, C. and Fitzpatrick, R. (2001). "Reduced item set for the amyotrophic lateral sclerosis assessment questionnaire: development and validation of the ALSAQ-5." Journal of Neurology, Neurosurgery & Psychiatry **70**(1): 70-73.

Jenkinson, C., Fitzpatrick, R., Swash, M. and Levvy, G. (2001). "ALSAQ user manual: amyotrophic lateral sclerosis assessment questionnaire." Health Services Research Unit, University of Oxford, Oxford.

Quanjer, P. H., Stanojevic, S., Cole, T. J., Baur, X., Hall, G. L., Culver, B. H., et al. (2012). "Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations." The European respiratory journal **40**(6): 1324-1343.

Ratitch, B. and O' Kelly, M. (2011). "Implementation of pattern-mixture models using standard SAS/STAT procedures." PharmaSUG, Paper-SP04.

Steer, R. A., Cavalieri, T. A., Leonard, D. M. and Beck, A. T. (1999). "Use of the Beck Depression Inventory for Primary Care to screen for major depression disorders." General hospital psychiatry **21**(2): 106-111.

Temple, R. (2006). "Hy's law: predicting serious hepatotoxicity." Pharmacoepidemiology and drug safety **15**(4): 241-243.

APPENDIX A. SCHEDULE OF EVENTS

Study Procedures	Screening	Day 1	Week 2	Week 4	Week 8	Week 12	FU Visit
Informed Consent	X						
Incl/Excl Criteria	X						
Demographics	X						
Medical History	X						
Concomitant Meds	X	X	X	X	X	X	X
Physical Exam[a]	X						X
Neurological Exam	X						X
Height	X						
Weight & BMI	X	X	X	X	X	X	X
12-Lead ECG	X			X			X
Vital Signs	X[b]	X	X	X	X	X	X
Clinical Safety Labs[c]	X	X	X	X		X	X
Pregnancy Test[d]	X						X
PK Sample[e]		X	X	X	X	X	
SVC	X	X	X	X	X	X	X
Muscle Strength	X	X	X	X	X	X	X
ALSFRS-R	X	X	X	X	X	X	X
Voice recording	X	X	X	X	X	X	X
Fine Motor Skills[f]	X	X	X	X	X	X	X
ALSAQ-5	X	X	X	X	X	X	X
Health Economic Outcomes Measurements		X	X	X	X	X	X
Ashworth Scale	X	X	X	X	X	X	X
Falls Assessments		X	X	X	X	X	X
Study Drug Dosing		X	X	X	X	X	
AE/SAE Evaluations		X	X	X	X	X	X
BDI-Fast Screen	X	X	X	X	X	X	X

a Complete physical examination at Screening Visit, abbreviated physical examination at FU visit

b Temperature only at Screening

b Oral temperature only at Screening

c TSH only at Screening and Follow-Up Visit

d Only for females of childbearing potential

d Serum pregnancy test only for females of childbearing potential

e PK sampling on Day 1 visit, Week 2 visit, Week 4 visit, Week 8 visit, and Week 12 visit; refer to Table 3 in the protocol

f If the device is suitable for use in that region

Schedule of Events for Home Testing

SVC*	To be done every Saturday independent of day of first dose
Voice recording	To be done every Saturday independent of day of first dose

*if the device is suitable for use in that region

APPENDIX B. ANALYSIS VISIT WINDOWS

Analysis Visit Windows for SVC, Muscle Strength, ALSFRS-R, Voice Recording, Fine Motor Skills, ALSAQ-5, Vital Sign, Ashworth Scale and BDI-Fast Screen

Visit	Scheduled Day	Lower Bound	Upper Bound
Screening	<1	<1	<1
Day 1	1	1	1
Week 2	15	2	21
Week 4	29	22	42
Week 8	57	43	70
Week 12	85	71	98
Follow-up	113	99	> 99

Analysis Visit Windows for 12-lead ECG

Visit	Scheduled Day	Lower Bound	Upper Bound
Screening	<1	<1	<1
Week 4	29	1	70
Follow-up	113	71	>71

Analysis Visit Windows for Clinical Safety Laboratories

Visit	Scheduled Day	Lower Bound	Upper Bound
Screening	<1	<1	<1
Day 1	1	1	1
Week 2	15	2	21
Week 4	29	22	56
Week 12	85	57	98
Follow-up	113	99	>99

Analysis Visit Windows for PK Concentration

Visit	Scheduled Day	Lower Bound	Upper Bound
Day 1	1	1	1
Week 2	15	2	21
Week 4	29	22	42
Week 8	57	43	70
Week 12	85	71	>71

Analysis Visit Windows for Neurological Exam

Visit	Scheduled Day	Lower Bound	Upper Bound
Screening	<1	<1	<1
Follow-up	113	1	>99

Analysis Visit Windows for SVC Assessed at Home

Visit	Scheduled Day	Lower Bound	Upper Bound
Day 1	1	1	1
Week 1	8	2	11
Week 2	15	12	18
Week 3	22	19	25
Week 4	29	26	32
Week 5	36	33	39
Week 6	43	40	46
Week 7	50	47	53
Week 8	57	54	60
Week 9	64	61	67
Week 10	71	68	74
Week 11	78	75	81
Week 12	85	82	88
Week 13	92	89	95
Week 14	99	96	102
Week 15	106	103	109
Week 16	113	110	>110

APPENDIX C. REGIONAL SITE POOLING FOR FAS

Pooled Site Number	Country	State/Province	Site Number	Patient Count	Sub-total of Patient Count
1	Australia	New South Wales	061078	3	20
1	Australia	New South Wales	061080	3	
1	Australia	Queensland	061079	8	
1	Australia	South Australia	061081	2	
1	Australia	Western Australia	061082	4	
2	Ireland	Dublin	353090	4	53
2	Netherlands	Utrecht	031089	11	
2	Spain	Madrid	034098	38	
3	Canada	Alberta	002065	13	49
3	Canada	Alberta	002068	10	
3	Canada	Ontario	002060	15	
3	Canada	Ontario	002070	2	
3	Canada	Ontario	002071	7	
3	Canada	Saskatchewan	002077	2	
4	Canada	Quebec	002061	35	52
4	Canada	Quebec	002063	6	
4	Canada	Quebec	002066	11	
5	United States	Arizona	001051	10	61
5	United States	California	001014	8	
5	United States	California	001016	5	
5	United States	California	001026	5	
5	United States	California	001054	8	
5	United States	Colorado	001019	9	
5	United States	Oregon	001013	8	
5	United States	Oregon	001050	4	
5	United States	Washington	001023	4	
6	United States	Illinois	001055	6	71
6	United States	Indiana	001043	3	
6	United States	Iowa	001030	4	
6	United States	Kansas	001003	2	
6	United States	Michigan	001036	9	
6	United States	Michigan	001046	10	
6	United States	Minnesota	001032	3	
6	United States	Minnesota	001059	4	
6	United States	Missouri	001005	2	
6	United States	Missouri	001033	3	
6	United States	Nebraska	001042	4	

Pooled Site Number	Country	State/Province	Site Number	Patient Count	Sub-total of Patient Count
6	United States	Ohio	001028	7	
6	United States	Ohio	001057	10	
6	United States	Wisconsin	001037	4	
7	United States	District of Columbia	001035	2	51
7	United States	Maryland	001008	13	
7	United States	Pennsylvania	001006	11	
7	United States	Pennsylvania	001015	3	
7	United States	Tennessee	001039	9	
7	United States	Virginia	001022	3	
7	United States	Virginia	001067	8	
7	United States	West Virginia	001004	2	
8	United States	Connecticut	001025	10	36
8	United States	Massachusetts	001045	3	
8	United States	New York	001001	3	
8	United States	New York	001017	5	
8	United States	New York	001027	10	
8	United States	Vermont	001056	5	
9	United States	Florida	001011	9	65
9	United States	Florida	001012	9	
9	United States	Florida	001066	1	
9	United States	Florida	001068	4	
9	United States	Georgia	001040	1	
9	United States	North Carolina	001010	8	
9	United States	North Carolina	001021	10	
9	United States	North Carolina	001047	9	
9	United States	Texas	001007	2	
9	United States	Texas	001020	3	
9	United States	Texas	001041	9	

APPENDIX D. MSPLINE VALUE FOR CALCULATION OF PREDICTED SVC

Table: Mspline Value

Age (yrs)	Male	Female	Age (yrs)	Male	Female
18	0.147849088	0.135507529	50	-0.006647706	0.028303776
19	0.160315109	0.140628299	51	-0.014542406	0.020206649
20	0.167159394	0.143647414	52	-0.022604908	0.011905392
21	0.169722148	0.145330204	53	-0.030845244	0.00339698
22	0.16923214	0.146039097	54	-0.039274925	-0.005323975
23	0.166543254	0.145870185	55	-0.04790158	-0.014258162
24	0.162315681	0.144942845	56	-0.056735557	-0.023411261
25	0.157092735	0.143626724	57	-0.065782826	-0.032797239
26	0.151293448	0.142211366	58	-0.07504859	-0.042417299
27	0.145106883	0.140771596	59	-0.084531216	-0.052260185
28	0.138681964	0.13919976	60	-0.094214527	-0.062313185
29	0.132266867	0.137441293	61	-0.104078877	-0.072556666
30	0.125876212	0.135494281	62	-0.114093666	-0.082975133
31	0.119459845	0.133330256	63	-0.124218952	-0.093558031
32	0.113049003	0.130878076	64	-0.134413719	-0.104301259
33	0.106735805	0.12804587	65	-0.14465155	-0.115203896
34	0.100550635	0.124811373	66	-0.154914171	-0.126261624
35	0.094499318	0.121203564	67	-0.165181495	-0.137466925
36	0.088531508	0.117238065	68	-0.175439763	-0.148808471
37	0.082567889	0.112889589	69	-0.185681902	-0.160268368
38	0.076537303	0.108171834	70	-0.195901978	-0.171827557
39	0.070402479	0.103107309	71	-0.20609542	-0.183468534
40	0.064129074	0.097699941	72	-0.216260542	-0.195173143
41	0.057677943	0.091939589	73	-0.226393699	-0.206921242
42	0.051046568	0.085825419	74	-0.236485333	-0.218692812
43	0.04427255	0.079389589	75	-0.246523325	-0.230468005
44	0.037387387	0.07268763	76	-0.256496316	-0.242227571
45	0.030394993	0.06577409	77	-0.266395583	-0.253951742
46	0.023277783	0.058677615	78	-0.276212134	-0.265621352
47	0.01602077	0.051384134	79	-0.285939277	-0.277219902
48	0.008623361	0.043889005	80	-0.295573257	-0.288731661
49	0.001072775	0.036196648			