STATISTICAL ANALYSIS PLAN

VERSION: 1.0

DATE OF PLAN:

16-JUN-2023

STUDY DRUG:

Reldesemtiv

PROTOCOL NUMBER:

CY 5032

STUDY TITLE:

A Phase 3, Open-Label Extension of COURAGE-ALS (CY 5031)

BASED ON:

Protocol Amendment 1: 16 December 2022

SPONSOR:

Cytokinetics, Inc.

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

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
AESI	Adverse event of special interest
ALP	Alkaline Phosphatase
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CI	Confidence Interval
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
CSR	Clinical Study Report
ED	Early Discontinuation
EDC	Electronic Data Capture
EOT	End of Treatment
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
FU	Follow-Up
ICH	International Council for Harmonisation
LLN	Lower Limit of Normal
LSM	Least Squares Mean
MedDRA	Medical Dictionary for Regulatory Activities Terminology
OLE	Open-label extension
PCS	Potential Clinical Significance
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System (SAS®)
SOC	System Organ Class
TDD	Total Daily Dose
TEAE	Treatment-Emergent Adverse Event

Abbreviation	Term
TESAE	Treatment-Emergent Serious Adverse Event
ULN	Upper Limit of Normal
WHO	World Health Organization

1. INTRODUCTION

This document describes the plan for the summarization and analysis of clinical data collected in CY 5032, an open-label extension of CY 5031. CY 5031 was terminated early by the Sponsor due to meeting the futility criteria at the CY 5031 second planned interim analysis. As a result, the analysis scope has been abbreviated, and certain analyses outlined in the protocol will not be conducted, see Section 9 for details.

2. OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of the study is to assess the long-term safety and tolerability of reldesemtiv in patients with ALS.

2.1.2. Secondary Objective

The secondary objective of the study is to assess the long-term effect of reldesemtiv on ALSFRS-R functional outcomes and hospitalization by comparing early-start to delayed-start groups from CY 5031.

2.2. Study Endpoints

2.2.1. Primary Endpoints

The primary safety endpoint is the incidence of adverse events (AEs) in the patient population.

2.2.2. Secondary Endpoints

The secondary outcome endpoints are listed as follows:

- Combined assessment of change in ALSFRS-R total score, time to dependence on assisted ventilation, and survival time from baseline of CY 5031 through CY 5032 Week 48 and from Week 24 of CY 5031 through CY 5032 Week 48. Dependence on assisted ventilation is defined as using non-invasive or invasive ventilation for ≥ 22 hours per day for ≥ 10 consecutive days.
- Time to the first occurrence of dependence on assisted ventilation or death from Day 1 in CY 5031 through CY 5032 Week 48
- Changes in ALSFRS-R total score from baseline of CY 5031 through CY 5032 Week 48 and from Week 24 of CY 5031 through CY 5032 Week 48
- Slopes of the changes in ALSFRS-R total score from baseline of CY 5031 through CY 5032 Week 48 and from Week 24 of CY 5031 through CY 5032 Week 48
- Time to the first hospitalization from Day 1 in CY 5031 through CY 5032 Week 48
- Time to recurrent hospitalization from Day 1 in CY 5031 through CY 5032 Week 48

3. STUDY DESIGN

3.1. Overall Design

This is an open-label extension study with, reldesemtiv, in patients with ALS who finished dosing (through Week 48) in CY 5031 (COURAGE-ALS).

Following enrollment, patients will continue the same dosing regimen of reldesemtiv, as in the parent study (CY5031); either 300 mg twice a day for a 600 mg total daily dose (TDD) for a period of 48 weeks; a patient who down-titrated for any reason to 150 mg twice daily in CY 5031 will continue with the down-titrated dose in CY 5032. Definitions

3.1.1. Study Drugs

This section describes the investigational product (IP) (ie, reldesemtiv) intended to be administered to a trial patient according to the protocol.

Arm Name	Active
IP/Product Name	Reldesemtiv
Type	Drug
Dose Formulation	Tablet
Unit Dose Strength(s)	150 mg
Dosage Level(s)	2 tablets twice a day for 600 mg TDD
Route of Administration	Oral or via gastrostomy tube
Use	Experimental
IMP	IMP
Sourcing	Patheon, Inc. Toronto Regional Operations (TRO) 2100 Syntex Court Mississauga, Ontario L5N 7K9 Canada
Packaging and Labeling	IP will be provided in bottles. Each bottle will be labeled as required per country requirement
Excipients in Active tablets	Microcrystalline cellulose Lactose monohydrate Croscarmellose sodium Providone Sodium lauryl sulfate Magnesium stearate

IMP = investigational medicinal product; NIMP = non-investigational medicinal product

3.1.2. Dates and Points of Reference

First dose date of CY 5032 (OLE Day 1)

For patients who roll over to the open-label extension from the parent study, the first dose date of CY 5032 will be defined as the date of first dose of study drug administration in CY 5032. The first dose date of CY 5032 may occur on the same day as the CY 5031 Week 48 visit if the rollover visit occurs in the morning, the next day following completion of the CY 5031 Week 48

visit if the rollover occurs in the afternoon, the Follow-Up (FU) visit of CY 5031, or as a separate Day 1 visit unique to CY 5032 that occurs after the CY 5031 FU visit.

3.2. Sample Size Considerations

This is an open-label, continuation study. Sample size will be determined by those eligible after successful completion of the preceding study, CY 5031. It is anticipated approximately 400 patients will be enrolled.

3.3. Schedule of Assessment

Schedule of activities and assessments for the CY 5032 study are defined in the study protocol in section 1.3 and provided in Table 1.

Table 1: Schedule of Activities

	Day 1[1]	Week 4	Week 6	Week 8	Week 12	Week 16	Week 18	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	FU (or ED): Week 52*
In Clinic	**X**				**X**				**X**			**X**			**X**	**X**
Remote Visit		**X**	**X**	**X**		**X**	**X**	**X**		**X**	**X**		**X**	**X**		
Informed Consent[2]	X															
Inclusion and Exclusion Criteria	X															
Demographics	X															
Physical Examination	X[2]															X
Neurological Exam	X[2]															X
Weight & BMI	X				X				X			X			X	X
Concomitant Med Review	X	X		X	X	X		X	X	X	X	X	X	X	X	X
Vital Signs	X				X				X			X			X	X
AE/SAE Evaluation	X	X		X	X	X		X	X	X	X	X	X	X	X	X
Clinical Safety Labs[3]	X		X[4]		X		X[4]		X			X			X	X
Pregnancy test (WOCBP only)	X[5]								X						X	
Study Drug Dosing	X	X		X	X	X		X	X	X	X	X	X	X	X	
ALSFRS-R	X	X		X	X	X		X	X	X	X	X	X	X	X	X
Hospitalizations	X	X		X	X	X		X	X	X	X	X	X	X	X	X
DME Use	X	X		X	X	X		X	X	X	X	X	X	X	X	X

ED=Early discontinuation; AE=adverse event; BMI=body mass index; SAE=serious adverse event; WOCBP=women of childbearing potential; ALSFRS-R=Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; DME=Durable Medical Equipment; FU = Follow-Up

*Drug dosing will not occur at the ED visit

1=Day 1 of CY 5032 may occur on the same day as the Week 48 Visit or the FU Visit of CY 5031 or as a separate Day 1 Visit unique to CY 5032 that occurs after the CY 5031 FU Visit. If Day 1 in CY 5032 occurs more than 6-weeks after completion of the FU Visit in CY 5031, the initial dose of study drug will not be taken by the patient until their safety lab results are available and the estimated Glomerular Filtration Rate $(eGFR)_{CysC} \geq 45$ ml/min/1.73m^2 and $eGFR_{Cr} \geq 45$ ml/min/1.73m^2, alanine aminotransferase (ALT)/aspartate aminotransferase (AST) <3 × upper limit of normal (ULN), and bilirubin is normal or if abnormal reported as non-clinically significant by the investigator.

2=Physical Exam and Neurological Exam: Day 1 exams are only required if the patient enrolls in the OLE on the same day as the Week 48 visit in CY 5031 or at a separate Day 1 Visit unique to CY 5032 that occurs after the CY 5031 FU Visit; however, if a patient enrolls in the OLE at the FU visit in CY 5031, these exams do not need to be repeated on Day 1 of the OLE.
3=Clinical safety labs to include: Chemistry (collected every 3 months): sodium, potassium gamma-glutamyl transferase, chloride, calcium, magnesium, phosphorus, urea nitrogen, creatinine, $eGFR_{Cr}$ (calculated using CKD-EPI creatinine equation), Total protein, cholesterol, bicarbonate, total bilirubin, direct bilirubin, indirect bilirubin, CK, ALP, LDH, AST (SGOT), ALT (SGPT), Cystatin C, $eGFR_{CysC}$ (calculated by CKD-EPI cystatin C equation), uric acid, albumin, triglycerides, and glucose
Urinalysis (collected every 3 months): specific gravity, pH, blood, protein, glucose, bilirubin, UPCR and microscopy
TSH on Day 1, bHCG as applicable for WOCBP, FSH as required to determine menopausal status at Day 1 per Appendix 3 (refer to study Protocol section 10.3)
4=Remote clinical safety labs to include: Chemistry (collected at Week 6 and Week 18): ALP, ALT (SGPT), AST (SGOT), direct bilirubin, and total bilirubin. Remote clinical safety labs may be collected by a home health vendor in the patient's home, or in the clinic, or by another method approved by the Sponsor.
5=Pregnancy test: If a WOCBP has had a negative pregnancy test within 30 days, a pregnancy test is not needed on Day 1. If it has been >30 days, then it is required.

3.4. Clinical Assessments

3.4.1. Efficacy Assessments

3.4.1.1. Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R).

The Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (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 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 will be set to missing.

The ALSFRS-R total score is calculated as the sum of the 12 ratings, and can range from 0 to 48 with higher scores indicating less functional impairment. If a single rating is missing, the ALSFRS-R total score will be set to missing.

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.

3.4.2. Safety Assessments

Safety assessments include adverse events and serious adverse events, laboratory assessments, neurological examinations, physical examinations and vital signs.

4. PLANNED ANALYSES

4.1. Interim Analyses

No formal interim analysis is planned for this open-label study.

4.2. Final Analyses

The final analysis was planned to be performed when all patients who enrolled in the CY 5032 study have completed the study, all outstanding queries resolved, and the database cleaned and finalized.

Since the study was terminated early by the Sponsor due to futility in the parent study, after the database has been cleaned to the extent for safety assessments and locked, one final analyses of all data will be conducted for an abbreviated CSR.

5. STATISTICAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

5.1. General Summary Table and Individual Subject Data Listing Considerations

Unless specified otherwise, analyses of efficacy endpoints will be performed based on the data collected during CY 5032.

Descriptive statistics to be presented in a table include count of patients, mean, median, standard deviation, Q1, Q3, minimum and maximum for continuous variables, and count of patients and the percentage for categorical variables.

For model-based analyses, least squares means and the corresponding standard errors and 95% confidence intervals (CIs) for the relative statistical inferences will be presented.

5.2. Data Management

Data will be entered into the clinical database with programmed edit checks and direct visual inspection to ensure integrity. Adverse events and concomitant medications will be coded programmatically while unique terms will be reviewed visually. Clinical safety laboratory will be provided in the pre-specified format from external laboratories or research organizations. Critical data will be identified at an early stage of the study to allow sufficient time to have data entered, reviewed, queried and cleaned throughout the study.

Every attempt will be made to obtain measurements to minimize the percent of missing data.

5.3. Data Presentation Conventions

The following conventions will be applied to data presentations:

- For continuous variables, 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 count and percentage of responses are presented in the form XX (XX.X%).
- Date variables are formatted as DDMMMYYYY for presentation. Time is formatted from 0:00 to 23:59 as HH:MM for presentation.
- Clinical safety laboratory test values will be presented in conventional and/or System International (SI) units.

The tables and listing shells and the table of contents as part of this SAP provide the expected layout and title of the tables, listings and figures. Any changes to format, layout, titles, numbering, or any other minor deviation will not necessitate a revision to this SAP nor will it be considered a deviation from planned analyses. Only differences in the analysis methods or data handling will require such documentation. The appropriate listings supporting the tables will be included and are not specified in the individual sections throughout the document.

5.4. Analysis Population

5.4.1. Safety Analysis Set

The Safety Analysis Set consists of all patients who receive any amount of study drug in this study.

5.5. Baseline Definition

For eligible patients who consent to participate in the open-label extension, the last available assessment taken prior to the administration of the first dose of CY 5032 study drug will serve as the baseline of CY 5032.

5.6. Derived and Transformed Data

5.6.1. Demographics and Other Baseline Characteristics Variables

Demographics and baseline characteristics will be obtained from the information collected at CY 5032 baseline.

5.6.2. Study Day

Study day will be using the CY 5032 first dose date (OLE Day 1) as reference. If the date of interest occurs on or after the first dose date in CY 5032, then study day will be calculated as (date of interest – OLE Day 1) + 1. If the date of interest occurs prior to the first dose date in CY 5032, then study day will be calculated as (date of interest – OLE Day 1).

5.6.3. Change from Baseline

For efficacy endpoints (e.g., ALSFRS-R), change from baseline will be calculated as (post-baseline value – baseline value). If either the baseline or the post-baseline value is missing, the change from baseline will be set to missing.

5.6.4. Analysis Visit Windows

All assessments will be summarized using analysis windows.

Measurements taken on or after the first dose of open-label study drug (i.e., OLE Day 1) will be assigned to the next scheduled analysis window.

For data collected at a scheduled post OLE Day 1 visit, the analysis window will be assigned based on the scheduled study day of the nominal visit as collected on the eCRF. Visits are identified as the nominal visits according to the eCRFs. Each visit will be identified with the visit descriptor (eg, “OLE Week 24”).

For unscheduled post-baseline visits, early discontinuation visits or follow-up visit, measurements taken on or after the first dose of open-label study drug will be assigned to an analysis window using defined lower and upper bounds for each analysis window. Measurements assigned in an analysis window will have study day greater than or equal to the lower bound but no greater than the upper bound of the analysis window. The lower bound and the upper bound for the analysis windows are defined as the midpoints of the scheduled visits for all assessments (see Section 11.3).

Visits are identified as the nominal visits according to the eCRFs. Each visit will be identified with the visit descriptor (eg, "OLE Week 24"). If a patient has two or more study visits in one analysis window, one record will be flagged as the "analyzed record" for that analysis window.

5.6.5. Multiple Assessments

Once analysis windows are assigned, a patient's individual analysis 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 analysis window, although the records from scheduled visit will take priority.

In the event of multiple visits falling within an analysis window, the following rules will be used in sequence to determine the "analyzed record" for the analysis window:

- If a scheduled visit occurred during the analysis window, then the measurement taken from the scheduled visit will be used.
- If more than one assessment from visits other than ET or EOS visits mapped to the same analysis visit and on the same day, the later one will be used for analysis.
- If no scheduled visit occurred during the analysis window, the measurement taken closest to the scheduled day will be used as the "analyzed record"
- If no scheduled visit occurred during the analysis window and there is a tie between unscheduled 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 analysis window will be summarized in a table. If there are other visit records within the analysis window, they will only be included in data listings. Composite scores such as ALSFRS-R total score will be calculated based on the "analyzed record".

5.7. Handling of Missing or Incomplete Dates/Times

5.7.1. Medication Start and Stop Dates

Incomplete concomitant medication start and/or stop dates will be imputed as follows:

- If either the start of medication date is completely missing or the month and/or year of the start date is missing, the start date will be set to the first dose date of CY 5032.
- If only the day is missing, the day will be set to the first day of the month except if the start month is the same as the first dose month. If the latter is true, the start day will be set to the first dose day.

No imputations will be applied to the stop date.

5.7.2. Adverse Event Start and Stop Dates

Events where the onset date is the same as study drug start date are assumed to be treatment-emergent. If an incomplete onset date was collected for an adverse event, the event will be assumed to be treatment-emergent unless there is other evidence that confirms that the event was not treatment-emergent (e.g., the event end date was prior to the study drug start date).

For missing or partial onset dates:

- If date is completely missing, assign the first dose date of CY 5032 unless there is other evidence that confirms that the event was not treatment-emergent (e.g., the event end date was prior to the first dose of CY 5032).
- If the day is missing, and the month and year match the month and year of the first dose date in CY 5032, then the day of the first dose date of CY 5032 will be used. Otherwise, the first of the month will be used and the treatment emergent status will be assessed relative to the first dose date of CY 5032.
- If the day and month are missing, and the year matches the year of the first dose date of CY 5032, the month and day of the first dose date of CY 5032 will be used. Otherwise, January 1st will be used and the treatment emergent status will be assessed relative to the first dose date of CY 5032.

For missing or partial end dates:

- If the day is missing and month and year are present, then assign to the last day of the month or the date of last contact with the patient, whichever is the earlier.
- If the day and month are missing and only the year is present, then assign to December 31st or the last date of contact with the patient, whichever is the earlier.
- For patients who discontinued early from the study drug and have missing end dates, assign to the last dosing date + 28 days or the last contact date with the patient, whichever is the later.
- For patients who completed the study and have missing end dates, assign to the date of the Follow-Up visit.
- If the end date is missing and the event is ongoing, the event will be noted as 'ongoing' in the end date column in data listings.

6. STUDY POPULATION

6.1. Subjects Dispositions

The count and percentage of patients who were enrolled, who received at least one dose of study drug, who completed the study treatment, and who prematurely discontinued from the study drug and/or from the study will be presented. Reasons for premature discontinuation will also be summarized.

6.2. Protocol Deviations

The clinical team will identify deviations and deviations will be recorded into the database.

6.3. Demographics and Baseline Characteristics

Demographic data, including age (in years), sex, race, ethnicity, height, weight, BMI, tobacco and alcohol use, etc., will be summarized in the FAS.

7. EFFICACY

The analysis on the efficacy endpoints has been condensed due to futility in the parent study. The change in ALSFRS-R from CY 5032 baseline will be summarized descriptively by visit.

8. SAFETY AND TOLERABILITY

All safety analyses will be performed by overall in the Safety Analysis Set. Safety assessments include:

- AE
- Laboratory tests
- Vital signs including temperature, blood pressure, pulse rate, and weight
- Physical and neurological examinations

Baseline is defined as last available assessment obtained in the preceding study CY 5031 or taken prior to the administration of the first dose of CY 5032 study drug.

8.1. Overall Summary of Tolerability

Overall summary table, including number of patients with:

- TEAEs
- Serious AEs (TESAEs)
- Study drug related TEAEs
- TEAEs by severity
- TEAEs leading to dose reduction
- TEAEs leading to treatment discontinuation
- TEAEs leading to death

8.2. Adverse Events

8.2.1. Summaries of Adverse Event Incidence Rates for All Subjects

Adverse events (AEs) will be coded by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities(MedDRA) version 26.0.

Analyses of AEs will be performed for those events that are considered treatment emergent AEs (TEAEs), where treatment emergence is defined as any adverse events with an onset after initiation of study drug dosing in CY 5032, or an AE present at initiation of study drug dosing that worsens in severity after initiation of study drug dosing. If an AE had the onset in the preceding study CY 5031 and carry over to the open-label extension, it will not be considered as treatment emergent in CY 5032 data.

The following summaries of AEs and serious AEs (SAEs) will be presented by overall:

- TEAEs by SOC and PT
- TEAEs by PT
- TEAEs by SOC, PT and Severity (Grade 1-5)
- TEAEs related to study drug by SOC and PT

- TEAEs related to study drug by PT
- TESAEs by SOC and PT
- TESAEs by PT
- TESAEs related to study drug by PT
- TEAEs leading to drug discontinuation by PT
- TEAEs leading to death

AE summaries will be presented by descending order of PT in the overall column, and if applicable, SOC will be ordered first, with PT sorted within the SOC.

A patient will be counted only once within each SOC and PT. For the summary of AEs by severity, patients will be counted only once within each primary SOC/preferred term and will only be counted under the maximum severity.

8.2.2. Summaries of Adverse Events of Special Interest

Adverse events of special interest (AESI) in the CY 5032 study are defined based on clinical and laboratory parameters. Results for AESI will be reviewed individually. No summary table will be provided.

Clinically significant elevated transaminases and/or (total and if available, direct) bilirubin and manifestations of liver toxicity (e.g., rash, abdominal pain, nausea and vomiting, fatigue, dark-colored urine, light-colored bowel movements, jaundice, loss of appetite, fever) including elevations that prompt study drug discontinuation are considered adverse events of special interest and should be reported to Cytokinetics Drug Safety within 24 hours of awareness on an AESI Report Form.

Any of the following criteria should be reported as Liver-Related AESIs:

- Manifestations of liver toxicity
- ALT or AST >8 × ULN
- ALT or AST >5 × ULN but <8 × ULN for ≥2 weeks
- ALT or AST > 5 × ULN but <8 × ULN and unable to adhere to monitoring
- ALT or AST >3 × ULN w/signs or symptoms consistent with hepatitis (i.e., right upper quadrant pain /tenderness, fever, nausea, vomiting, jaundice)
- TBL >3 X ULN
- TBL >2 X ULN or INR >1.5 AND ALT or AST >3 x ULN AND no alternative cause is apparent

Manifestations of renal toxicity, including clinically significant decreases in $eGFR_{Cr}$ and $eGFR_{CysC}$ and increases of UPCR, are also considered adverse events of special interest and should be recorded on the appropriate CRF and reported to Cytokinetics Drug Safety within 24 hours of awareness on an AESI Report Form.

Any of the following criteria should be reported as Renal-Related AESIs:

- Manifestations of renal toxicity
- Both $eGFR_{Cr}$, $eGFR_{CysC}$ < 30.0 ml/min/1.73m^2

- UPCR ≥ 3 mg protein/g creatinine (or ≥ 339 mg protein/mmol creatinine)

In addition, if reldsemtiv has been temporarily interrupted or permanently discontinued related to renal labs that don't meet the above criteria, this is also considered as Renal-Related AESIs. Study drug dose management with the potential for a dosing interruption and down-titration of dose will be applied.

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

Total duration of treatment and exposure of study drug per day will be summarized overall.

8.4. Concomitant and Other Medications

Concomitant medications reported on the eCRF will be listed. The WHO Drug Dictionary will be used to classify medications by therapeutic class (ATC Class 3) and preferred name. Coding will be performed using WHO Drug Dictionary Enhanced with Herbal Dictionary, B3, SEP 2020.

8.5. Clinical Laboratory Data

Abnormal post-baseline results in Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP) and Total Bilirubin (BILI) will be summarized by overall in the Safety Analysis Set, with the following categories:

For ALT or AST:

- ≤ Upper Limit of Normal (ULN),
- >ULN - 3x ULN,
- >3x ULN - 5x ULN,
- >5x ULN - 8x ULN,
- >8x ULN

For Total Bilirubin:

- ≤ ULN,
- >ULN - 2x ULN,
- >2x ULN – 3x ULN
- >3x ULN

For more than one liver function test:

- ALT or AST > 3x ULN and total bilirubin > 2x ULN
- ALT or AST > 3x ULN and total bilirubin > 2x ULN and ALP < 2xULN
- ALT or AST > 3 x ULN with signs/symptoms including nausea, vomiting, abdominal pain, fatigue, rash, dark-colored urine, light-colored bowel movements, jaundice, loss of appetite or fever.

The lower limit of normal (LLN) and upper limit of normal (ULN) provided by the laboratories will be used as the criteria to determine 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 unscheduled visits or the Follow-up Visit will be included in the summary.

Patients fulfilling any of the individual criteria (ALT/AST, ALP, or BILI) will be listed, and the listing will include all available ALT, AST, BILI, and ALP, sorted by assessment date in ascending order.

9. CHANGES TO PROTOCOL-SPECIFIED ANALYSES

As the study is prematurely stopped by Sponsor's decision, no formal statistical analysis will be produced. Only disposition, demographic and baseline characteristics, an overview of AEs and abnormal liver lab results will be summarized by table. By-subjects data listing will be produced for those with liver abnormality.

10. REFERENCES

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.

11. APPENDIX

11.1. Table of Contents for Data Display Specifications

Table of contents for data display specifications will be provided in a separate document.

11.2. Data Display Specifications

Data display specifications will be provided in a separate document.

11.3. Analysis Windows

Table 2: Analysis Windows for ALSFRS-R

Visit	Scheduled Day [Lower bound, Upper bound]
OLE Day 1	1 [<=OLE Day 1]
OLE Week 4	29 [2, 42]
OLE Week 8	57 [43, 70]
OLE Week 12	85 [71, 98]
OLE Week 16	113 [99, 126]
OLE Week 20	141 [127, 154]
OLE Week 24	169 [155, 182]
OLE Week 28	197 [183, 210]
OLE Week 32	225 [211, 238]
OLE Week 36	253 [239, 266]
OLE Week 40	281 [267, 294]
OLE Week 44	309 [295, 322]
OLE Week 48	337 [323, 350]
OLE Week 52	365 [>=351]

Table 3. Analysis Windows for Clinical Safety Laboratory Measurements

Visit	Scheduled Day [Lower bound, Upper bound]
OLE Day 1	1
OLE Week 6	43 [2, 63]
OLE Week 12	85 [64, 105]
OLE Week 18	127 [106, 147]
OLE Week 24	169 [148, 210]
OLE Week 36	253 [211, 294]
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1: Electronic Approvals

Name/Signature	Title	Date	Meaning/Reason
Stuart Kupfer (SKUPFER)	SVP, Chief Medical Officer	27 Jun 2023, 10:40:54 AM	Approved
Michael Chiu (MCHIU)	Associate Director, Biostatistics	27 Jun 2023, 10:42:08 AM	Approved
Lisa (Lixin) Meng (LMENG)	Vice President, Biometrics	27 Jun 2023, 09:05:27 PM	Approved
Andrew Wolff (AWOLFF)	SVP Senior Fellow, CR&D	28 Jun 2023, 11:16:30 AM	Approved