PROTOCOL CY 5031

A PHASE 3, MULTI-CENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF RELDESEMTIV IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Trial Name:	COURAGE-ALS
Protocol Version and Date:	Amendment 5: 24 February 2023
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Product:	CK-2127107
Product Name:	Reldesemtiv
Regulatory Authority Identifier Number(s):	IND 134567 EudraCT Number 2020-004040-29
Sponsor:	Cytokinetics, Inc. 350 Oyster Point Blvd South San Francisco, CA 94080, USA

INVESTIGATOR SIGNATURE PAGE

Protocol Number:	CY 5031
Protocol Title:	A Phase 3, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Reldesemtiv in Patients with Amyotrophic Lateral Sclerosis (ALS)
Protocol Version and Date:	Amendment 5: 24 February 2023

Principal Investigator Commitment

I, the undersigned Principal Investigator, submit this statement of commitment as evidence that I understand my responsibilities pursuant to the International Conference on Harmonisation (ICH) E6(R2) Good Clinical Practice (GCP) guidelines, as well as with any and all applicable federal, state and/or local laws and regulations, and agree to conduct this study in accordance with the protocol referenced herein.

Investigator Name: _____ Date: _____

Investigator Signature: _____

PROTOCOL APPROVAL PAGE

Protocol Number:	CY 5031
Protocol Title:	A Phase 3, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Reldesemtiv in Patients with Amyotrophic Lateral Sclerosis (ALS)
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Sponsor:	Cytokinetics, Inc. 350 Oyster Point Blvd South San Francisco, CA 94080

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Date:

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1.1. Synopsis

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Reldesemtiv, a fast skeletal muscle troponin activator (FSTA), is being investigated as a potential therapy to slow the decline of skeletal muscle function in patients with ALS. This pivotal trial with reldesemtiv is being conducted in ALS patients and is designed to assess the effect of reldesemtiv on functional outcomes during treatment up to 48 weeks. The first trial with reldesemtiv in ALS patients (FORTITUDE-ALS [CY 5022]) after 12 weeks of dosing, showed that patients on all doses of reldesemtiv tended to decline less than patients on placebo for slow vital capacity (SVC) and ALS Functional Rating Scale-Revised (ALSFRS-R), with larger and clinically meaningful differences emerging over time. The results support progression in a further clinical trial with a longer dosing duration.</td></tr>
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• To assess the effect of reldesemtiv versus placebo on ventilatory function
• To assess the effect of reldesemtiv versus placebo on quality of life
• To assess the effect of reldesemtiv versus placebo on handgrip strength</td><td>• Combined assessment of change in ALSFRS-R total score, time to dependence on assisted ventilation (use of non-invasive or invasive ventilation for ≥ 22 hours per day for ≥ 10 consecutive days), and survival time up to Week 24
• Change from baseline to Week 24 in the percent predicted FVC
• Change from baseline to Week 24 in the ALSAQ-40 total score
• Change from baseline to Week 24 in handgrip strength (average of both hands)</td></tr>
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Exploratory	
• To assess the effect of reldesemtiv versus placebo on the progression of ALS	• Time to the patient being prescribed and patient agrees to it, time to first receipt, time to first use, time to daily use, time to dependence and number used of any of the following durable medical equipment items (manual wheelchair, power wheelchair, augmentative and alternative communication device, non-invasive ventilation (NIV) and/or gastrostomy tube) from randomization to the end of the 24-week double-blind, placebo-controlled period and to the end of Week 48. Time to dependence on invasive ventilation will also be recorded. • Change from baseline to Week 24 in the four subdomain scores of the ALSFRS-R • Time spent in each MiToS stage and number of patients to transition stages from baseline to Week 24 • Change from baseline to Week 48 in ALSFRS-R total score • Change from baseline to Week 48 in forced vital capacity (FVC) • Combined assessment of change in ALSFRS-R total score, time to dependence on assisted ventilation (use of non-invasive or invasive ventilation for ≥ 22 hours per day for ≥ 10 consecutive days), and survival time up to Week 48 • Change from baseline to Week 24 in the mega-score of muscle strength measured by hand-held dynamometry (HHD) in bilateral first dorsal interosseous muscles, abductor pollicus brevis muscles, and abductor digiti minimi muscles • Change from baseline to Week 24 and Week 48 in the EQ-5D-5L • Change from baseline to Week 24 and Week 48 in the EQ-Visual Analogue Scale (VAS) • Time to event for first hospitalization to Week 24 and Week 48
Safety	
• To assess the safety and tolerability of reldesemtiv compared to placebo	• Patient incidence of adverse events and serious adverse events

Overall Design:

This is a Phase 3, double-blind, randomized, placebo-controlled trial of reldesemtiv in patients aged 18 to 80 with ALS.

The screening and qualification period for the trial will be no more than 21 days in duration. Approximately 555 eligible ALS patients will be randomized (2:1) to receive the following dose of reldesemtiv or placebo (stratified by riluzole use/non-use and edaravone use/non-use) for the first 24 weeks (double-blind, placebo-controlled period):

- 300 mg reldesemtiv twice a day for a 600 mg total daily dose (TDD)
- Placebo twice daily

At the end of the 24-week double-blind, placebo-controlled period, patients will transition to the active drug period, where all patients will receive the following dose of reldesemtiv for the next 24 weeks:

- 300 mg reldesemtiv twice a day for a 600 mg TDD for patients who were not down titrated during the 24 weeks of blinded dosing
- 150 mg reldesemtiv twice a day for a 300 mg TDD for patients who were down titrated for any reason during the 24 weeks of blinded dosing

For the entire 48 weeks of dosing, patients and sites shall remain blinded to the randomized treatment assignment patients received during the first 24 weeks.

Study drug should be taken twice daily, morning and afternoon (at least 8 hours apart) and should be taken either with food or within a 2-hour period following food.

Study Visits:

There will be up to eight clinic visits and nine remote assessment visits (with most requiring an accompanying phone or video call) as follows:

- Screening: clinic visit/lab
- Day 1 (start of dosing): clinic visit/lab
- End of Week 2: remote - lab only
- End of Week 4: clinic visit/lab
- End of Week 8: remote visit/lab
- End of Week 12: clinic visit/lab
- End of Week 16: remote visit/lab
- End of Week 20: remote visit/lab
- End of Week 24 (last dose of double-blind dosing): clinic visit/lab
- End of Week 26: remote - lab only
- End of Week 28: remote visit/lab
- End of Week 32: remote visit/lab
- End of Week 36: clinic visit/lab
- End of Week 40: remote visit/lab
- End of Week 44: remote visit/lab
- End of Week 48 (last dose of active drug dosing): clinic visit/lab
- Follow-Up (4 weeks after last dose of study drug): clinic visit/lab

For patients who complete Week 48 and want to enter the open label extension (OLE), they will not have the follow-up visit; instead they will enter the OLE on the same day as their Week 48 visit. If the patient does not want to enter the OLE, or if the OLE has not yet been approved at the site, the follow-up visit will take place as above.

Since we plan to conduct the trial in different regions of the world, including Europe, Canada, Australia and the US, standard of care regarding ALS for the local region, as determined by the physician in discussion with the patient, should be followed.

Study Center(s):

Patients will be enrolled from approximately 85 clinical trial sites, in US, Canada, Europe and Australia.

Number of Patients:

Approximately 740 patients will be screened in order to randomize/enroll approximately 555 patients, such that approximately 444 evaluable patients complete the 24-week of double-blind period of the trial.

Key Eligibility Criteria:

A full listing of eligibility criteria can be found in Section 5. Patients are eligible to be included in the trial only if all criteria are met.

Key Inclusion Criteria

- Males or Females between the ages of 18 and 80 years of age, inclusive
- Diagnosis of familial or sporadic ALS (defined as meeting the laboratory-supported probable, probable, or definite criteria for ALS according to the World Federation of Neurology El Escorial criteria published in 2000 [Brooks 2000]). Patients who meet the possible criteria are eligible if they have lower motor neuron findings; those who have purely upper motor neuron findings are ineligible.
- First symptom of ALS ≤ 24 months prior to screening. The qualifying first symptoms of ALS are limited to manifestations of weakness in extremity, bulbar, or respiratory muscles. Cramps, fasciculations, or fatigue should not be taken in isolation as a first symptom of ALS.
- ALSFRS-R total score ≤ 44 at screening. Patients with a total score of 45 or higher may be rescreened 60±7 days following the original screening date and be deemed eligible if their ALSFRS-R total score is ≤ 44 or if their score is 2 or more points less than at initial screening. Such patients must continue to meet all other inclusion/exclusion criteria at the time of rescreening.
- Upright FVC ≥ 65.0% of predicted for age, height, sex and ethnicity at screening according to Global Lung Initiative equation
- Able to perform reproducible pulmonary function tests defined as being able to perform FVC at screening with variability of the 2 highest raw values of less than 10% with a maximum of 5 trials permitted. Screening FVC results must be reviewed and approved by the central review process prior to randomization.
- Must be either on riluzole for ≥ 30 days prior to screening or have not taken it for at least 30 days prior to screening

- Must have completed at least 2 cycles of edaravone at the time of screening or have not received it for at least 30 days prior to screening
- Able to swallow whole tablets at the time of screening
- Clinical laboratory findings within the normal range, or if outside the normal range, not deemed clinically significant by the Investigator, except as specifically indicated as laboratory exclusion
- Must be either on the combination product (brand name only) of sodium phenylbutyrate and taurursodiol (also known as TUDCA, ursodoxicoltaurine or Tauroursodeoxycholic acid) for ≥51 days or have not received it for at least 30 days prior to screening

Key Exclusion Criteria

- $eGFR_{Cr}$ and $eGFR_{CysC}$ < 45.0 mL/min/1.73 m^2 at screening
- Urine protein/creatinine ratio > 1 mg/mg (113 mg/mmol) at screening
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3-times the upper limit of normal (ULN)
- Total bilirubin (TBL), direct or indirect bilirubin above the ULN.
- Cognitive impairment, related to ALS or otherwise that impairs the patient's ability to understand and/or comply with study procedures and provide informed consent
- Other medically significant neurological conditions that could interfere with the assessment of ALS symptoms, signs or progression.
- Presence at screening of any medically significant cardiac, pulmonary, gastrointestinal, 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
- Has a tracheostomy

Investigational Product:

Reldesemtiv will be administered as 150 mg tablets, at a dose of 300 mg twice a day for a 600 mg TDD and matching placebo.

Reldesemtiv and matching placebo tablets will be supplied to the clinical site in bottles. Patients will receive one or more bottles of study drug (reldesemtiv or matching placebo) at each clinic visit.

The study research coordinator or designated site staff will be responsible for patient randomizations, using an interactive web response system (IWRS).

Patients must interrupt study drug for certain specified laboratory abnormalities . Hepatic related interruptions are permanent discontinuations. For renal related laboratory abnormalities, the interruption continues until the laboratory value in question has returned to the threshold specified in the protocol for re-initiation of treatment. Patients may then resume dosing at 1 table twice a day thereafter (150 mg twice daily). Patients also may be down-titrated to 1 tablet twice a day by the Investigator in the case of adverse events felt to be related to study drug. Once patients have been down-titrated to one tablet twice daily for any reason, their dose may not be returned to two tablets twice daily.

Data Monitoring Committee:

An independent Data Monitoring Committee (DMC) will periodically assess patient safety in an unblinded manner during the course of the trial.

Interim Analyses:

Twelve (12) weeks after approximately one-third or more of the planned sample size is randomized, the first interim analysis may be triggered. Its purpose is to determine if there is a lack of effect of reldesemtiv on the ALSFRS-R in CY 5031, a finding that would be inconsistent with the prior observed effect on the change from baseline at 12 weeks in ALSFRS-R total score in the Phase 2 trial, CY 5022. At this interim analysis, the DMC will receive unblinded efficacy data from the independent, third-party biostatistical group supporting them and assess the effect of reldesemtiv on the change from baseline to Week 12 in the ALSFRS-R total score. At this interim assessment, if the treatment difference for change from baseline to Week 12 in ALSFRS-R total score has a one-sided p-value larger than or equal to 0.5 (ie, the estimated treatment difference of the change from baseline at Week 12 in ALSFRS-R total score is favoring placebo), the DMC may recommend stopping the trial due to futility. This futility analysis based on the data of change from baseline to Week 12 in ALSFRS-R will not have any alpha spending in the final analysis of the trial. The Sponsor will monitor the blinded aggregate standard deviation of the change from baseline to Week 12 in ALSFRS-R total score periodically and possibly adjust the specified p-value before this interim analysis is conducted.

Twenty-four (24) weeks after at least one-third or more of the planned sample size is randomized, the second interim analysis will be triggered. The goal of the second interim analysis is to evaluate whether the proposed Phase 3 trial has adequate power to achieve a statistically significant effect on the primary endpoint in the final primary analysis, given the planned enrollment, or if continuing the trial is futile. At this interim analysis, the DMC will receive unblinded efficacy data from the independent, third-party biostatistical group supporting them and assess the effect of reldesemtiv on the primary endpoint. In terms of futility, the DMC may recommend stopping the trial if the conditional power (CP) is less than 0.10 for the primary endpoint.

If the CP of the primary endpoint is within a pre-specified promising zone from 0.40 to 0.90, the DMC may recommend increasing the sample size by 150 patients unless there is any safety concern or other concerns that preclude this recommendation. This interim analysis will spend a 2-sided alpha of 0.0001 for the primary endpoint and all individual secondary endpoints. The DMC is also expected to recommend stopping this trial due to superiority if a two-sided p-value is ≤ alpha of 0.0001 for the primary endpoint as well as all individual secondary endpoints. Therefore, the significance level of 2-sided alpha of 0.0499 would be used for the final primary analysis for the primary endpoint to control familywise error rate at overall alpha of 0.05.

Statistical Methods:

Sample Size Justification:

With a 2:1 randomization ratio to reldesemtiv and placebo groups, respectively, a sample size of approximately 555 patients is required to achieve at least 90% power to detect at least a 1.8 point treatment difference between reldesemtiv and placebo in the change from baseline to Week 24 in ALSFRS-R total score. This calculation is based on a two-sample t-test with two-sided alpha at 0.05 level and a common standard deviation (SD) of 5.5 points, accounting for missing data and early treatment terminations.

Statistical Methods:

Unless specified otherwise, efficacy analyses will be performed on the full analysis set (FAS), which includes all randomized subjects who receive at least one dose of randomized study drug and have a baseline and at least one post-baseline efficacy assessments or have survival status recorded, by randomized treatment group.

The analysis for the primary endpoint is to test the global null hypothesis that there is no treatment difference in the change from baseline to Week 24 in ALSFRS-R total score between patients randomized to placebo and those randomized to reldesemtiv during the double-blind, placebo-controlled period in the FAS. The FAS consists of all randomized patients who receive any amount of study drug and who have a baseline and at least one post baseline efficacy assessment during the first 24-week double-blind placebo-controlled period.

The primary analysis will be conducted using a Mixed Model for Repeated Measures (MMRM) with a restricted maximum likelihood method (SAS® PROC MIXED default). At randomization, patients will be stratified by riluzole use/non-use and edaravone use/non-use and the primary model will include terms of treatment group, baseline ALSFRS-R value, visit, baseline riluzole use, and baseline edaravone use as well as the interaction terms of baseline-by-visit and treatment group-by-visit. An unstructured variance-covariance matrix will be used in the model. Prior to applying the MMRM, missing data will be imputed using the multiple imputation procedure (Rubin 1987) for the primary analysis, and the estimates from each imputed dataset will be combined into one set of overall estimates using the SAS® PROC MIANALYZE procedure. . The extent of missing data and the pattern of missing data reasons will be tabulated. Imputation details will be pre-specified in the SAP. Least square means (LSM), LSM difference and the corresponding standard errors, 95% confidence intervals (CI) and p-values will be presented.

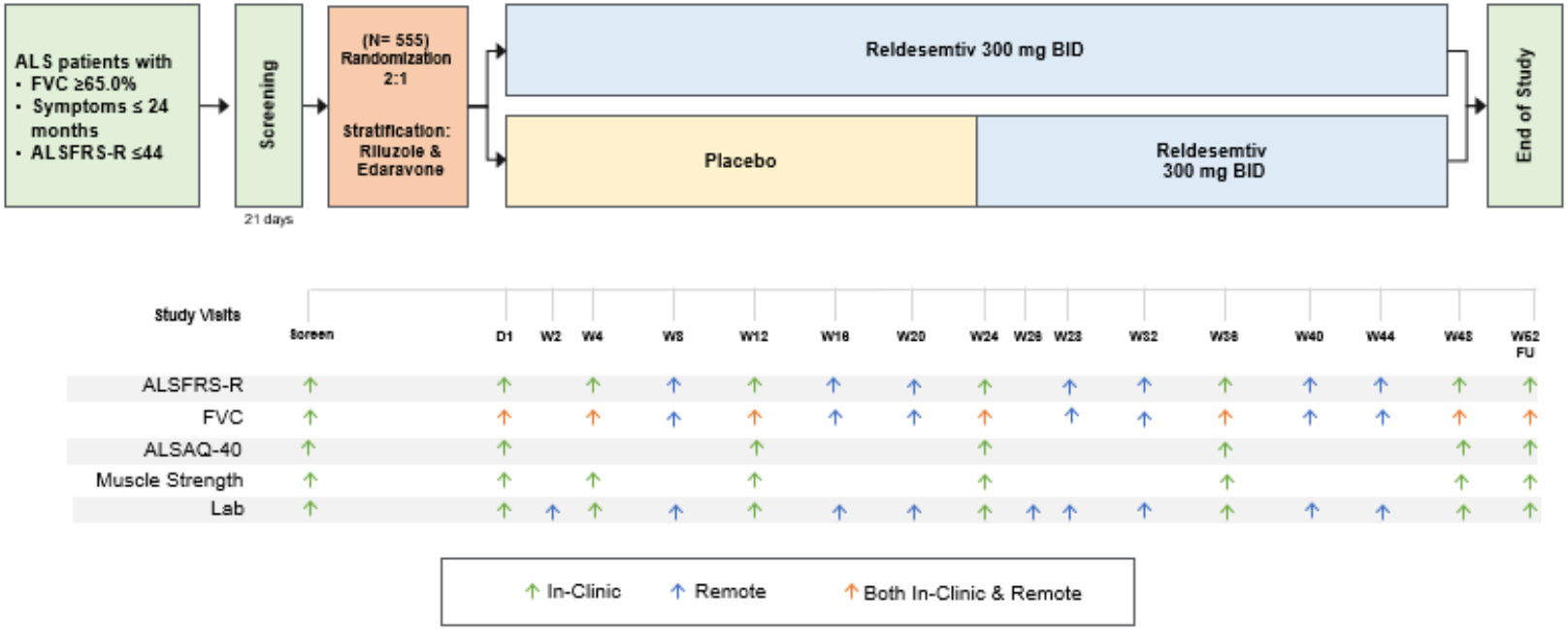
Multiplicity will be addressed using closed testing procedure. The testing sequence below the first secondary endpoint will be provided in the statistical analysis plan (SAP).

Safety data will be analyzed descriptively in the safety analysis set, including patients who take at least one dose of study drug. All AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Primary system organ class (SOC) and preferred term (PT) of the Treatment Emergent Adverse Events (TEAEs) will be tabulated by the early-start and delayed-start treatment groups and period (placebo-controlled period and active drug period). TEAEs will also be summarized by severity and relationship to study drug. AEs that led to early discontinuation from treatment or trial will be summarized.

General and additional analysis methods will be detailed in the SAP.

1.2. Schema

Figure 1: Study Schema



1.3. Schedule of Activities

		Double-Blind, Placebo-Controlled Period								Active Drug Period							
	Scree -ning	**Day 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 26**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48 (or ED)**	**FU**
In Clinic	X	**X**		**X**		**X**			**X**				**X**			**X**	X
Remote Visit and/or Lab Draw			**X**[1]		**X**		**X**	**X**		**X**[1]	**X**	**X**		**X**	**X**		
Informed Consent	X																
Inclusion and Exclusion Criteria	X																
Demographics & Medical History	X																
Physical Examination	X																X
Weight & BMI	X	X		X		X			X				X			X	X
Concomitant Med Review	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X
Neurological Exam	X								X								X
Vital Signs	X	X		X		X			X				X			X	X
12-lead ECG	X	X							X							X	X
AE/SAE Evaluation	X[2]	X		X	X	X	X	X	X		X	X	X	X	X	X	X[7]
Clinical Safety Labs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (WOCBP only)	X	X							X							X	
Randomization		X															
PK Sample[4]				X		X			X				X[5]				
Biomarker sample[6]		X							X								
Genetic Sample (optional)		X															
Study Drug Dosing		X	X	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	X
FVC (Clinic)	X	X		X		X			X				X			X	X

		Double-Blind, Placebo-Controlled Period								Active Drug Period							
	Scree -ning	**Day 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 26**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48 (or ED)**	**FU**
In Clinic	X	**X**		**X**		**X**			**X**				**X**			**X**	X
Remote Visit and/or Lab Draw			**X[1]**		**X**		**X**	**X**		**X[1]**	**X**	**X**		**X**	**X**		
FVC (Home)[8] **		X		X	X	X	X	X	X		X	X	X	X	X	X	X
Health Economics Outcomes Measure (DME Use)	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X
ALSAQ-40	X	X				X			X				X			X	X
Grip Strength	X	X		X		X			X				X			X	X
HHD	X	X		X		X			X				X			X	X
EQ-5D-5L and EQ VAS	X	X				X			X				X			X	X
BDI-FS	X	X		X		X			X				X			X	X

ED=Early discontinuation; AE=adverse event; ECG=electrocardiogram; BMI=body mass index; PK=pharmacokinetics; SAE=serious adverse event; WOCBP=women of childbearing potential, FVC=forced vital capacity; FU=Follow-Up; ALSFRS-R=Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; BDI-FS=Beck Depression Inventory-Fast Screen; ALSAQ-40=Amyotrophic Lateral Sclerosis Assessment Questionnaire; DME=Durable Medical Equipment; HHD=Hand-Held Dynamometry; EQ-5D-5L=EuroQol-5D-5L; EQ VAS=EuroQol Visual Analog Scale

*Drug dosing will not occur at the ED visit

**Dosing should take place prior to the telemedicine contact on the dosing day such that the FVC is performed approximately 2 hours after taking the dose

1=Remote visit lab draw only (no phone call) at Week 2 and Week 26; all other remote visits include video call and home lab draw

2= During the interval between the time of signing the informed consent form and immediately before the first dose of study drug, serious adverse events considered by the investigator to be related to study protocol-mandated procedure should be collected in the AE CRF. All other medical conditions should be collected as medical history prior to the first dose of study drug.

3=Clinical safety labs to include:

Chemistry: 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, glucose

Hematology: hemoglobin, hematocrit, RBC, RDW, MCV, MCH, MCHC, WBC, platelets

Urinalysis: specific gravity, pH, blood, protein, glucose, bilirubin, UPCR and microscopy

TSH at screening; bHCG as applicable for WOCBP, FSH as required to determine menopausal status at Screening per Appendix 3 (Section 10.3)

4=PK sample at Week 4, Week, 12, and Week 24 at pre-dose and 2-4 hrs post-dose

5=PK samples at Week 36 for Sub-Study at pre-dose and at 0.5, 1, 2, 3, 4 and 6 hrs post-dose

6=Biomarker samples at Day 1 pre-dose and Week 24 pre-dose

7=Additional testing to be conducted if AEs of special interest are not resolved at the 4-week FU visit

8= Refer to Section 8.1.2 for details of timing of home spirometry relative to FVC performed at in-clinic visits

1.4. Key Contacts

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2. INTRODUCTION

This trial of reldesemtiv is being conducted in patients with amyotrophic lateral sclerosis (ALS).

2.1. Study Rationale

Reldesemtiv, a fast skeletal muscle troponin activator (FSTA), is being investigated as a potential therapy to slow the decline of skeletal muscle function in patients with ALS. This pivotal trial with reldesemtiv is being conducted in ALS patients and is designed to assess the effect of reldesemtiv on functional outcomes during treatment up to 48 weeks. The first trial with reldesemtiv in ALS patients (FORTITUDE-ALS [CY 5022]) after 12 weeks of dosing, showed that patients on all doses of reldesemtiv tended to decline less than patients on placebo for slow vital capacity (SVC) and ALS Functional Rating Scale-Revised (ALSFRS-R), with larger and clinically meaningful differences emerging over time. The results support progression in a further clinical trial with a longer treatment duration.

2.2. Background

2.2.1. Amyotrophic Lateral Sclerosis

ALS is a disease of the nerve cells in the brain and spinal cord that control voluntary muscle movement. In ALS, progressive death of motor neurons leads to denervation of skeletal muscles. Surviving motor units attempt to compensate for dying ones by innervating more muscle fibers (a process called sprouting) but are only partially successful (Kiernan 2011). Over time, progressive denervation and its consequent skeletal muscle atrophy lead to weakness, fatigue, and eventually complete paralysis and death, primarily from respiratory complications.

No curative therapies for ALS exist. Rilutek® (riluzole) is the first drug approved for the treatment of ALS in 1995 and 1996 in the US and EU, respectively, and has a modest benefit on survival (Lacomblez 1996). While non-invasive ventilation (NIV) use has been demonstrated to provide a survival benefit in ALS patients, a third of ALS patients may be non-compliant, and non-compliance may be even higher in those with bulbar involvement and frontotemporal dysfunction (Bourke 2006; Kleopa 1999). Improvements in the ventilation machines have likely led to improved tolerability in more recent years, however, NIV may still be under-utilized (Lechtzin 2018). While patients may undergo gastrostomy tube placement with disease progression, it is less clear if the use of enteral feeding prolongs survival with studies showing inconsistent results (Forbes 2004; Burkhardt 2017).

As of July 2020, Radicava® (edaravone) was approved to treat patients with ALS in in Japan, South Korea, United States (US), Canada, Switzerland and China. The efficacy of edaravone was demonstrated in a 6-month clinical trial conducted in Japan wherein 137 participants were randomized to receive edaravone or placebo. At Week 24, individuals receiving edaravone declined less on a clinical assessment of daily functioning (ALSFRS-R) compared to those receiving placebo (Abe 2017). Oral Radicava® (edaravone) was approved for ALS in the US based upon bioequivalence data. (Shimizu 2021).

The combination product of sodium phenylbutyrate and taurursodiol (also known as TUDCA, ursodoxicoltaurine or Tauroursodeoxycholic acid) was approved in Canada and the US on the basis of a 6-month clinical trial conducted in the US involving 137 participants randomized to 2 to 1 to

either active drug or placebo. The primary endpoint was rate of change in the ALSFRS-R; the decline was -1.24 points per month in the active arm and -1.66 points per month in the placebo arm (p = 0.033) (Paganoni 2020).

To date, there are no available treatments that slow the decline of skeletal muscle strength or slow the decline of respiratory function. This clinical protocol is a double-blind, randomized, dose-ranging, placebo-controlled trial to evaluate the efficacy, safety, and tolerability of reldesemtiv in patients with ALS.

2.2.2. Reldesemtiv

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 selectively activates the fast skeletal muscle troponin complex by increasing its affinity for calcium. In intact rat skeletal muscle in vivo, reldesemtiv increases muscle force at sub-maximal nerve stimulation frequencies, increases muscle power, and decreases muscle fatigability. Reldesemtiv is selective for the troponin complex in fast skeletal muscle and does not activate the slow skeletal troponin complex or the cardiac troponin complex. It has similar potencies in muscle fibers from preclinical species and human fast skeletal muscle fibers. It is expected that reldesemtiv may provide benefit to patients with a wide variety of disorders characterized by muscle weakness and/or fatigue.

Please refer to the Investigator's Brochure (IB) for detailed information on the nonclinical and clinical studies of reldesemtiv.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

In CY 5022, treatment emergent adverse events (TEAEs) reported more frequently for the reldesemtiv groups than for the placebo group (with a difference in patient incidence of > 5%) were cystatin C increased, GFR decreased, and fatigue. TEAEs that appeared to increase in frequency with increasing dose included fatigue, nausea, cystatin C increased, GFR decreased, alanine aminotransferase (ALT) increased, and aspartate aminotransferase (AST) increased.

Serum cystatin C was obtained in CY 5022 and used to determine the estimated glomerular filtration rate ($eGFR_{CysC}$) as it was previously recognized that exposure to reldesemtiv resulted in a rise in creatinine; this was attributed to Organic Cation Transporter 2 (OCT2) inhibition. There was a dose dependent decline in $eGFR_{CysC}$ from baseline in CY 5022 and therefore the rise in creatinine observed in prior studies could not be ascribed solely to OCT2 inhibition. Mean eGFR declined to an essentially stable level by 2 weeks of active treatment and tended to recover after 4 weeks off drug. Decline in $eGFR_{CysC}$ was the most common reason for early termination of study drug due to AEs, occurring in 7/457 (1.5%) participants. No patients had significant sequalae related to the decline in $eGFR_{CysC}$ such as requiring dialysis or developing hyperkalemia.

Elevations in ALT or AST greater than 3×upper limit of normal (ULN) occurred in 25 patients; 24 (7.0%) were assigned reldesemtiv and 1 (0.9%) assigned placebo. Overall, the transaminase elevations appeared to be transient, dose dependent, mild to moderate, and not associated with increase in bilirubin or any clinical manifestations.

A total of 6 patients (none of whom had concurrent elevations in ALT or AST > 5×ULN), all on reldesemtiv and 5 in the 450 mg bid group, had a postbaseline total bilirubin value > 2×ULN. All elevations were observed within approximately 1 month of starting reldesemtiv dosing and resolved or were normalizing at last contact.

2.3.1.1. Mitigation Strategy

For both the renal and hepatic findings in CY 5022, the frequency was highest in those patients on the highest dose of reldesemtiv (450 mg twice a day); thus, the highest dose that will be used in the current trial is reldesemtiv 300 mg twice a day and a careful monitoring of renal function and liver enzymes will be implemented during the trial.

Renal Safety

For renal safety, the mitigation strategy includes specific inclusion and exclusion criteria to reduce the risk of a drop in eGFR below a clinically meaningful threshold, renal function monitoring (at least monthly, more frequently at dose initiation) and detailed study drug dose management with the potential for a dosing interruption and down-titration of dose, as described in Section 7.3.

Key Relevant Exclusion Criteria:

- $eGFR_{Cr}$ and $eGFR_{CysC}$ less than 45.0 mL/min/1.73m^2
- Urine protein/creatinine ratio greater than 1 mg/mg

Hepatic Safety

For hepatic safety, the mitigation strategy includes specific inclusion and exclusion criteria, liver function monitoring (at least monthly, more frequently at dose initiation) and detailed study drug management as described in Section 7.4.

Key Relevant Exclusion Criteria:

- Total, indirect, or direct bilirubin values greater than the ULN
- ALT or AST greater than or equal to 3×ULN
- History of Gilbert's Disease, Dubin-Johnson syndrome, or Rotor syndrome

2.3.2. Benefit Assessment

Given that patients in this trial will be symptomatic and progressing on their existing background therapy, reldesemtiv may afford those randomized to reldesemtiv an opportunity to slow the decline in their function. For details regarding potential benefits of reldesemtiv in ALS, please see Section 4.2 which provides the results of the Phase 2 trial (CY 5022) of reldesemtiv in patients with ALS.

Patient contributions to the performance of this trial may yield a new therapeutic modality for the treatment of their disease.

3. OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives and Endpoints

Objectives	Endpoint(s)
Primary	
• To assess the effect of reldesemtiv versus placebo on functional outcomes in ALS	• Change from baseline to Week 24 in ALSFRS-R total score
Secondary	
• To assess the effect of reldesemtiv versus placebo on combined functional and survival outcomes in ALS • To assess the effect of reldesemtiv versus placebo on ventilatory function • To assess the effect of reldesemtiv versus placebo on quality of life • To assess the effect of reldesemtiv versus placebo on handgrip strength	• Combined assessment of change in ALSFRS-R total score, time to dependence on assisted ventilation (use of non-invasive or invasive ventilation for ≥ 22 hours per day for ≥ 10 consecutive days), and survival time up to Week 24 • Change from baseline to Week 24 in the percent predicted forced vital capacity (FVC) • Change from baseline to Week 24 in the Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ-40) total score • Change from baseline to Week 24 in handgrip strength (average of both hands)
Exploratory	
• To assess the effect of reldesemtiv versus placebo on the progression of ALS	• Time to the patient being prescribed and patient agrees to it, time to first receipt, time to first use, time to daily use and time to dependence and number used of any of the following durable medical equipment items (manual wheelchair, power wheelchair, speech generating device, NIV and/or gastrostomy tube) from randomization to the end of the 24-week double-blind, placebo-controlled period and to the end of Week 48. Time to dependence on invasive ventilation will also be recorded. • Change from baseline to Week 24 in the four subdomain scores of the ALSFRS-R • Time spent in each MiToS stage and number of patients to transition stages from baseline to Week 24

Objectives	Endpoint(s)
	• Change from baseline to Week 48 in ALSFRS-R total score • Change from baseline to Week 48 in FVC • Combined assessment of change in ALSFRS-R total score, time to dependence on assisted ventilation (use of non-invasive or invasive ventilation for ≥ 22 hours per day for ≥ 10 consecutive days), and survival time up to Week 48 • Change from baseline to Week 24 in the mega-score of muscle strength measured by hand held dynamometry (HHD) in bilateral first dorsal interosseous muscles, abductor pollicus brevis muscles, and abductor digiti minimi muscles • Change from baseline to Week 24 and Week 48 in the EQ-5D-5L • Change from baseline to Week 24 and Week 48 in the EuroQol Visual Analog Scale (EQ-VAS) • Time to event for first hospitalization to Week 24 and Week 48
Safety	
• To assess the safety and tolerability of reldesemtiv compared to placebo	• Patient incidence of adverse events and serious adverse events

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, double-blind, randomized, placebo-controlled trial of reldesemtiv in patients aged 18 to 80 with ALS.

The screening and qualification period for the trial will be no more than 21 days in duration. Approximately 555 eligible ALS patients will be randomized (2:1) to receive the following dose of reldesemtiv or placebo (stratified by riluzole use/non-use and edaravone use/non-use) for the first 24 weeks (double-blind, placebo-controlled period):

- 300 mg reldesemtiv twice a day for a 600 mg total daily dose (TDD)
- Placebo twice daily

At the end of the 24 week double-blind, placebo-controlled period, patients will transition to the active drug period, where all patients will receive the following dose of reldesemtiv for the next 24 weeks:

- 300 mg reldesemtiv twice a day for a 600 mg TDD for patients who were not down titrated during the 24 weeks of blinded dosing
- 150 mg reldesemtiv twice a day for a 300 mg TDD for patients who were down titrated for any reason during the 24 weeks of blinded dosing

For patients being seen in the morning of the Week 24 visit:

- Following the pre-dose PK, the last dose of double-blind study drug will be taken from the bottle received at the prior drug dispensation visit
- The patient will take their second dose of the day (which will be unblinded reldesemtiv) at home from the new bottle dispensed at the Week 24 visit approximately 8 hours after the first dose

If a patient is being seen in the afternoon for the Week 24 visit and taking their second dose of the day in the clinic:

- Following the pre-dose PK, the last dose of blinded study drug will be taken from the bottle received at the prior drug dispensation visit and they will take no further doses that day
- The following morning, the patient will start taking unblinded study drug (reldesemtiv) from the new bottle dispensed at Week 24.

For the entire 48 weeks of dosing, patients and sites shall remain blinded to the randomized treatment assignment the patients received during the first 24 weeks.

Study drug should be taken twice daily, morning and afternoon (at least 8 hours apart) and should be taken within a 2-hour period following food.

Study Visits:

There will be up to eight clinic visits and nine remote assessment visits (with most requiring an accompanying phone/video call) as follows:

- Screening: clinic visit/lab

- Day 1 (start of dosing): clinic visit/lab
- End of Week 2: remote visit (lab only)
- End of Week 4: clinic visit/lab
- End of Week 8: remote visit/lab
- End of Week 12: clinic visit/lab
- End of Week 16: remote visit/lab
- End of Week 20: remote visit/lab
- End of Week 24 (last dose of double-blind dosing): clinic visit/lab
- End of Week 26: remote (lab only)
- End of Week 28: remote visit/lab
- End of Week 32: remote visit/lab
- End of Week 36: clinic visit/lab
- End of Week 40: remote visit/lab
- End of Week 44: remote visit/lab
- End of Week 48 (last dose of active drug dosing): clinic visit/lab
- Follow-Up (4 weeks after last dose of study drug): clinic visit/lab

For patients who complete Week 48 and want to enter the open label extension (OLE), they will not have the follow-up visit; instead they will enter the OLE on the same day as their Week 48 visit. If the patient does not want to enter the OLE, or if the OLE has not yet been approved at the site, the follow-up visit will take place as above.

Remote Visits

Remote visits are defined as any of the following contacts with the patient: home (or other location outside of the clinic) phlebotomy draw, telephone calls, telemedicine, and video contact. Patients will be provided a device to enable telemedicine contact for the remote visits. Screening and Day 1 visits must occur in-clinic; in addition, it is strongly encouraged that Week 24 and Week 48 visits take place in the clinic. Week 48 must take place in clinic if the patient is enrolling in the OLE study at the Week 48 visit. In-clinic visits can be converted to remote visits in the event the clinic is closed to patient care, or if the investigator believes the health of the patient would be best served by replacing the in-clinic visit with a remote one. The medical monitor must be contacted in advance of converting an in-clinic visit to a remote visit.

Standard of Care for ALS

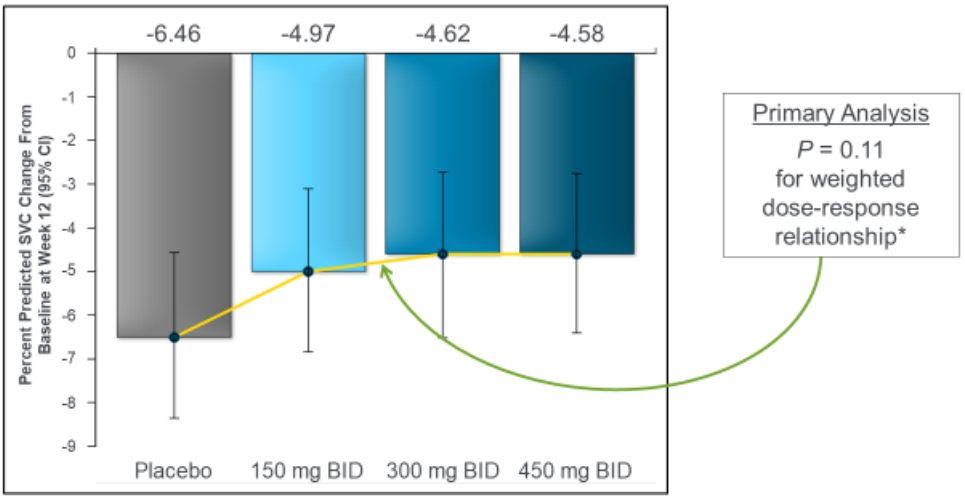
Since we plan to conduct the trial in different regions of the world, including Europe, Canada, Australia and the US, standard of care regarding ALS for the local region as determined by the physician in discussion with the patient should be followed. Standard of care may include, but is not limited to, therapies for the treatment of ALS that have been approved in the respective regions where the trial is conducted.

4.2. Scientific Rationale for Study Design

CY 5031 is a Phase 3 clinical trial intended to evaluate the safety and efficacy of reldesemtiv for the treatment of patients with ALS, based on the results of a Phase 2 clinical trial, CY 5022. In

CY 5022, 458 patients with ALS were randomized 1:1:1:1 to 12 weeks of treatment with placebo versus reldesemtiv at 150 mg, 300 mg, or 450 mg twice daily. The primary efficacy analysis of the weighted dose response of change from baseline to 12 weeks in slow vital capacity (SVC, analyzed using a Mixed Model for Repeated Measures (MMRM) with multiple contrasts) was not statistically significant (p = 0.11); however, the decline in SVC was less than on placebo in all three reldesemtiv treatment groups (Figure 2).

Figure 2: CY 5022 Primary Endpoint – SVC Change from Baseline to Week 12



*Based on Mixed Model for Repeated Measures (MMRM) with the contrasts of (-5, -1, 3, 3) for placebo, reldesemtiv 150 mg, 300 mg and 450 mg bid, respectively

In a post-hoc analysis, the change from baseline to 12 weeks in the ALSFRS-R total score for all three reldesemtiv dose groups pooled versus placebo did achieve nominal statistical significance (LS mean difference = 0.9 points favoring reldesemtiv, p = 0.01; Figure 3). In addition, when the CY 5022 population was divided into tertiles based on the calculated rates of pre-study ALS progression, the apparent benefit of reldesemtiv in the three active treatment groups pooled versus placebo was particularly evident among the two faster progressing tertiles relative to the slowest progressing tertile (Figure 4). This replicates earlier observations that a reduction in measures of ALS disease progression by an intervention is less easily demonstrated among patients whose ALS was progressing relatively slowly prior to enrollment.

Figure 3: CY 5022 – ALSFRS-R Change from Baseline Over Time (All Active vs Placebo)

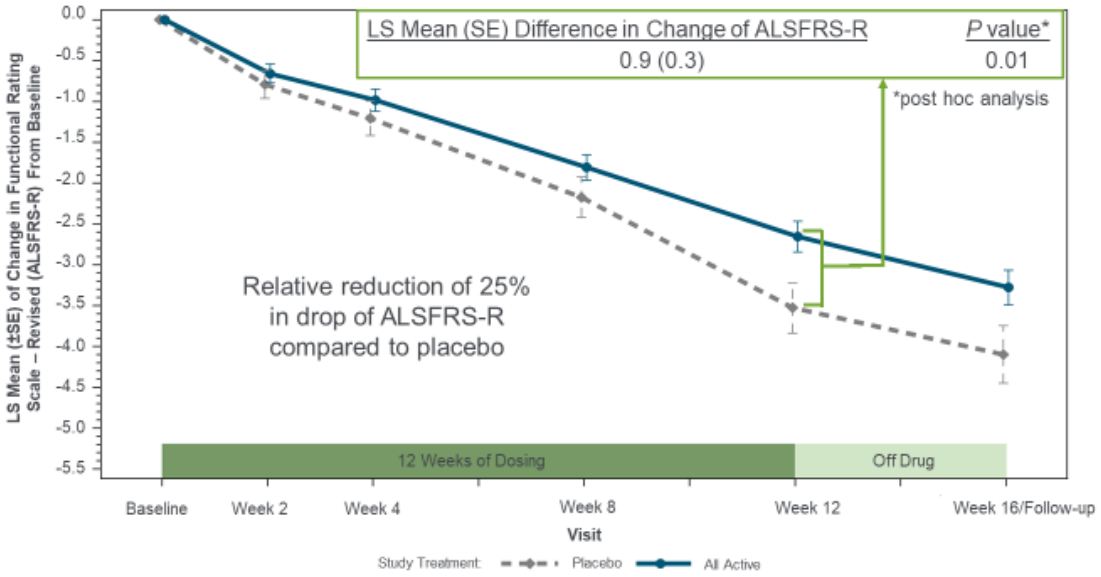
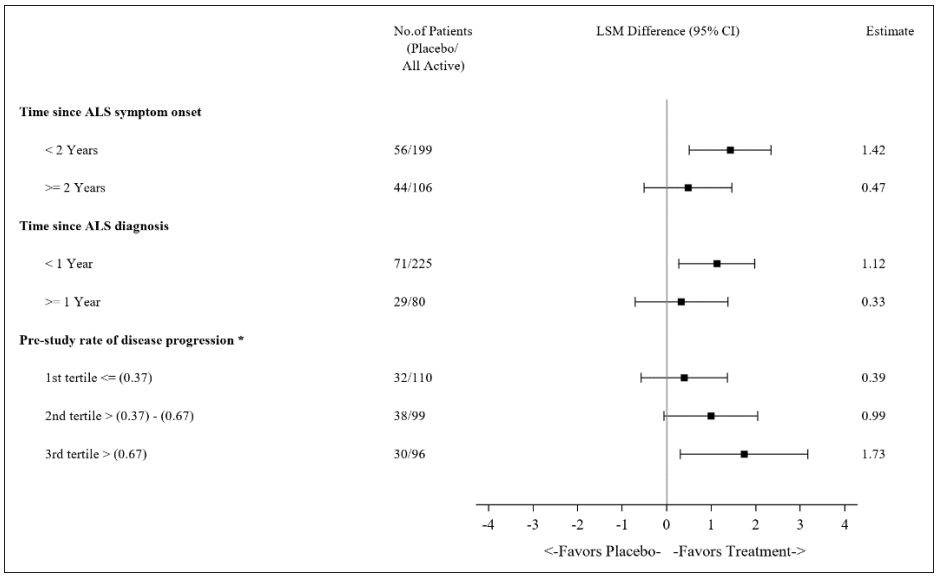


Figure 4: CY 5022 – Subgroup Analyses of ALSFRS-R Total Scores



Subsequent examination of the data from CY 5022 revealed that most (but not all) patients in the slowest progressing tertile had ALS symptoms for > 24 months and/or an ALSFRS-R total score at baseline > 44. Consistent with the above observations, the apparent effect of reldesemtiv to decrease the decline in the ALSFRS-R total score from baseline to 12 weeks versus placebo was substantially more evident in the group of patients in CY 5022 with ALS symptoms for ≤ 24 months and an ALSFRS-R total score at baseline ≤ 44. Consequently, in CY 5031, patients with ALS symptoms for > 24 months are excluded as are patients with an ALSFRS-R total score at screening > 44 (with certain exceptions as set forth in Section 5.1).

A placebo control and double-blinded approach are employed in this trial to avoid bias in data collection, including the safety assessments and pharmacodynamics (PD) measures that comprise the primary and secondary endpoints.

4.3. Justification for Dose

The principle for dose selection is to ensure the potential benefits outweigh the risks of treatment with reldesemtiv, based on data from the dose ranging trial of CY 5022. In the Full Analysis Set (FAS), all three reldesemtiv dose levels appeared to be pharmacodynamically active. The totality of data in CY 5022 suggested that the three reldesemtiv dose levels had similar effects on ALSFRS-R and SVC; however, the more complete experience in the reldesemtiv clinical development program (as well as the clinical experience with tirasemtiv, another fast skeletal muscle troponin activator with a mechanism of action identical to that of reldesemtiv) indicates that higher exposures are associated with greater increases relative to placebo in skeletal muscle force production. Consequently, there is a rationale for using the highest dose of reldesemtiv that is safe and well tolerated in CY 5031.

The 450 mg dose level was associated with a higher rate of AEs related to nausea, decline in eGFR, elevations in ALT and AST and early terminations (compared to the 300 mg and 150 mg dose levels) in CY 5022. The dose selected for CY 5031 is 300 mg bid based on better tolerability compared to 450 mg bid with relatively similar efficacy between the two doses. A down titration to one tablet bid (for those assigned reldesemtiv, the dose would then be 150 mg bid) may be implemented for patients who experience an adverse event (AE) that is believed to be study drug related. See Section 6.6 for details regarding dose modification. Since elevations in transaminases and declines in $eGFR_{CysC}$ were dose related, by resuming drug at a lower dose for the remainder of the trial, the reoccurrence of the lab abnormality is expected to be less likely to occur.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last patient in the trial.

5. STUDY POPULATION

Before patients begin any study-specific activities/procedures, Cytokinetics requires a copy of the site's institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form (ICF), and all other patient information and/or recruitment material, if applicable. A signed ICF must be obtained from each patient before commencement of any study-specific activities/procedures.

A patient is considered entered into the trial after signing the informed consent. After confirming the patient has met all eligibility criteria, randomization will then occur before the first dose on Day 1 is administered. The site is to document the informed consent signature and randomization date in the patient's medical record and in/on the case report form (CRF).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exceptions, is not permitted.

5.1. Inclusion Criteria

Patients are eligible to be included in the trial only if all the following criteria apply:

101. Able to comprehend and willing to sign an ICF and willing to comply with all study procedures and restrictions for the duration specified in the Schedule of Activities (SoA; Section 1.3). If patient is able to comprehend and is willing to sign the ICF, but cannot physically sign the ICF, an impartial witness must sign the ICF form.
102. Males and females between 18 and 80 years of age, inclusive, at screening.
103. Diagnosis of familial or sporadic ALS (defined as meeting the laboratory-supported probable, probable, or definite criteria for ALS according to the World Federation of Neurology El Escorial criteria published in 2000 [Brooks 2000]). Patients who meet the possible criteria are eligible if they have lower motor neurone findings; those who have purely upper motor neurone findings are ineligible.
104. First symptom of ALS ≤ 24 months prior to screening. The qualifying first symptoms of ALS are limited to manifestations of weakness in extremity, bulbar, or respiratory muscles. Cramps, fasciculations, or fatigue should not be taken in isolation as a first symptom of ALS.
105. ALSFRS-R total score ≤ 44 at screening. Patients with a total score of 45 or higher may be rescreened 60±7 days following the original screening date and be deemed eligible if their ALSFRS-R total score is ≤ 44 or if their score is 2 or more points less than at initial screening. Such patients must continue to meet all other inclusion/exclusion criteria at the time of rescreening.
106. Upright FVC ≥ 65.0% of predicted for age, height, sex and ethnicity at screening according to Global Lung Initiative equation (Quanjer 2012).
107. Able to perform reproducible pulmonary function tests defined as being able to perform FVC at screening with variability of the 2 highest raw values of less than 10% with a maximum of 5 trials permitted. Screening FVC results must be reviewed and approved by the central review process prior to randomization.

108. Must be either on riluzole for ≥ 30 days prior to screening or not have taken it for at least 30 days prior to screening
109. Must have completed at least 2 cycles of edaravone at the time of screening or not have received it for at least 30 days prior to screening
110. Clinical laboratory findings within the normal range, or if outside the normal range, not deemed clinically significant by the Investigator, except as specifically indicated as laboratory exclusion in Section 5.2.
111. Able to swallow whole tablets.at the time of screening
112. Male patients, who have not had a vasectomy with medical assessment of surgical success, or a confirmed sperm count of zero, are eligible to participate if they agree to the following during the trial and for at least 10 weeks after the last dose of study drug:

    a. Refrain from donating sperm

    Plus when their female partner is of childbearing potential must either:

    b. Be abstinent from heterosexual intercourse and agree to remain abstinent

    OR

    Must agree to use a male condom AND have his female partner use a highly effective method of contraception during the study (as described in Appendix 3 [Section 10.3]) , and also for at least 4 weeks after the last dose of study drug.
113. A female patient is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

    a. Is not a woman of childbearing potential (WOCBP; as described in Appendix 3 [Section 10.3])

    OR

    Is a WOCBP and using a highly effective method of contraceptive during the study (as described in Appendix 3 [Section 10.3]) and also for at least 4 weeks after the last dose of study drug, and her male partner must agree to use a male condom during the trial and for at least 4 weeks after the last dose of study drug.

    b. A WOCBP must have a negative pregnancy test (urine or serum as required by local regulations) within 3 days before the first dose of study drug.

    Note: The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

    Contraceptive use by men or WOCBPs should be consistent with the guidance in Appendix 3 (Section 10.3) and local regulations regarding the methods of contraception for those participating in clinical studies.
114. Able to complete all screening procedures.
115. Must be either on the combination product (brand name only) of sodium phenylbutyrate and taurursodiol (also known as TUDCA, ursodoxicoltaurine or Tauroursodeoxycholic

acid) for ≥ 51 days prior to screening or not have taken it for at least 30 days prior to screening

5.2. Exclusion Criteria

Patients will be excluded from the trial if any of the following criteria apply:

201. Other medically significant neurological conditions that could interfere with the assessment of ALS symptoms, signs or progression.
202. Presence at screening of any medically significant cardiac, pulmonary, gastrointestinal, 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. Poorly controlled systemic hypertension
    b. Clinically significant electrocardiogram (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
    e. Gastrointestinal disorder that is likely to impair absorption of study drug from the gastrointestinal tract
    f. $eGFR_{Cr}$ and $eGFR_{CysC}$ < 45.0 mL/min/1.73 m^2 at screening
    g. ALT or AST ≥ 3×ULN at screening
    h. Urine protein creatinine ratio > 1 mg/mg (113 mg/mmol) at screening
    i. Total bilirubin (TBL), direct or indirect bilirubin above the ULN.
    j. History of Gilbert's Disease, Dubin-Johnson syndrome, or Rotor syndrome
    k. Poorly controlled or brittle diabetes mellitus
    l. Amputation of a limb
    m. Cognitive impairment, related to ALS or otherwise that impairs the patient's ability to understand and/or comply with study procedures and provide informed consent
    n. Cancer currently being treated (other than basal cell carcinoma, carcinoma in situ of the cervix, or squamous cell carcinoma of the skin excised with clean margins) or a history of cancer with an expected survival of less than 5 years. Breast cancer survivors with an expected survival of ≥ 5 years who are on long-term endocrine therapy are eligible.
    o. Any other condition, impairment or social circumstance that, in the opinion of the Investigator, would render the patient not suitable to participate in the trial
    p. Patient judged to be actively suicidal or a suicide risk by the Investigator
203. Known to have received reldesemtiv or tirasemtiv in any previous clinical trial
204. Has received or is considering receiving during the course of the trial any form of gene therapy (including antisense therapy) for the treatment of ALS
205. Has received or is considering receiving during the course of the study any form of stem cell therapy for the treatment of ALS
206. Has received or is considering obtaining during the course of the trial a diaphragmatic pacing system

207. 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
208. Use of a medication that is an OCT1/OCT2 substrate within 7 days prior to first dose of study drug per Appendix 4 (Section 10.4)
209. Currently participating in another trial, managed access program, open label extension, early access program, or through the right to try act is receiving an investigational drug or received an investigational drug or device within 30 days (or 5 half-lives for drugs, whichever is longer) prior to screening. Patients also cannot be taking outside of a clinical trial certain investigational drugs (which includes drugs, supplements, and nutraceuticals) within 30 days of screening (or 5 half-lives for drugs, whichever is longer) that are currently being studied or have been studied for the treatment of ALS. A full listing of excluded agents can be found in the Study Manual.
210. Has a tracheostomy
211. Known to have hypersensitivity to study drug, placebo or excipients

5.3. Lifestyle Considerations

Not applicable.

5.4. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical trial but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics, reason for screen failure, eligibility criteria, and any serious adverse events (SAEs) related to study-related procedures.

The screening eligibility period is 21 days as defined in Section 4.1. An individual who does not meet the criteria for participation in this trial is referred to as a screen failure.

5.4.1. Rescreening

Patients may be rescreened one time after initial screening for any of the following reasons:

- ALSFRS-R value at original screening > 44. To be eligible, a patient's ALSFRS-R total score at rescreening must be ≤ 44 OR there is a drop in the score of 2 or more points compared to their original screening score. Rescreening for this reason must be done 60 days (±7 days) after initial screening
- Not on stable edaravone or riluzole doses at original screening. To be eligible, if taking riluzole, must be on riluzole for 30 days prior to rescreening or not taking it for 30 days prior to rescreening; if taking edaravone, must have completed at least 2 cycles of edaravone at the time of rescreening or not received it for at least 30 days prior to rescreening. If taking the combination product (brand name only) of sodium phenylbutyrate and taurursodiol, must be on it for ≥ 51 days prior to rescreening or not

have taken it for at least 30 days prior to rescreening. Rescreening may occur once the necessary time interval has passed.

- Poorly controlled systemic hypertension at original screening. Rescreening may occur once the hypertension is adequately controlled
- Received an investigational device or drug or a prohibited drug as described in Section 5.2, Item 209, within 30 days (or less than 5 half-lives, whichever is longer), at original screening. Rescreening may occur once the necessary time interval has passed.
- Was outside the screening window for their original Day 1 visit. Rescreening may occur once scheduling permits both rescreen and Day 1 visits to occur within the 21-day window

Patients must re-sign an informed consent before they are rescreened. At rescreening, they must meet all inclusion/exclusion criteria at the time of rescreening and have all elements of the screening visit performed again to be eligible. Patients may only rescreen once.

If an element of the screening visit could not be performed for logistical reasons (eg, trained evaluator was out sick, lab kits or outcome measure device was unavailable) the patient can return within the screening eligibility period to complete the visit.

Retesting for abnormal lab work within the original screening period may also be performed if there is reason to believe the repeat labs may improve and not be clinically significant and the patient is otherwise eligible to participate. Patients cannot be retested for abnormal bilirubin laboratory results. Patients who are retested for abnormal laboratory results during the original screening eligibility period do not need to re-sign an informed consent.

No waivers will be granted regarding inclusion/exclusion criteria.

6. INVESTIGATIONAL PRODUCT

This section describes any study drug: investigational product (IP) (ie, reldesemtiv) or placebo intended to be administered to a trial patient according to the protocol.

6.1. Study Drug Administered

Table 2: Study Drug

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

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

6.2. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IP received and any discrepancies are reported and resolved before use of the IP.

Only patients randomized in the trial may receive study drug and only authorized site staff may supply or administer study drug. All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. Study drug may be shipped to patients by the site to avoid drug interruption.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, chain of custody, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study drug are provided in the Pharmacy Manual.

IP should be stored at or below 25°C.

6.3. Measures to Minimize Bias: Randomization and Blinding

All patients will be centrally assigned to randomized study drug using an Interactive Web Response System (IWRS). Before the trial is initiated, the log in information & directions for the IWRS will be provided to each site.

Study drug will be dispensed at the study visits summarized in the SoA (Section 1.3). Returned study drug should not be re-dispensed to the patients.

The IWRS will be programmed with blind-breaking instructions and the unblinding procedure is documented in the IWRS User Manual. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact Cytokinetics prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, Cytokinetics must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF, as applicable.

An unblinded physician (unmasked to renal labs but blinded to treatment assignments) who is not on the study team may direct a study drug interruption and a down-titration of patients based upon review of unmasked renal function laboratory values that meet the prespecified criteria (Section 6.6 and Section 7.3). In order to preserve blinding of site staff and the study operation team, a small number of placebo patients will be selected for dummy down-titration during the study by the unblinded Clinical Research Organization (CRO) physician and will undergo repeat laboratory testing similar to what could be directed for patients receiving active treatment with laboratory abnormalities. The blinded down-titration selection criteria and records will be documented by the unblinded physician and the unblinded statistician separately. In order to maintain the blind, placebo patients who had a dummy down-titration during the double-blind dosing period will take 150 mg bid of reldesemtiv during the active drug period.

The randomization treatment assignments for individual patients will remain blinded to site staff and patients until the entire study is completed and the database is locked.

6.4. Study Drug Compliance

When patients are dosed at the site, the route, the date and time of the dose administered in the clinic will be recorded in the source documents and recorded in the CRF.

When patients self-administer study drug at home, compliance with study drug will be assessed at each visit. Compliance will be assessed by counting returned tablets during the in-clinic visits,

through documentation in the patient's dosing diary, the source documents and the CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

All study drug should be taken either with food or within 2 hours following eating food. Water may be consumed ad libitum.

- During the study, patients who lose the ability to swallow tablets can continue in the study taking crushed tablets. The crushed tablet dose can be administered either as: Crushed tablets in approximately 30 mL (2 tablespoons) of applesauce (or a vehicle of similar consistency) administered orally, followed by up to 250 ml (one cup) of water
- Crushed tablets suspended in approximately 3 tablespoons of water administered through a PEG tube, preceded and followed by 118 mL (1/2 cup) of water to flush the tube

A record of the number of study drug tablets dispensed to and taken by each patient must be maintained and reconciled with study drug and compliance records. Study drug dosing start and stop dates, including dates for dosing delays and/or dose reductions, and date of route change, will also be recorded in the CRF.

6.5. Concomitant Therapy

Any medication, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, that the patient is receiving at the time of enrollment or receives during the trial must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose, frequency and route of administration

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Patients may continue to take prescription medications and non-prescription medications which in the opinion of the investigator and the Medical Monitor, will not interfere with the trial.

During the trial, medications and doses should remain stable whenever appropriate. However, investigators may prescribe or adjust any concomitant medication or treatment deemed necessary to provide adequate supportive care.

Prior use of riluzole, edaravone and the combination product (brand name only) of sodium phenylbutyrate and taurursodiol, even if stopped prior to screening, will be recorded along with the reason why it was stopped (patient choice, adverse event, cost). Patients should neither stop nor start edaravone, riluzole or the combination product of sodium phenylbutyrate and taurursodiol following randomization. However, it is recognized that changes in medications may occur including those due to the development of adverse events potentially related to these medications or changes in insurance coverage. Patients who start or stop edaravone, riluzole and the combination product (brand name only) of sodium phenylbutyrate and taurursodiol following randomization will be permitted to continue in the trial.

Drug-Drug Interactions

Medications that strongly inhibit the activity of CYP3A4 should be avoided from 7 days before the start of dosing (Day 1) through the last day of dosing (Week 48). Medications that strongly induced the activity of CYP3A4 should be avoided from 14 days before the start of dosing (Day 1) through the last day of dosing (Week 48). Please refer to Appendix 4 (Section 10.4) for the most common strong inhibitors and inducers of CYP3A4. Medications that are OCT1/OCT2 substrates should be avoided from 7 days before the start of dosing or used with caution during the trial, as reldesemtiv may have the potential to inhibit OCT1 and OCT2-mediated transport. Please refer to Appendix 4 (Section 10.4) for the most common OCT1/OCT2 substrates that should be avoided or used with caution.

6.6. Dose Modification

Any dose interruption, as described in Section 7.1 must be documented in the CRF and include the reason for stopping, the stop date, and the restart date. For study drug dose management in relation to renal or hepatic abnormal laboratory values, see Section 7.3 and Section 7.4.

Following a dose interruption for adverse events other than those related to renal labs, if the adverse event is thought to be potentially related to study drug, the investigator may restart the study drug when symptom(s) have resolved or have substantially improved, and there are no safety concerns before resuming the study drug. If the patient has been off study drug for more than 7 days, the investigator may choose to see the patient in the clinic or via telemedicine prior to resuming study drug. While investigators are encouraged to resume dosing at 2 tablets twice a day, down-titration of the dose to 1 tablet twice a day is an option. If the patient resumed the study drug at 2 tablets twice a day and has recurrence of the AE, the investigator once again should have the patient temporarily interrupt dosing until the symptom(s) have resolved or have substantially improved, and there are no safety concerns before resuming the study drug. If the study drug is resumed, the patient should be down-titrated to 1 tablet twice a day.

Once down-titration occurs for any reason, no subsequent up-titration to the prior dose should occur.

6.7. Access to Investigational Product after the End of the Study

Assuming continuing development of reldesemtiv in ALS, Cytokinetics has put in place an open label extension study for patients who complete dosing through Week 48 in CY 5031. Participation in the open label extension study is at the discretion of the patient and not a condition of participation in CY 5031.

7. TEMPORARY INTERRUPTION OF STUDY DRUG, DISCONTINUATION OF STUDY DRUG, AND PATIENT CONSENT WITHDRAWAL

Unless a safety concern arises, the investigator should make every effort to keep a patient on study drug for as long as possible during the trial. The degree to which a patient withdraws from the trial varies. There are three types of discontinuation: temporary study drug interruption, permanent study drug discontinuation and patient withdrawal of consent.

7.1. Temporary Study Drug Interruption

Initially, any study drug interruption should be considered temporary unless permanent study drug discontinuation is mandated by the protocol.

A temporary study drug interruption:

- Will be implemented when a predefined safety threshold has been met (see Section 7.3 for Renal Function Monitoring.
- May be considered by the investigator in the case of an AE/SAE or for another reason.

If a temporary study drug interruption occurred because a safety threshold was met, blinded treatment may be resumed at a lower dose as outlined in Section 7.3 (Renal Function Monitoring).

If the study drug was temporarily interrupted because of an AE/SAE that was not felt to be related to study drug, the investigator should make the best effort to resume study drug as soon as practically possible, assuming there are no remaining safety concerns.

If dosing is interrupted for more than 7 consecutive days, based upon clinical judgement, the investigator may choose to see the patient in clinic or via telemedicine prior to study drug resumption.

All temporary study drug interruptions (stop and start dates and times and reason for interruption) should be recorded in the CRF and the Medical Monitor should be notified.

7.2. Permanent Discontinuation of Study Drug

There are two types of permanent discontinuation of study drug:

- Temporary study drug interruption that becomes a permanent discontinuation:
    - After a temporary study drug interruption, if a safety concern for the patient has not stabilized or resolved or if the investigator suspects that study drug may be responsible, the investigator may consider the temporary interruption to be a permanent discontinuation. Permanent discontinuation of study drug should be considered as a last resort.
    - The investigator should make best efforts to contact the Medical Monitor before considering any temporary interruption as a permanent discontinuation.
- Permanent study drug discontinuation that is not preceded by a temporary study drug interruption

- The investigator should make best efforts to contact the Medical Monitor before considering any permanent study drug discontinuation.

In all cases, patients should be encouraged to discuss stopping study drug with the investigator or the investigator's designee. See Section 6.6 regarding potential dose reduction of study drug. Best efforts should be made to address the patient's questions, adjust concomitant medical therapies if needed and arrange follow-up safety assessments. All patients should undergo an early discontinuation visit as soon as possible following their last dose taken, unless discontinuation is due to death, withdrawal of consent, or the patient has been lost to follow-up. Refer to Section 7.2.1 for management of patients that permanently discontinue study drug.

Any permanent discontinuation of study drug should be recorded in the CRF including the reason for permanent discontinuation, if a patient is willing to provide it. If the patient is unwilling to provide the reason, that too should be documented.

Reasons for permanent study drug discontinuation may include any of the following:

- Patient request
- Adverse event
- Pregnancy
- Criteria for possible renal toxicity are met (Section 7.3)
- Criteria for possible hepatotoxicity are met (Section 7.4)
- The investigator judges that continued administration of study drug would be detrimental to the patient's safety or well-being
- Protocol violation
- Lost to follow-up
- Any breaking of the study blind requested by the investigator
- Death
- The Sponsor requests that the patient permanently discontinue study drug

7.2.1. Management of Patients after Permanent Discontinuation of Study Drug

If study drug is permanently discontinued, the patient should be encouraged to remain in the trial to continue to obtain outcome measures and safety data.

There are several options for a patient after permanently discontinuing study drug:

- Patient agrees to continue to return to clinic for all remaining in-clinic study visits and agrees to all planned remote visits.
- Patient only agrees to complete the early discontinuation (ED) visit as soon as possible after the decision is made, the follow-up visit 4 weeks after the last dose taken, and additional follow-up visits dependent upon lab results; it is preferred these are done in clinic but can be done remotely if that is not feasible.

- Patient only agrees to complete the ED visit; it is preferred this is done in clinic but can be done remotely if that is not feasible.
- Patient only agrees to remote visits to obtain patient study data. Patients should be strongly encouraged to come into the clinic for Week 24.
- Patient agrees to a mix of remote and in-clinic visits to obtain study data. Patients should be strongly encouraged to come into the clinic for Week 24.
- Patient only agrees to allowing contact for determination of vital status at Week 24 and Week 48
- Patient withdraws consent (see Section 7.6) and does not agree to any further study procedures or visits.

Assessments obtained at the early discontinuation and subsequent follow-up visit are listed in the Schedule of Activities. Details of the assessments to be performed at the additional visits following drug discontinuation, should the patient agree to be followed via either in-clinic or remote visits, can be found in the Study Manual.

Patients that have not withdrawn consent and have difficulty returning for all remaining study visits can be contacted by phone or video call to obtain patient study data.

7.3. Renal Function Monitoring and Study Drug Management

Study drug will be held if:

- $eGFR_{Cr}$ and $eGFR_{CysC}$ < 30.0 ml/min/1.73m^2 or
- urine protein creatinine ratio (UPCR) is ≥ 3 mg protein/mg creatinine (or ≥339 mg protein/mmol creatinine)

Study drug may be restarted at half the dose, or 1 tablet twice a day (150 mg bid for those assigned to reldesemtiv) when:

- $eGFR_{Cr}$ and $eGFR_{CysC}$ is > 40.0 ml/min/1.73m^2 and
- UPCR is ≤ 1.5 mg protein/mg creatinine (or ≥170 mg protein/mmol creatinine)

Serum cystatin C, $eGFR_{CysC}$, serum creatinine, $eGFR_{Cr}$ and urine protein/creatinine ratio in a spot urine will be obtained and a microscopic urinalysis will be performed to look for cells and casts in accordance with the schedule of events; the medical monitors will be blinded to the UPCR (and the associated urinary creatinine and urinary protein), creatinine, serum cystatin C, $eGFR_{CysC}$, and $eGFR_{Cr}$ results. These renal related laboratory results will be reviewed by an unblinded physician who is not serving as the medical monitor for the trial. The unblinded physician will be unmasked to the renal lab results but will remain blinded to treatment assignments. The unblinded physician will contact the clinical trial investigator and medical monitors if laboratory results meet the criteria as described above that necessitate a study drug interruption. The Sponsor, all personnel charged with conduct of the trial outside of monitoring these laboratory data, and study sites will be blinded to the UPCR (and the associated urinary creatinine and urinary protein), creatinine, serum cystatin C, $eGFR_{CysC}$, $eGFR_{Cr}$ results.

Abnormal renal function tests meeting the above criteria will be repeated as directed by the unblinded physician, who will monitor repeat testing. The site investigator and medical monitors should discuss and agree that study drug can be resumed or alternatively permanently discontinued. Agreement by the patient, site investigator, and medical monitor must occur to determine that:

1. The study drug may be re-initiated at the lower dose of 150 mg bid (or placebo), or
2. The study drug should be permanently discontinued

To accomplish this, the unblinded physician may direct the laboratory assessments (serum cystatin C, $eGFR_{CysC}$, serum creatinine $eGFR_{Cr}$, UPCR) to be repeated as often as 2-3 times weekly until a final disposition is reached (ie, re-initiation of study drug or placebo at 150 mg bid or permanent discontinuation) is reached.

Manifestations of renal toxicity, including clinically significant decreases in $eGFR_{CysC}$ and $eGFR_{Cr}$, as well as increases of UPCR, as noted above, are 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.

Criteria for permanent discontinuation of study drug due to potential renal toxicity

Study drug **must** be discontinued permanently if the patient requires hemodialysis.

7.4. Liver Function Monitoring and Study Drug Management

ALT, AST, alkaline phosphatase (ALP) and total, direct, and indirect bilirubin will be obtained in accordance with the schedule of events.

Patients with abnormal hepatic laboratory values [ie, ALP, AST, ALT, total bilirubin (TBL)] or signs/symptoms of hepatitis should be evaluated to determine if the criteria for permanent discontinuation of study drug have been met. Patients who meet the criteria for permanent discontinuation must not be re-challenged. If a PI decides to hold study drug for abnormal lab values that don't meet the mandated threshold, this is also considered a permanent discontinuation and the patient must not be re-challenged.

Criteria for permanent discontinuation of study drug due to potential hepatotoxicity

- Elevation of either AST or ALT according to the following schedule:

Baseline AST or ALT Value	AST or ALT Elevation
Any	>8 × ULN at any time
Any	>5 × ULN but <8 × ULN for ≥2 weeks
Any	>5 × ULN but <8 × ULN and unable to adhere to enhanced monitoring schedule
Any	>3 × ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice)

OR

- TBL >3 × ULN at any time

Study drug **must** be also discontinued permanently if ALL of the criteria below are met:

- TBL >2 × ULN or international normalized ratio (INR) >1.5

  AND

- increased AST or ALT from the relevant baseline value as specified below:

Baseline AST or ALT Value	AST or ALT Elevation
<ULN	>3 × ULN

  AND

- no other cause for the combination of the above laboratory abnormalities is apparent. Important alternative causes for elevated AST/ALT and TBL values include, but are not limited to:
  - hepatobiliary tract disease
  - viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, toxoplasmosis, and Parvovirus)
  - right sided heart failure, hypotension, or any cause of hypoxia to the liver causing ischemia
  - exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
  - heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
  - alpha-one antitrypsin deficiency
  - alcoholic hepatitis
  - autoimmune hepatitis
  - Wilson's disease and hemochromatosis
  - nonalcoholic fatty liver disease including steatohepatitis
  - nonhepatic causes (eg, rhabdomyolysis, hemolysis)

Patients who clearly meet the criteria for permanent discontinuation must never be re-challenged.

Additional Clinical Assessments and Observation

All patients in whom the study drug is permanently discontinued due to meeting the hepatic safety threshold as described above are to undergo a repeat test and a period of "close

observation" until abnormalities have stabilized and returned to normal (or returned to the patient's baseline levels). Assessments that are to be performed during this period include:

- Retesting of AST, ALT, ALP, bilirubin (total and direct), and obtaining an INR within 48 hours
- In cases of TBL >2 × ULN or INR >1.5, retesting of liver tests, bilirubin (total and direct), and INR within 48 hours

Confirmed abnormal liver function tests (LFTs) should be repeated 2-3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the patient is asymptomatic. Follow the patient and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal.

- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL:
  - Obtain complete blood count (CBC) with differential to assess for eosinophilia
  - Obtain serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
  - Obtain serum acetaminophen (paracetamol) levels
  - Obtain viral serologies
  - Obtain creatine phosphokinase, haptoglobin, lactate dehydrogenase, and peripheral blood smear
  - Perform appropriate liver imaging if clinically indicated
- Obtain a more detailed history of:
  - Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity type reactions, fatigue, nausea, vomiting and fever
  - Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Obtain appropriate blood sampling for pharmacokinetics (PK) analysis if this has not already been collected
- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)

Clinically significant elevated transaminases and/or bilirubin and manifestations of liver toxicity (eg, 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 must be recorded on the appropriate CRF and reported to Cytokinetics Drug Safety within 24 hours of awareness.

7.5. Discontinuation from Study Procedures

Not applicable.

7.6. Patient Consent Withdrawal

Patients have the right to withdraw consent and no longer participate in the trial at any time and for any reason without prejudice to their future medical care by the physician or at the institution. Consent withdrawal means the patient no longer wishes to undergo any follow-up visits, study procedures, investigator contact, and non-patient contact follow-up (eg, medical records check).

- Discontinuing study drug should be distinguished from consent withdrawal for follow-up since the patient may agree to undergo study procedures or still be contacted even though they have stopped taking study drug.
- Consent withdrawal should be accompanied by documentation of the reason for withdrawal for patients willing to provide it. If the patient is unwilling to provide the reason, that should be recorded.

Patients who withdraw consent should be asked explicitly about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented.

Preferably, the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unable, the site should document and sign the reason for the patient's failure to withdraw consent in writing; if the patient is unwilling to provide the reason, that too should be documented. The ICF for the trial should note that although a patient is free to leave the trial and stop taking study drug, the investigators hope the patient will remain for follow-up status evaluations.

For patients who have withdrawn consent for further follow-up, investigators and/or a third party retained by Cytokinetics may review public records as permitted by the ICF and applicable law to determine vital status of the patient at the end of the trial or before.

7.7. Lost to Follow Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient or the patient's family and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether the patient wishes to and/or should continue in the trial.
- Before a patient is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the patient or the patient's family (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.

- Should the patient continue to be unreachable, he/she will be considered to have discontinued from the trial and are lost to follow-up.

Closing of specific sites or discontinuation of the trial are handled as part of Appendix 1 (Section 10.1.8).

8. STUDY ASSESSMENTS AND PROCEDURES

There will be up to eight clinic visits and nine remote visits (with most requiring an accompanying phone or video call), with windows to aid in scheduling as shown in Table 3. If a patient visit must be scheduled outside the visit window, the Medical Monitor should be contacted. If a patient is scheduled for an in-clinic visit outside the visit window, the ALSFRS-R should be obtained by phone or video call during the visit window when possible, while the other visit related procedures will be obtained outside of the visit window when the patient is seen in clinic. Day 1 anchors all subsequent study visits.

Table 3: CY 5031 Visit Windows

Visit	Visit Window	Home FVC Window*
Screening: clinic visit/lab		
Start of Dosing (Day 1): clinic visit/lab	Up to 21 days following Screening	1-3 days prior to Day 1
End of Week 2: remote – lab only	14 days ±2 days	
End of Week 4: clinic visit/lab	28 days ±4 days	±2 days of clinic visit
End of Week 8: remote visit/lab	56 days ±4 days	
End of Week 12: clinic visit/lab	84 days ±4 days	±2 days of clinic visit
End of Week 16: remote visit/lab	112 days ±4 days	
End of Week 20: remote visit/lab	140 days ±4 days	
End of Week 24 (last dose of double-blind dosing): clinic visit/lab	168 days ±4 days	1-3 days prior to clinic visit
End of Week 26: remote – lab only	182 days ±2 days	
End of Week 28: remote visit/lab	196 days ±4 days	
End of Week 32: remote visit/lab	224 days ±4 days	
End of Week 36: clinic visit/lab	252 days ±4 days	±2 days of clinic visit
End of Week 40: remote visit/lab	280 days ±4 days	
End of Week 44: remote visit/lab	308 days ±4 days	
End of Week 48 (last dose of active drug dosing): clinic visit/lab	336 days ±4 days	1-3 days prior to clinic visit
Follow-Up (4 weeks after last dose of study drug): clinic visit/lab	364 days ±4 days	1-3 days prior to clinic visit

*With the exceptions noted, home FVC is performed on the same day as other procedures are done for the remote visit

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exceptions are not allowed for inclusion/exclusion criteria.

Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study drug.

Adherence to the trial design requirements, including those specified in the SoA (Section 1.3), is essential and required for trial conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

If scheduled in-clinic visits are not possible, remote visits will be made and documented to review trial assessments, safety, adverse events, provide safety laboratory samples, and concomitant medications as detailed in the Study Manual (see Section 4.1, Overall Study Design for additional details on converting in-clinic visits to remote visits).

8.1. Efficacy Assessments

The sequence of all trial related procedures including the relationship of procedures relative to dosing should be followed as detailed in the Study Manual.

8.1.1. ALSFRS-R

The ALSFRS-R will be performed at each study visit (both in-clinic and remote) as described in the Study Manual. MiToS staging will be determined based upon the responses on the applicable items of the ALSFRS-R.

8.1.2. Pulmonary Function Assessment

The pulmonary function assessment in this trial will be FVC. Pulmonary function assessment will be performed in the clinic at all in-clinic study visits (Screening, Day 1, Week 4, Week 12, Week 24, Week 36, Week 48 and Follow-up [FU]), safety permitting, as described in the Study Manual. It will also be performed using the home spirometer ±2 days of the date of the in-clinic visits for Weeks 4, 12, and 36 in addition to 1 to 3 days prior to Day 1, Weeks 24, 48 and FU as shown in Table 3. Finally, it will be done using the home spirometer during the scheduled remote visits at Weeks 8, 16, 20, 28, 32, 40, and 44. If a patient can be seen in the clinic for screening, but FVC cannot be performed for safety reasons, the patient will be provided a home spirometer and perform a home FVC within 2 days following the screening visit; that value will be used for eligibility. If on subsequent in-clinic visits, the FVC cannot be performed in the clinic for safety reasons, that should be documented and only the home FVC linked to that in-clinic visit will be obtained. For all home FVC testing, the test will be performed during a telemedicine call with a trained FVC evaluator.

When an FVC falls below 50%, the site will record if the potential use of NIV was discussed, and if the patient refuses NIV, the reason(s) for the refusal. Details can be found in the Study Manual.

8.1.3. Hand Grip Strength

Hand grip strength will be assessed at all in-clinic study visits as described in the Study Manual. If an in-clinic visit needs to become a remote visit, it will not be performed.

8.1.4. Muscle Strength

Muscle strength measurements of selected muscles will be performed using HHD at all in-clinic study visits as described in the Study Manual. If an in-clinic visit needs to become a remote visit, it will not be performed.

8.1.5. Health Economic Outcomes Measures

During the course of the trial, if the patient is prescribed and agrees to obtain, and/or receives any of the following durable medical equipment (DME), reason for obtaining, timing and extent of use will be recorded as described in the Study Manual:

- Non-invasive ventilation (including type of device)
- Gastrostomy tube
- Manual wheelchair
- Power wheelchair
- Augmentative and alternative communication (including type of device)

Obtaining information about the DME use should be obtained at every in-clinic and remote visit.

EQ-5D-5L and the EQ-VAS are standardized measures of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. They will be administered at time points as indicated in the SoA (Section 1.3) and as described in the Study Manual. If an in-clinic visit in which the EQ-5D-5L and the EQ-VAS are scheduled to be performed becomes a remote visit, they will both still be obtained.

8.1.6. Quality of Life

The following quality of life questionnaire will be utilized at multiple study visits as specified in the SoA (Section 1.3) and described in the Study Manual:

- ALSAQ-40

If an in-clinic visit in which the ALSAQ-40 is scheduled to be performed becomes a remote visit, the ALSAQ-40 will still be obtained.

8.1.7. Structured Patient Interviews

At a subset of participating US centers, English language-speaking patients enrolled will have a qualitative patient interview within two weeks of completing the Week 24 visit (sometime between Week 22 and Week 24).

The interview will be conducted by phone and will collect information in the patient's words regarding their perceptions of functionality and ALS symptom burden, activities of daily living, and experiences in the trial.

8.1.8. Hospitalizations

Hospitalizations experienced by a patient following randomization and occurring in the context of a serious adverse event will be determined by the Investigator as being either related to ALS, unrelated to ALS, or indeterminate. Hospitalizations deemed related to ALS cover those that are

both related to disease progression, hospitalizations that may occur to address an ongoing ALS symptom or to be preventative (such as hospitalization for a PEG / RIG tube), as well as those to address a complication of a treatment being received for ALS. This information will be recorded and entered into the EDC. Hospitalizations that are for social reasons, or those that were planned prior to the patient signing the ICF are not considered SAEs and therefore relationship to ALS will not be recorded. Further details are described in the Study Manual.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

A routine physical examination will be performed at Screening, and an abbreviated physical examination (consisting of an examination of general appearance, skin, lungs, cardiovascular and abdomen) will be performed at the Follow-Up visit. If the Follow-up visit is converted to a remote visit, the parts of the exam that can be done utilizing telemedicine/video call should be performed.

8.2.2. Vital Signs

Heart rate, blood pressure, and respiratory rate (measured after the patient has been resting and seated for at least 3 minutes), will be obtained at all in-clinic study visits. Temperature will also be obtained at the Screening visit. Height is obtained only at the screening visit; it should only be a historical height if the patient is unable to stand. Weight will be obtained at each in-clinic study visit; and body mass index (BMI) will be calculated at screening and subsequent visits. If the pulse is <50 or >100 bpm, mean systolic blood pressure <90 or >160 mm Hg; mean diastolic blood pressure <50 or >100 mm Hg or the respiratory rate is <10 or >20 breaths per minute, the out of range vital sign should be re-checked following the patient resting for 10 minutes in the seated position. If the in-clinic visit is converted to a remote visit, vital signs will not be performed.

8.2.3. Electrocardiograms

A 12-lead ECG will be obtained as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

Patients should be sitting or supine prior to the ECG for at least 5 minutes. The investigator may perform additional ECG recordings as needed for the care of the patient.

For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings.

Unscheduled ECGs may be collected at additional time points, for example in case of an AE or based on vital signs, as determined by the investigator or the Medical Monitor.

All ECG tracings will be kept as part of the patient's permanent study file at the clinical site. Digital recordings will be analyzed and stored at a central ECG laboratory.

If an in-clinic visit is converted to a remote visit, an ECG will not be obtained.

8.2.4. Neurological Examinations

A brief neurological exam will include assessments of specific cranial nerves (eye, face, and tongue movements), motor strength in specific muscles, evaluation of deep tendon and bilateral plantar reflexes, sensory testing, and tests of co-ordination (limited to finger-to-nose and heel-to-shin when possible to assess). This will be administered at screening, Week 24, and at Follow-Up visit as described in the Study Manual. If the Week 24 or Follow-up visits are converted to a remote visit, the parts of the exam that can be performed using telemedicine/video call should be performed.

8.2.5. Laboratory Assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and see the SoA (Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the trial in the AE section of the CRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease; if the abnormal laboratory finding is felt to be associated with the underlying disease but is judged by the investigator to be more severe than expected for the patient's condition it should be recorded as such.

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

8.2.6. Beck Depression Inventory-Fast Screen (BDI-Fast Screen)

The BDI-Fast Screen will be assessed at all in-clinic study visits as described in the Study Manual. If an in-clinic visit is converted to a remote visit, the BDI-Fast Screen will not be obtained; however, while asking the patient about adverse events, the site will query the patient about symptoms of depression or suicidal thoughts.

8.3. Adverse Events and Serious Adverse Events

8.3.1. Adverse Events

8.3.1.1. Definition of Adverse Event

An **AE** is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not related to study drug.

Adverse events include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after IP administration even though it may have been present before the start of the trial.

- Abnormal assessments, eg, change on physical examination, ECG findings, if they represent a clinically significant finding that was not present at trial start or worsened during the course of the trial.
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which was not present at trial start or worsened during the course of the trial, require treatment, or led to dose reduction, interruption or permanent discontinuation of IP. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

8.3.1.2. Definition of Serious Adverse Event

A **SAE** is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening, NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is an important medical event

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events include invasive or malignant cancers; intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

An adverse event would meet the criterion of “requires hospitalization,” if the event necessitated an admission to a health care facility (eg, overnight stay).

The following reasons for hospitalization are exempted from being reported:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons.

- Hospitalization for pre-planned (ie, planned prior to signing informed consent) surgery or standard monitoring of a pre-existing disease or medical condition that did not worsen, eg, hospitalization for coronary angiography in a patient with stable angina pectoris.

However, complications that occur during an exempted hospitalization are AEs or SAEs (for example if a complication prolongs a pre-planned hospitalization).

8.3.1.3. Severity of Adverse Events

The investigator must assess the severity for each AE and SAE reported during the trial.

Severity describes the intensity (severity) of a specific event and is different from seriousness, which is based on patient/event outcome or action criteria and serves as a guide to determine the regulatory reporting obligations. The severity should be assessed by assigning a Grade of 1, 2, 3, 4 or 5 according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, as defined below:

- Grade 1 (Mild): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 (Moderate): minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*.
- Grade 3 (Severe): Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
- Grade 4 (Life-Threatening): Life-threatening consequences; urgent intervention is indicated
- Grade 5 (Fatal): Death related to AE

* Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

If the severity of an AE worsens during IP administration, only the worst severity should be reported on the AE page. If the AE lessens in intensity, no change in the severity is required.

8.3.1.4. Relationship to Study Drug

Each AE must be assessed by the investigator, based on clinical judgment, as to whether or not there is a reasonable possibility of causal relationship to study drug and reported as either related or unrelated.

- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Cytokinetics. However, it is very important that the investigator always assesses causality for every event before the initial transmission of the SAE data to Cytokinetics.
- The investigator may change his/her opinion of causality considering follow-up information and send an SAE follow-up report with the updated causality assessment.

8.3.1.5. Relationship to Study Procedures

An AE is defined as related to study procedures if it appears to have a reasonable possibility of a causal relationship to protocol-required procedures.

8.3.1.6. Reporting of AEs

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the patient that occur after starting the study drug through end of study are recorded in the AE CRF. In addition, during the screening period (after signing of the informed consent until study drug administration), serious adverse events considered related to study procedures are also to be recorded in the AE CRF.

ALS is a progressive and uniformly fatal neurodegenerative disorder associated with relentlessly progressive loss of motor function, including appendicular, craniobulbar, and respiratory function due to the degeneration of the upper and lower motor neurons which control and innervate the voluntary skeletal muscles. The following conditions are anticipated to occur in the study population as signs/symptoms of ALS progression and do not need to be recorded as an AE unless they meet the criteria for an SAE, are felt to be related to the study drug, or they are occurring outside what is expected for the normal course of the disease (Brown 2017).

Table 4: Signs and Symptoms Commonly Associated with ALS

MedDRA Preferred Term[a]	MedDRA Preferred Term[a]
Dysarthria	Muscle spasticity
Dysphagia	Muscle contractions involuntary
Dyspnoea	Muscle spasms
Gait disturbance	Muscular weakness

[a] MedDRA Version 23.0

8.3.1.7. Reporting Procedures for SAEs

Prompt notification by the investigator to Cytokinetics of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of an IP under clinical investigation are met.

The investigator is responsible for ensuring that all SAEs observed by the investigator or reported by the patient that occur after study drug initiation through end of study, or four weeks

after the last administration of study drug, whichever is later, and SAEs related to study procedures occurring during the screening period (from signing the informed consent until study drug initiation), are recorded in the AE CRF and reported to Cytokinetics on an SAE Report Form and within 24 hours following the investigator's knowledge of the event.

SAE Report forms must be emailed or faxed to Cytokinetics Drug Safety (contact details are provided on the SAE Report form):

Email: CY5031DrugSafety@cytokinetics.com

Facsimile: +1 (650) 243-4199

The investigator must attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

The investigator must complete the SAE Report form in English and must assess the causal relationship of the event to study drug.

If the patient is hospitalized in a hospital other than the study site, it is the investigator's responsibility to contact this hospital to obtain all SAE relevant information and documentation.

New information relating to a previously reported SAE must be reported to Cytokinetics within 24 hours following knowledge of the new information. Cytokinetics Drug Safety may contact the investigator to obtain further information.

8.3.1.8. Follow-up of AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Cytokinetics to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a patient dies during participation in the trial or during a recognized follow-up period, the investigator is encouraged to provide Cytokinetics with a copy of any post-mortem findings including histopathology if it has been performed.

Non-serious adverse events must be followed until they resolve or until the patient completes the trial, whichever comes first. Serious adverse events and events of special interest still ongoing at the end of study must be followed up until resolution or stabilization, or until the event outcome is provided, eg, death. Reporting may continue after the follow-up visit and database lock.

New SAEs occurring after the 4-week follow-up period must be reported to the Cytokinetics Drug Safety department within 24 hours of the investigator's knowledge of the event, only if considered by the investigator to be causally related to previous exposure to the study drug.

8.3.1.9. Regulatory Reporting

The reference safety document to assess expectedness of a suspect serious adverse reaction and reported by Cytokinetics to Health Authorities, IRBs/IECs, and investigators is the reference safety information section of the IB for reldesemtiv.

Cytokinetics will report SAEs and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and good clinical practice.

The investigator is to notify the appropriate IRB/IEC of SAEs occurring at the site and other adverse event reports received from Cytokinetics, in accordance with local procedures and statutes.

8.3.1.10. Pregnancy and Breastfeeding

Female Patients Who Become Pregnant

If a female patient becomes pregnant while on study drug, study drug must be discontinued. The investigator must counsel the patient and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

Please refer to Appendix 3 (Section 10.3) regarding contraceptive guidance. Irrespective of the treatment received by the patient, any pregnancy occurring in a female patient, or female partner of a male patient, after study drug initiation up to 4 weeks following study drug discontinuation must be reported to Cytokinetics within 24 hours of the investigator's knowledge of the event.

Pregnancies must be recorded in the CRF and reported on the Cytokinetics Pregnancy Report Form, which is emailed or faxed to Cytokinetics Drug Safety (contact details are provided on the Pregnancy Report Form):

Email: CY5031DrugSafety@cytokinetics.com

Facsimile: +1 (650) 243-4199

Note: Sites are not required to provide any information on the Pregnancy Report Form that violates the country or region's local privacy laws.

Details of all pregnancies in female patients and female partners of male patients will be collected after the start of study drug and until the conclusion of the pregnancy. The follow-up of an infant (if applicable) will be conducted up to 12 months after the birth of the child.

Any pregnancy complication or elective termination of a pregnancy for medical reasons must be reported as an AE or SAE.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

A developmental delay of an infant, or suspected adverse reactions in a neonate will be reported as an adverse event or serious adverse event.

Any post-study pregnancy-related SAE considered reasonably related to study drug by the investigator will be reported to Cytokinetics as described in Section 8. While the investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.

Male Patients with Partners Who Become Pregnant

If a male subject fathers a child while on study drug, he may continue receiving treatment; however, he must use barrier method (ie, condom) during sexual intercourse to avoid further fetal exposure.

The investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this trial.

After obtaining the necessary signed ICF from the pregnant female partner directly, the investigator must complete the Pregnancy Report Form and submit it to Cytokinetics within 24 hours of receipt of the partner's consent. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Cytokinetics.

Female Patients Who Breastfeed

If a female patient breastfeeds while on study drug, study drug will be discontinued.

The investigator will collect breastfeeding information on any female patient who breastfeeds while taking the study drug through 5 days after the end of study drug treatment. The mother and infant health information will be recorded on the Pregnancy Report Form and submitted to Cytokinetics immediately and no later than 24 hours following the investigator's knowledge of event.

8.4. Treatment of Overdose

There is no established treatment for an overdose.

In the event of an overdose, the investigator should:

- Contact the Medical Monitor immediately who may recommend:
  a. Close monitoring of the patient for any AEs/SAEs and laboratory abnormalities.
  b. Obtaining a plasma sample for PK analysis as soon as practical and note the date of the last dose of study drug.
- Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient.

8.5. Pharmacokinetics

Blood samples of approximately 6 mL will be collected for measurement of plasma concentrations of reldesemtiv as specified in the SoA (Section 1.3). Samples will be used to evaluate the PK of reldesemtiv and its metabolites. Instructions for the collection and handling of biological samples will be provided in the laboratory manual.

The actual date and time (24-hour clock time) of each sample will be recorded. The time of administration of study drug on the day of PK sampling will be recorded in the CRF. It is

important to provide instructions to patients that they should not take their morning dose on the day of their clinic visit until in the clinic.

See Table 5 for a summary of PK sampling time points at all sites. Drug concentration information that would unblind the trial will not be reported to investigative sites or blinded personnel until the trial has been unblinded.

If an in-clinic visit is converted to a remote visit, PK sampling will not be performed.

Table 5: Summary of PK Time Points

Visit	PK Time Point
Week 4	Pre-dose and another sample 2-4 hours post dose
Week 12	Pre-dose and another sample 2-4 hours post-dose
Week 24	Pre-dose and another sample 2-4 hours post-dose

An intensive PK sub-study will be conducted in 15 patients taking reldesemtiv 300 mg BID at a limited number of sites at the Week 36 visit.

Table 6: PK Sub-Study Time Points

Visit	PK Time Point
Week 36	Pre-dose and at 0.5, 1, 2, 3, 4 and 6 hours post-dose

8.6. Genetics

Where authorized by the applicable IRB/EC/Research Ethics Board (REB) approved informed consent and authorized by the patient, a blood sample of approximately 6 mL will be obtained at the Day 1 visit and stored for possible future genetic testing related to ALS (genes known or suspected to cause, modify, or alter the risk of ALS) and for research purposes only. Details on the process for collection and shipment of these samples can be found in the laboratory manual.

8.7. Biomarkers

Biomarkers are objective measures or indicators of normal biological processes, pathological processes or pharmacological responses to a therapeutic intervention. Biomarker development may be useful to identify disease subtypes, to guide therapy, detect a response to therapy, better understand the development of an adverse event, or predict disease severity. Where authorized by the applicable IRB/EC/REB approved informed consent, blood samples of approximately 6 mL for biomarker development will be collected at the time points shown in Table 7.

Table 7: Biomarker Samples

Visit	Sample Time Points
Day 1	Pre-AM dose
Week 24	Pre-AM dose

Plasma samples will be stored for future biomarker analyses.

8.8. Immunogenicity Assessments

No immunogenicity assessments will be done for this trial.

8.9. Sample Storage

Any laboratory samples remaining at the central laboratory or any other specialty laboratory at the end of the study will continue to be stored until reldesemtiv has been granted marketing authorization in any country or Cytokinetics decides to stop development of reldesemtiv. Cytokinetics may move the samples to another company where they store samples from other research studies.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary global null hypothesis is that there is no treatment difference in the change from baseline to Week 24 in ALSFRS-R total score between patients randomized to placebo and those randomized to reldesemtiv during the double-blind, placebo-controlled period in the FAS. The global null hypothesis for the first secondary endpoint is that the Mann-Whitney probability is 0.5 for the combined assessment of change in ALSFRS-R total score, time to dependence on assisted ventilation (use non-invasive or invasive ventilation for ≥ 22 hours per day for ≥ 10 consecutive days), and survival time up to Week 24 between patients randomized to placebo and those randomized to reldesemtiv in the FAS.

9.2. Sample Size Determination

With a 2:1 randomization ratio to reldesemtiv and placebo groups, respectively, a sample size of approximately 555 patients is required to achieve at least 90% power to detect a 1.8 point treatment difference between reldesemtiv and placebo in the change from baseline to Week 24 in ALSFRS-R total score. This calculation is based on a two-sample t-test with two-sided alpha at 0.05 level, a common standard deviation (SD) of 5.5 points, and accounting for missing data and early treatment termination.

9.3. Populations for Analyses

The analysis populations are defined in Table 8.

Table 8: Analysis Sets

Analysis Set	Description
All Screened Set	All patients who signed the ICF.
All Randomized Set	Patients who were randomized to receive reldesemtiv or placebo.
Full Analysis Set	All randomized patients who received any amount of study drug and have a baseline and at least one post baseline efficacy assessment or have survival status recorded during the double-blind placebo-controlled period. Patients will be analyzed according to the treatment to which they were assigned at randomization.
Safety Analysis Set	All randomized patients who received any amount of study drug. Patients will be analyzed according to the actual treatment received during the double-blind placebo-controlled period.
Pharmacokinetics Analysis Set	All patients who have at least one measurable plasma concentration of reldesemtiv, provided they have no major protocol violations deviations that could affect the PK of reldesemtiv.

9.4. Statistical Analyses

The Statistical Analysis Plan (SAP) will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General 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, overall and by treatment in the planned analysis sets. For model-based analysis, least squares means, difference of least squares means between treatments, their standard errors and 95% confidence intervals (CI), 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% CIs of median, and 1st and 3rd quartiles. Events and censored data points will be summarized by count and percentage. Hazard ratios between treatments and the corresponding 95% CIs and p-values will also be presented. Baseline is defined as the last available measurement taken before the first dose of randomized study drug received in the placebo control double-blind period unless otherwise specified. Analyses will be conducted by study period including the first 24-week double blind placebo-controlled period, the second 24-week active drug period, and the randomized delayed-start 48 weeks of treatment, and follow-up period.

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

Unless specified otherwise, efficacy, safety and pharmacokinetics analyses will be performed on the full analysis set, safety analysis set and pharmacokinetics analysis set, respectively. Statistical analysis methods will be detailed in the SAP.

9.4.1.1. Multiplicity Adjustment

The null hypothesis for the primary and secondary efficacy variables in the FAS will be tested in the pre-specified order using a closed testing procedure. The first secondary endpoint is the combined assessment of change in ALSFRS-R total score, time to dependence on assisted ventilation (use non-invasive or invasive ventilation for ≥ 22 hours per day for ≥ 10 consecutive days), and survival time up to Week 24. The primary endpoint will be tested first, and if this comparison between the two treatments is statistically significant, then the first secondary endpoint will be tested. The pre-specified order of the rest of the secondary efficacy endpoints will be provided in the SAP. This procedure will maintain the family-wise error rate at 5% for all hypotheses tested in a confirmatory sense.

9.4.1.2. Timing of Final Analyses

When all patients complete or discontinue from the 48 weeks of planned treatment and the safety follow-up visits, the database will be locked for this study and final analyses will be conducted.

9.4.2. Primary Endpoint

The primary endpoint of the trial is the change from baseline to Week 24 in ALSFRS-R total score. The primary estimand is the difference in the mean changes from baseline to Week 24 in ALSFRS-R total score between patients randomized to placebo and those randomized to reldesemtiv during the placebo-controlled double-blind treatment in the full analysis set.

The primary analysis (main estimator) of the primary endpoint is as follows:

The primary endpoint will be analyzed using a MMRM based on a restricted maximum likelihood method (SAS® PROC MIXED default). The model terms will include treatment group, baseline ALSFRS-R total score, visit, riluzole use status at baseline, edaravone use status at baseline as well as baseline-by-visit and treatment group-by-visit interactions. An unstructured variance-covariance matrix will be used in the model. Additional important baseline covariates may be included to the primary analysis model if they are key predictor variables for the change from baseline to Week 24 in ALSFRS-R total score. Details of the selection procedure for the potential baseline covariates will be pre-specified in the SAP. The selection of the potential baseline covariates will be performed before the database lock.

Prior to applying the MMRM, missing data will be imputed using the multiple imputation procedure (Rubin 1987) for the primary analysis, and the estimates from each imputed dataset will be combined into one set of overall estimates using the SAS® PROC MIANALYZE procedure. The extent of missing data and the pattern of missing data reasons will be tabulated. Imputation details will be pre-specified in the SAP. Least square means (LSM), LSM difference and the corresponding standard errors, 95% CI and p-values will be presented.

Sensitivity analyses will be conducted to support the robustness of the primary analysis results. Using the ANCOVA model with the MAR-based multiple imputation for all missing ALSFRS-R assessments as the base model, the tipping point analyses will be conducted having the imputed values for the deaths successively worse only for the reldesemtiv treatment, while maintaining the MAR-based imputed values for the placebo treatment. Another sensitivity analysis will be to repeat the ANCOVA base model with missing ALSFRS-R assessments imputed as if the reldesemtiv patients were in the placebo arm. Other sensitivity analyses and the details will be included in the SAP.

9.4.3. Secondary Endpoint(s)

The secondary endpoint(s) of the trial are:

- Combined assessment of change in ALSFRS-R total score, time to dependence on assisted ventilation (invasive or non-invasive) , and survival time up to Week 24.
    - Dependence on assisted ventilation is defined as patients using non-invasive or invasive ventilation for ≥ 22 hours per day for ≥ 10 consecutive days
    - Patients with dependence on assisted ventilation are ranked lower than those with the largest drops in ALSFRS-R scores but higher than those who have died
- Change from baseline to Week 24 in the percent predicted FVC
- Change from baseline to Week 24 in the ALSAQ-40 total score
- Change from baseline to Week 24 in hand grip strength (average of both hands)

The analyses of the secondary endpoints are as follows:

The estimand of the first secondary endpoint of combined assessment of change in ALSFRS-R total score, time to dependence on assisted ventilation, and survival time up to Week 24 is the Mann-Whitney probability for more favorable status at week 24 for reldesemtiv than placebo in the paradigm where deaths have the worst ranks, patients with dependence on assisted ventilation have the next worst ranks, and the more favorable changes from baseline at week 24 in ALSFRS total score have the better ranks using a joint-rank test in the FAS (Berry 2013). The detailed ranking and imputation methods for missing data will be provided in the SAP. The joint ranks will be determined based on the combined assessments and analyzed using a stratified Wilcoxon test that compares the ranks between reldesemtiv and placebo groups while adjusting for baseline riluzole use status and baseline edaravone use status. Stratified Mann-Whitney test statistics as well as the p-value will be presented. Sensitivity analyses and associated details will be included in the SAP.

Analyses for the remaining other secondary endpoints will be performed using a MMRM with the following model terms: treatment group, baseline ALSFRS-R total score, visit, riluzole use status at baseline, edaravone use status at baseline as well as baseline-by-visit and treatment group-by-visit interactions, using an unstructured variance-covariance matrix.

To support the analysis results of the key secondary endpoints, the joint rank analyses will also be performed for change from baseline up to Week 24 in the percent predicted FVC, and for change from baseline up to Week 24 in the ALSAQ-40 total score.

9.4.4. Exploratory Endpoint(s)

The exploratory endpoints of the trial are:

- Time to the patient being prescribed and patient agrees to it, time to first receipt, time to first use, time to daily use, time to dependence and number used of any of the following DME items (manual wheelchair, power wheelchair, augmentative and alternative and augmentative communication device, NIV and/or gastrostomy tube) from randomization to the end of the 24-week double-blind, placebo-controlled period and to Week 48 as well as reasons to receive the above DME. Time to dependence for invasive ventilation will also be recorded. Definitions for patient being prescribed and agrees to it, first receipt, first use, daily use, and dependence for the DME items of interest can be found in the Study Manual.
- Change from baseline to Week 24 in the four subdomain scores of the ALSFRS-R
- Time spent in each MiToS stage and number of patients to transition stages from baseline to Week 24
- Change from baseline to Week 48 in ALSFRS-R total score
- Change from baseline to Week 48 in FVC
- Combined assessment of change in ALSFRS-R total score, time to dependence on assisted ventilation, and survival time up to Week 48

- Change from baseline to Week 24 in the mega-score of muscle strength measured by HHD in bilateral first dorsal interosseous muscles, abductor pollicus brevis muscles, and abductor digiti minimi muscles
- Change from baseline to Week 24 and Week 48 in the EQ-5D-5L
- Change from baseline to Week 24 and Week 48 in the VAS of EQ-5D
- Time from first hospitalization through Week 24 and through Week 48
- All above endpoints are also applied to the end of the study

The analyses of the exploratory endpoints are as follows:

Time-to-event analyses will be conducted for the endpoints of durable medical equipment items. A MMRM will be used to analyze endpoints of change from baseline to the specified time point. Descriptive statistics will be presented for time spent in each MiToS stage and transition of stages. A joint-rank test will be used to analyze the combined assessment of change in ALSFRS-R total score, time to dependence on assisted ventilation, and survival time up to Week 48.

In addition, the comparisons listed below may also be performed as exploratory analyses of 1) change of ALSFRS-R total score from baseline, 2) combined assessment of change of ALSFRS-R, dependence on assisted ventilation, and survival time, or 3) change of other measures (as appropriate):

- Compare changes from baseline to Week 24 between the reldesemtiv and placebo groups
- Compare changes from Week 24 to Week 48 between the early-start and delayed-start treatment groups
- Compare changes from baseline to Week 48 between the early-start and delayed-start treatment groups
- Compare changes from Week 24 to Week 48 versus those from baseline to Week 24 in the delayed-start group

9.4.5. Safety Analysis

Safety data will be analyzed descriptively in the safety analysis set, including all patients who take any amount of study drug.

9.4.5.1. Adverse Events

All AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Primary system organ class (SOC) and preferred term (PT) of the TEAEs will be tabulated by the early-start and delayed-start treatment groups and periods (placebo-controlled period and active drug period). TEAEs will also be summarized by severity and relationship to study drug. AEs that led to early discontinuation from treatment or the trial and events of special interest will be summarized. Listings will be presented for patients who discontinued due to TEAEs.

9.4.5.2. Serious Adverse Events

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

9.4.6. Pharmacokinetic Endpoints

Plasma concentrations of reldesemtiv will be summarized using descriptive statistics including mean, standard deviation, geometric mean, coefficient of variation, median, and range. Geometric mean concentrations over time will be graphically displayed.

9.4.7. Patient Disposition

The number of patients who are randomized, who complete the planned treatment, and who prematurely discontinue from the planned treatment and/or the trial will be presented by study period, treatment group and overall. Reasons for premature discontinuation as recorded on the termination page of the CRF will be summarized overall and by randomized treatment and for each period separately.

9.4.8. Demographics and Other Baseline Characteristics

Patient demographics and other baseline characteristics will be summarized descriptively by treatment and overall. To assess the comparability of treatment groups, demographic and baseline characteristics will be compared between treatments for the FAS using Cochran-Mantel-Haenszel tests for binary categorical variables, van Elteren tests for ordinal categorical measures, or analysis of variance (ANOVA) for continuous variables, stratified by riluzole use/non-use, edaravone use/non-use.

9.4.9. Investigational Product Exposure

IP exposure will be summarized overall and by treatment and study period, including, total number of doses administered, total amount of drug administered, and the total duration of IP administration, defined as the date of the last dose minus the date of first dose + 1.

9.4.10. Concomitant Medications

Concomitant medications will be summarized and classified by drug class and preferred term using the World Health Organization (WHO) Drug Dictionary. The version of the WHO Drug Dictionary will be specified in the clinical study report.

9.4.11. Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values and changes from baseline at each protocol specified assessment time point will be presented.

9.4.12. Vital Signs

Descriptive statistics for vital signs and changes from baseline at each protocol specified assessment time point will be presented.

9.4.13. Electrocardiogram

Descriptive statistics for ECG parameters (eg, heart rate, PR interval, QRS interval, QT interval, and QTc interval [both Bazett's and Fridericia's corrections]) and changes from baseline at each protocol specified assessment time point will be presented.

9.5. Interim Analyses

Two interim analyses are planned for this trial. The interim analysis methods and the specifications of the data snapshots will be detailed in an interim analysis plan.

Twelve (12) weeks after approximately one-third or more of the planned sample size is randomized, the first interim analysis may be triggered. Its purpose is to determine if there is a lack of effect of reldesemtiv on the ALSFRS-R in CY 5031, a finding that would be inconsistent with the prior observed effect on the change from baseline at 12 weeks in ALSFRS-R total score in the Phase 2 trial, CY 5022. At this interim analysis, the Data Monitoring Committee (DMC) will receive unblinded efficacy data from the independent, third-party biostatistical group supporting them and assess the effect of reldesemtiv on the change from baseline to Week 12 in the ALSFRS-R total score. At this interim assessment, if the treatment difference for change from baseline to Week 12 in ALSFRS-R total score has a one-sided p-value larger than or equal to 0.5 (ie, the estimated treatment difference of the change from baseline at Week 12 in ALSFRS-R total score is favoring placebo), the DMC may recommend stopping the trial due to futility. This futility analysis based on the data of change from baseline to Week 12 in ALSFRS-R will not have any alpha spending. The Sponsor will monitor the blinded aggregate standard deviation of the change from baseline to Week 12 in ALSFRS-R total score periodically and possibly adjust the specified alpha before this interim analysis is conducted.

Twenty-four (24) weeks after at least one-third of the planned sample size is randomized; the second interim analysis will be triggered. The goal of the second interim analysis is to evaluate whether the proposed Phase 3 trial has adequate power to achieve a statistically significant effect on the primary endpoint in the final primary analysis, given the planned enrollment, or if continuing the trial is futile. At this interim analysis, the DMC will receive unblinded efficacy data from the independent, third-party biostatistical group supporting them and assess the effect of reldesemtiv on the primary endpoint. In terms of futility, the DMC may recommend stopping the trial if the conditional power (CP) is less than 0.10. The futility boundary is non-binding. The DMC is to make a recommendation to stop the trial using their collective judgment and the totality of evidence available. The DMC may consider the first secondary endpoint in a similar fashion.

If the CP of primary endpoint is within a pre-specified promising zone from 0.40 to 0.90, the DMC may recommend increasing the sample size by 150 unless there is any safety concern or other concerns that preclude the recommendation. This method is referred to as the CDL adaptive method and was initially proposed by Chen, DeMets, and Lan (2004) as later extended by Gao, Ware and Mehta (2008) and Mehta and Pocock (2011) (Chen 2004; Gao 2008; Mehta 2011, respectively). It is used to control type-1 error for sample size increase based on unblinded interim data. Within the pre-specified promising zone and a pre-specified fixed **increase** of the sample size, the CDL method could allow the final analysis to include all data before and after the interim look without inflating the type-1 error. This interim analysis will spend a very small 2-sided alpha of 0.0001 for the primary endpoint as well as all individual secondary endpoints.

The DMC is also expected to recommend stopping this trial due to superiority if a two-sided p-value is ≤ alpha of 0.0001 for the primary endpoint as well as all individual secondary endpoints. Therefore, the significance level of 2-sided alpha of 0.0499 would be used for the final analyses for the primary endpoint and all individual secondary endpoints to control familywise error rate at overall alpha of 0.05.

9.6. Data Monitoring Committee

An unblinded DMC will review the planned unblinded interim analysis results to be provided by an independent, third-party biostatistical group and make recommendations as to stop or continue the trial. The DMC may also provide recommendation(s) on the trial conduct. In addition, the DMC will review regularly the emerging 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.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This trial will be conducted in accordance with the protocol and with the following:

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

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the trial is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to patients.

The investigator will be responsible for the following:

- Providing summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the trial at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide Cytokinetics with sufficient, accurate financial information as requested to allow Cytokinetics to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the trial to the patient or his/her legally authorized representative and answer all questions regarding the trial.

Patients must be informed that their participation is voluntary. Patients must be able to comprehend and be willing to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that informed consent was obtained before any study-specific activities/procedures were performed and the date the consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the trial.

A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

10.1.4. Data Protection

Patients will be assigned a unique identifier by Cytokinetics. Any patient records or datasets that are transferred to Cytokinetics will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by Cytokinetics in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the ICF.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Cytokinetics, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

The study organization will include an Executive Committee (EC), Steering Committee (SC) and DMC.

The EC will contribute to trial design, implementation, data analysis, and communication of trial results and will consist of experts external to Cytokinetics who are qualified by their medical and scientific expertise and experience. The responsibilities of the EC will be described in an EC charter.

The SC will contribute to implementation of the trial, data analysis, and communication of trial results. The SC members will be ALS experts external to Cytokinetics and represent the different geographies the trial will be conducted in. The responsibilities of the SC will be described in a SC charter.

The DMC will be established and be responsible for periodic review of study data to ensure the safety of patients, and for review of SAEs on an ongoing basis. The DMC will include external experts with relevant expertise, including a neurologist(s) specializing in ALS, statistician, hepatologist and nephrologist eg, representing clinical science and biostatistics. The independent DMC membership will exclude the individuals from Cytokinetics or the study team involved in trial conduct. The DMC members will have access to treatment assignments and patient level data from the clinical trial database. DMC membership, responsibilities, relationship with

Cytokinetics, and the purpose and timing of the meetings will be further described in the DMC charter.

10.1.6. Data Quality Assurance

All patient data relating to the trial will be recorded on printed or electronic CRF unless transmitted to Cytokinetics or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory authority inspections and provide direct access to source data documents.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

Cytokinetics or designee is responsible for the data management of this trial including quality checking of the data.

Cytokinetics assumes accountability for actions delegated to other individuals (eg, CROs).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator in accordance with the strictest regulation applicable to this study and as obligated by the clinical trial agreement. No records may be destroyed during the retention period without the approval of Cytokinetics. No records may be transferred to another location or party without notification to Cytokinetics.

10.1.7. Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.

Data reported in the CRF or entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial. Also, current medical records must be available.

10.1.8. Study and Site Start and Closure

The trial start date is the date on which the clinical trial will be open for recruitment of patients.

The first act of recruitment is the first site activated.

Cytokinetics or designee reserves the right to close the study site or terminate the trial at any time for any reason at the sole discretion of Cytokinetics. Study sites will be closed upon trial completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by Cytokinetics or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local regulatory authorities, Cytokinetics's procedures, or GCP guidelines
- Inadequate recruitment of patients by the investigator
- Discontinuation of further IP development

If the trial is prematurely terminated or suspended, Cytokinetics shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 9 will be performed by the central laboratory.

Local laboratory testing may be used only if central laboratory testing is not feasible. If local testing is conducted, it is important that the sample for central analysis is obtained at the same time, if feasible.

Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations.

Table 9: Protocol-Required Safety Laboratory Assessments

Chemistry		Urinalysis	Hematology	Other Assessments
Sodium	Total bilirubin	Specific gravity	Hemoglobin	TSH at screening
Potassium	Direct bilirubin	pH	Hematocrit	
Gamma-glutamyl transferase	Indirect bilirubin	Blood	RBC	Serum Beta Human Chorionic Gonadotropin[2]
Chloride	CK	Protein	RDW	FSH[3]
Calcium	ALP	Glucose	MCV	
Magnesium	LDH	Bilirubin	MCH	
Phosphorus	AST (SGOT)	UPCR	MCHC	
Urea nitrogen	ALT (SGPT)	Microscopy	WBC	
Creatinine[1]	Cystatin C[1]		Platelets	
$eGFR_{Cr}$[1] (calculated using the CKD-EPI creatinine equation)	$eGFR_{CysC}$[1] (calculated using the CKD-EPI cystatin C equation)			
Glucose	Uric acid			
Total protein	Albumin			
Cholesterol	Triglycerides			
Bicarbonate				

ALP = alkaline phosphatase; CK = creatine kinase; FSH = follicle-stimulating hormone; LDH = lactic acid dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; RDW = red cell distributions width; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell; TSH = Thyroid Stimulating Hormone; UPCR=urine protein creatinine ratio
Investigators must document their review of each laboratory report.
Laboratory results that could unblind the trial will not be reported to sites or other blinded personnel until the trial has been unblinded.
1=Sites blinded to results
2=Pregnancy test is required for WOCBP (see Appendix 3 [Section 10.3]);
3=FSH only at Screening to confirm menopausal status if patient age < 55 years and spontaneous menses within the past 1 year but currently amenorrheic (eg, spontaneous or secondary to hysterectomy) to confirm FSH levels > 40 IU/L.

10.3. Appendix 3: Contraceptive Guidance

Definitions:

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study drug, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining trial entry.

   Note: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.
3. Postmenopausal
4. Menopause is defined as:
   - ≥ 12 months of spontaneous and continuous amenorrhea in a female ≥ 55 years old; or
   - no spontaneous menses for at least two years in a female < 55 years old; or
   - age < 55 years and spontaneous menses within the past 1 year but currently amenorrheic (eg, spontaneous or secondary to hysterectomy) and with follicle-stimulating hormone (FSH) levels > 40 IU/L, or postmenopausal estradiol levels (< 5 ng/dL), or according to the definition of "postmenopausal range" for the laboratory involved

Highly Effective Method of Contraception

A highly effective method of contraception is one that has a failure rate of <1% per year when used consistently and correctly.

Examples of highly effective contraception that have low user dependency are:

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- Intrauterine device (IUD)

- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner, only when the absence of sperm has been confirmed and vasectomized partner is the sole sexual partner of the female patient

Examples of highly effective contraception that are user-dependent are:

- Combined hormonal methods of birth control include oral, intravaginal, transdermal, injectable, or implantable
- Oral or injectable progestogen-only hormone contraception associated with the inhibition of ovulation
- Sexual abstinence

  Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the patient. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.

Contraception Guidance:

Women of Childbearing Potential

WOCBP must use at least one highly effective method of birth control. If a user-dependent, hormonal form of contraception is used as a highly effective method of birth control, a male condom must also be used. Male condom and female condom should not be used together (due to risk of failure with friction).

WOCBP should refrain from donating ova/eggs at least 10 weeks after the last dose of study drug.

If additional medications are given during treatment, the investigator is to review the prescribing information/summary of product characteristics for all concomitant therapy, as they may alter the contraceptive requirements. These additional medications may require an increase in the number of contraceptive methods and/or length of time that contraception is to be utilized after the last dose of protocol-required therapies. The investigator is to discuss these changes with the patient.

10.4. Appendix 4: Common Medications and Foods that Inhibit or Induce CYP3A4 or are OCT1/OCT2 Substrates

CYP3A4 Inhibitors	CYP3A4 Inducers
Strong Inhibitors: (Avoid)	**Strong Inducers: (Avoid)**
indinavir	avasimibe
nelfinavir	carbamazepine
ritonavir	phenobarbital
clarithromycin	phenytoin
itraconazole	St. John's Wort
nefazodone	rifampin
ketoconazole	rifabutin
grapefruit	
Seville oranges	
Moderate Inhibitors: (Use with caution)	**Moderate Inducers: (Use with caution)**
erythromycin	bosentan
diltiazem	efavirenz
verapamil	etravirine
suboxone	modafinil
	nafcillin
	nevirapine
	glucocorticoids (systemic)
Weak Inhibitors:	**Weak Inducers:**
cimetidine	amprenavir
	aprepitant
	armodafinil
	echinacea
	pioglitazone
	prednisone
	rufinamide
	clobazam
	lesinurad

OCT1 Substrates (Avoid)	OCT2 Substrates (Avoid)
oxaliplatin	pindolol
dofetilide	varenicline
	pilsicainide
OCT1 Substrates (Use with Caution)	**OCT2 Substrates (Use with Caution)**
aciclovir	metformin
ganciclovir	

10.5. Appendix 5: Abbreviations

Abbreviation/Term	Explanation
ADL	Activities of daily living
AE	Adverse event
ALP	Alkaline phosphatase
ALS	Amyotrophic lateral sclerosis
ALSAQ-40	Amyotrophic Lateral Sclerosis Assessment Questionnaire
ALSFRS-R	ALS Functional Rating Scale-Revised
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibody
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
BDI-FS	Beck Depression Inventory-Fast Screen
BID	Twice a day
BMI	Body mass index
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatinine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CP	Conditional power
Cr	Creatinine
CRF	Case report form
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
CysC	Cystatin C
DILI	Drug induced liver injury
DMC	Data monitoring committee
DME	Durable medical equipment
EC	Executive Committee

Abbreviation/Term	Explanation
ECG	Electrocardiogram
ED	Early Discontinuation
eGFR	Estimated glomerular filtration rate
EQ-5D-5L	EuroQol-5D-5L
EQ-VAS	EuroQol Visual Analog Scale
FAS	Full analysis set
FSH	Follicle stimulating hormone
FSTA	Fast skeletal muscle troponin activator
FU	Follow-up
FVC	Forced vital capacity
GCP	Good Clinical Practice
HHD	Hand held dynamometry
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IgG	Immunoglobulin G
IMP	Investigational medicinal product
INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IWRS	Interactive web response system
LAM	Lactational amenorrhoea method
LDH	Lactic acid dehydrogenase
LFT	Liver function test
LKM1	Liver Kidney Microsomal Antibody 1
LSM	Least square means
MAR	Missing at random
MCH	Mean corpuscular hemoglobin

Abbreviation/Term	Explanation
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medication Dictionary for Regulatory Activities
MiToS	Milano-Torino Staging
MMRM	Mixed Model for Repeated Measures
NIMP	Non-investigational medicinal product
NIV	Non-invasive ventilation
OCT	Organic cation transporter
OLE	Open Label Extension
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred term
RBC	Red blood cell
RDW	Red cell distributions width
REB	Research Ethics Board
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Steering Committee
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SoA	Schedule of activities
SOC	System organ class
SVC	Slow vital capacity
TBL	Total bilirubin
TDD	Total daily dose
TEAE	Treatment emergent adverse events
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
UPCR	Urine protein creatinine ratio
WBC	White blood cell
WHO	World Health Organization

Abbreviation/Term	Explanation
WOCBP	Women of childbearing potential

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