PROTOCOL CY 5032

A PHASE 3, OPEN-LABEL EXTENSION OF COURAGE-ALS (CY 5031)

Trial Name:	COURAGE-ALS OLE
Protocol Version and Date:	Amendment 1: 16 December 2022
Previous Version(s):	17 March 2022
Product:	CK-2127107
Product Name:	Reldesemtiv
Regulatory Authority Identifier Number(s):	IND 134567 NCT 05442775 EudraCT 2021-004727-33
Sponsor:	Cytokinetics, Inc. 350 Oyster Point Blvd South San Francisco, CA 94080, USA

INVESTIGATOR SIGNATURE PAGE

Protocol Number:	CY 5032
Protocol Title:	A Phase 3, Open-Label Extension of COURAGE-ALS (CY 5031)
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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

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Sponsor:	Cytokinetics, Inc. 350 Oyster Point Blvd South San Francisco, CA 94080

DocuSigned by:
Andrew R. Wolff
Signer Name: Andrew Wolff
Signing Reason: I approve this document
Signing Time: Dec-20-2022 | 10:04:40 PST
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Andrew Wolff, MD, FACC
Senior Vice President
Senior Fellow, Clinical Research and Development

Date:

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1.1. Synopsis

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Reldesemtiv, a fast skeletal muscle troponin activator, is being investigated as a potential therapy to slow the decline of skeletal muscle function in patients with ALS. Patients who have completed the Phase 3 clinical trial (COURAGE-ALS [CY 5031]) of reldesemtiv in patients with ALS may continue to receive reldesemtiv in the open label extension (OLE), CY 5032. During the last 24 weeks of dosing in CY 5031, all patients receive open-label reldesemtiv; consequently, all patients eligible for and entering CY 5032 will have already demonstrated acceptable tolerance of reldesemtiv when they begin dosing. The OLE permits patients to continue to receive reldesemtiv after completion of CY 5031. The study will extend the overall duration of long-term safety, tolerability, and durability of effect during treatment of patients with ALS with reldesemtiv.</td></tr>
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Overall Design:

CY 5032 is an open-label extension with the selective fast skeletal muscle troponin activator, reldesemtiv, in patients with ALS who finished dosing (through Week 48) in CY 5031 (COURAGE-ALS). Approximately 400 patients from the sites that participated in CY 5031 are expected to be enrolled in the open-label extension, CY 5032.

Following enrollment, patients will continue dosing with reldesemtiv, 300 mg twice a day for a 600 mg total daily dose (TDD) for a period of 48 weeks; however, a patient down-titrated for any reason to 150 mg twice daily in CY 5031 will continue with the down-titrated dose in CY 5032. Reldesemtiv should be taken twice daily, morning and afternoon (at least 8 hours apart).

At the end of 48 weeks, patients may transition to a reldesemtiv Managed Access Program (MAP). If the treating physician agrees to participate in the program, the treating physician's patient(s) may be eligible to transition from the OLE to the MAP.

Study Visits:

Patient visits will occur as follows (6 in clinic, 2 remote lab visits, and 8 remote visits):

- Day 1 (will be dependent upon protocol approval at the site, can be Week 48 or Week 52 visit for CY 5031 or later when approval is received)
- End of Week 4 (remote visit)
- End of Week 6 (remote lab visit)
- End of Week 8 (remote visit)
- End of Week 12 (in clinic)
- End of Week 16 (remote visit)
- End of Week 18 (remote lab visit)
- End of Week 20 (remote visit)
- End of Week 24 (in clinic)
- End of Week 28 (remote visit)
- End of Week 32 (remote visit)
- End of Week 36 (in clinic)
- End of Week 40 (remote visit)
- End of Week 44 (remote visit)
- End of Week 48 (in clinic)

- FU: End of Week 52 (in clinic)

If a patient decides to discontinue reldesemtiv, the patient will come into the clinic for the Reldesemtiv Discontinuation Visit as soon as possible after the last dose was taken.

Study Center(s):

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

Assessments:

The following assessments will be performed:

- Collection of Demographic Data
- Physical Exam / Neurological Exam
- Vital Signs
- Clinical Safety Labs
- Serum Pregnancy Test for Women of Childbearing Potential
- ALSFRS-R
- AE evaluation and concomitant medication assessment (since last visit)

Eligibility Criteria:

Key Inclusion Criteria

- Able to comprehend and willing to sign an Informed Consent Form (ICF). If patient is able to comprehend, but non-written consent is given, an impartial witness must sign the ICF form
- Completed dosing in CY 5031

Key Exclusion Criteria

- Has taken an investigational study drug (other than reldesemtiv) prior to dosing, within 30 days or five half-lives of the prior agent, whichever is greater

Investigational Product:

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

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

Patients must interrupt reldesemtiv for certain specified laboratory abnormalities until the laboratory value in question has returned to the threshold specified in the protocol for re-initiation of treatment. Patients must then resume dosing at 1 tablet 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.

Patients who experience a laboratory abnormality requiring interruption of reldesemtiv while receiving 150 mg twice daily may resume reldesemtiv 150 mg twice daily once the laboratory value in question has returned to the threshold specified in the protocol for re-initiation of reldesemtiv; however, should the same laboratory abnormality requiring interruption of reldesemtiv recur, the patient must be permanently discontinued from reldesemtiv.

Statistical Methods:

Unless specified otherwise, efficacy analyses will be performed to compare early-start and delayed-start treatment groups based on the data collected during CY 5031 from the patients in the full analysis set (FAS) of CY 5031 plus the data collected during CY 5032 from the patients who were in the FAS of CY 5031 and enrolled into CY 5032.

The combined assessment of change in ALSFRS-R total score, time to dependence on assisted ventilation, and survival time from baseline of CY 5031 through CY 5032 Week 48 will be analyzed using the joint-rank test. A stratified Wilcoxon test will be applied to compare the standardized joint ranks between the early-start and delayed-start treatment groups with adjustment for riluzole and edaravone use at CY 5031 baseline. The stratified Mann-Whitney probability as well as the p-value will be presented.

If data permit, the analyses of change from baseline will be conducted using a Mixed Model for Repeated Measures (MMRM) based on a restricted maximum likelihood method (SAS® PROC MIXED default). The model terms will include early-start and delayed-start treatment groups, CY 5031 baseline ALSFRS-R total score, visit, riluzole use at CY 5031 baseline, edaravone use at CY 5031 baseline as well as the interaction terms of baseline-by-visit and treatment-by-visit. Least square means (LSM), LSM difference and the corresponding standard errors, 95% confidence intervals (CI) and p-values will be presented.

Slope endpoints will be analyzed using a mixed model which will include early-start and delayed-start treatment groups, CY 5031 baseline value, time from CY 5031 baseline, riluzole use at CY 5031 baseline, edaravone use at CY 5031 baseline as well as interaction terms for treatment-by-baseline, and treatment-by-time, assuming random slope effect. The estimated slope and the slope difference as well as their standard errors will be presented.

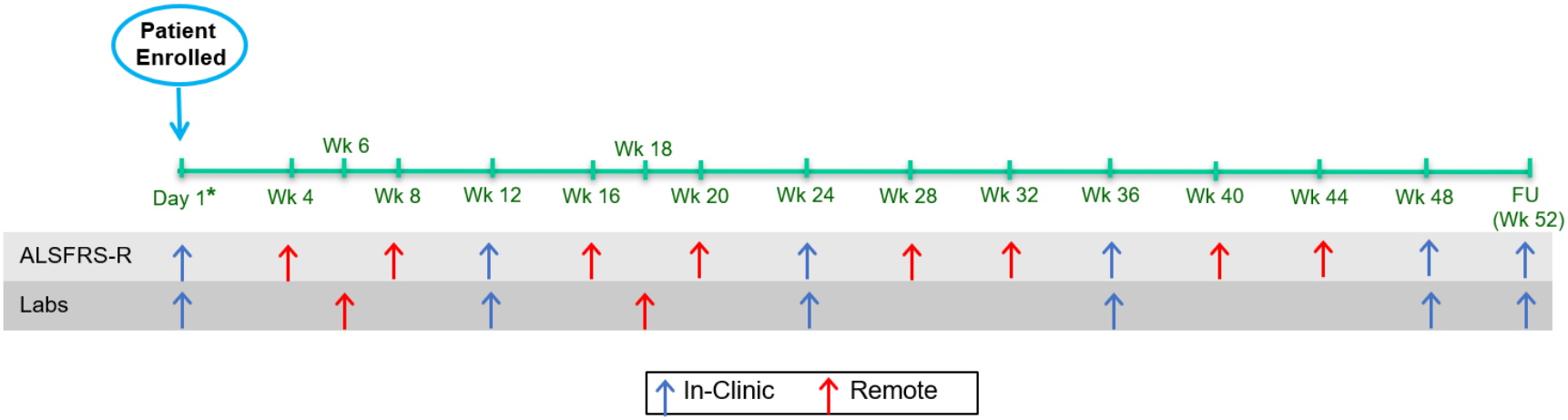
The time to event analyses will be conducted using proportional hazard Cox regression models and the Kaplan-Meier method. Time to event will be summarized by number of events, number of patients at risk, median, 95% CIs of median, and 1st and 3rd quartiles. Events and censored data points will be summarized by count and percentage. Hazard ratios between early-start and delayed-start treatment groups and the corresponding 95% CIs and p-values will also be presented. A negative binomial regression method will be used to analyze for time to recurrent hospitalizations. Number of hospitalizations and total number of days in hospital will be summarized descriptively.

Safety data will be analyzed descriptively in the safety analysis set of CY 5032, including all 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. 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



* Day 1 will be dependent upon protocol approval at the site; it can be Week 48 or Week 52 visit for CY 5031 or later when approval is received

1.3. Schedule of Activities

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

ED=Early discontinuation; AE=adverse event; BMI=body mass index; SAE=serious adverse event; WOCBP=women of childbearing potential; ALSFRS-R=Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; DME=Durable Medical Equipment
*Drug dosing will not occur at the ED visit
1=Day 1 of CY 5032 may occur on the same day as the Week 48 Visit or the FU Visit of CY 5031 or as a separate Day 1 Visit unique to CY 5032 that occurs after the CY 5031 FU Visit. If Day 1 in CY 5032 occurs more than 6-weeks after completion of the FU Visit in CY 5031, the initial dose of study drug will not be taken by the patient until their safety lab results are available and the estimated Glomerular Filtration Rate $(eGFR)_{CysC} \geq 45$ ml/min/1.73m^2 and $eGFR_{Cr} \geq 45$ ml/min/1.73m^2, alanine aminotransferase (ALT)/aspartate aminotransferase (AST) <3 × upper limit of normal (ULN), and bilirubin is normal or if abnormal reported as non-clinically significant by the investigator.
2=Physical Exam and Neurological Exam: Day 1 exams are only required if the patient enrolls in the OLE on the same day as the Week 48 visit in CY 5031 or at a separate Day 1 Visit unique to CY 5032 that occurs after the CY 5031 FU Visit; however, if a patient enrolls in the OLE at the FU visit in CY 5031, these exams do not need to be repeated on Day 1 of the OLE.

3=Clinical safety labs to include: Chemistry (collected every 3 months): sodium, potassium gamma-glutamyl transferase, chloride, calcium, magnesium, phosphorus, urea nitrogen, creatinine, $eGFR_{Cr}$ (calculated using CKD-EPI creatinine equation), Total protein, cholesterol, bicarbonate, total bilirubin, direct bilirubin, indirect bilirubin, CK, ALP, LDH, AST (SGOT), ALT (SGPT), Cystatin C, $eGFR_{CysC}$ (calculated by CKD-EPI cystatin C equation), uric acid, albumin, triglycerides, and glucose
Urinalysis (collected every 3 months): specific gravity, pH, blood, protein, glucose, bilirubin, UPCR and microscopy
TSH on Day 1, bHCG as applicable for WOCBP, FSH as required to determine menopausal status at Day 1 per Appendix 3 (Section 10.3).
4=Remote clinical safety labs to include: Chemistry (collected at Week 6 and Week 18): ALP, ALT (SGPT), AST (SGOT), direct bilirubin, and total bilirubin. Remote clinical safety labs may be collected by a home health vendor in the patient's home, or in the clinic, or by another method approved by the Sponsor.
5=Pregnancy test: If a WOCBP has had a negative pregnancy test within 30 days, a pregnancy test is not needed on Day 1. If it has been >30 days, then it is required.

1.4. Key Contacts

Sponsor's Study Contact:	Jacqueline Lee Senior Director, Clinical Operations Email: CY5032ClinicalOperations@cytokinetics.com Phone: +1 (650) 624-3017 Cell: +1 (650) 291-5533
Sponsor's Medical Monitor:	Andrew Wolff, MD, FACC Senior Vice President Senior Fellow, Clinical Research and Development Email: CY5032MedicalMonitor@cytokinetics.com Phone: +1 (650) 624-3008 Cell: +1 (415) 603-9353
Serious Adverse Event Reporting:	Drug Safety Email: CY5032DrugSafety@cytokinetics.com Fax: +1 (650) 243-4199
Lead Investigator:	Jeremy Shefner, MD, PhD Professor & Chair of Neurology Barrow Neurological Institute Email: jeremy.shefner@dignityhealth.org Cell: +1 (315) 378-8531

2. INTRODUCTION

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

2.1. Study Rationale

Reldesemtiv, a fast skeletal muscle troponin activator, is being investigated as a potential therapy to slow the decline of skeletal muscle function in patients with ALS. Patients who have completed the Phase 3 clinical trial of reldesemtiv in patients with ALS, CY 5031, may continue to receive reldesemtiv in CY 5032. During the last 24 weeks of dosing in CY 5031, all patients receive open-label reldesemtiv; consequently, patients eligible for and entering CY 5032 all will have already demonstrated acceptable tolerance of reldesemtiv when they begin dosing. The OLE permits patients to continue to receive reldesemtiv after completion of CY 5031. The study will extend the overall duration of long-term safety, tolerability, and durability of effect during treatment of patients with ALS with reldesemtiv.

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 United States (US) and European Union (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).

Intravenously administered Radicava® (edaravone) was approved to treat patients with ALS in in Japan, South Korea, 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 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).

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

All patients enrolled in CY 5032 will have completed dosing in CY 5031, and therefore will have tolerated reldesemtiv at a daily dose of at least 150 mg twice a day (BID) for at least 24 weeks (and potentially for as long as 48 weeks) before enrolling in CY 5032.

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 this OLE is reldesemtiv 300 mg twice a day and careful monitoring of renal function and liver enzymes will be implemented during the trial.

Renal Safety

For renal safety, the mitigation strategy includes renal function monitoring and detailed study drug dose management with the potential for a dosing interruption and down-titration of dose, as described in Section 7.3.

Hepatic Safety

For hepatic safety, the mitigation strategy includes liver function monitoring and reldesemtiv discontinuation criteria as described in Section 7.4.

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 an opportunity to slow the decline in their function.

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 long-term safety and tolerability of reldesemtiv in patients with ALS	• The incidence of adverse events (AEs) in the patient population
Secondary	
• To assess the long-term effect of reldesemtiv on ALSFRS-R functional outcomes and hospitalization by comparing early-start to delayed-start groups from CY 5031	• 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 from baseline of CY 5031 through CY 5032 Week 48 and from Week 24 of CY 5031 through CY 5032 Week 48 • Time to the first occurrence of dependence on assisted ventilation or death from Day 1 in CY 5031 through CY 5032 Week 48 • Changes in ALS Functional Rating Scale – Revised (ALSFRS-R) total score from baseline of CY 5031 through CY 5032 Week 48 and from Week 24 of CY 5031 through CY 5032 Week 48 • Slopes of the changes in ALSFRS-R total score from baseline of CY 5031 through CY 5032 Week 48 and from Week 24 of CY 5031 through CY 5032 Week 48 • Time to the first hospitalization from Day 1 in CY 5031 through CY 5032 Week 48 • Time to recurrent hospitalizations from Day 1 in CY 5031 through CY 5032 Week 48

4. STUDY DESIGN

4.1. Overall Design

This is an open-label extension with the selective fast skeletal muscle troponin activator, reldesemtiv, in patients with ALS who finished dosing (through Week 48) in CY 5031. Approximately 400 patients from the sites that participated in CY 5031 are expected to be enrolled in the open-label extension, CY 5032.

Following enrollment, patients will continue the same dosing regimen of reldesemtiv as in the parent study (CY 5031); either 300 mg twice a day for a 600 mg total daily dose (TDD) for a period of 48 weeks, or if a patient down-titrated for any reason to 150 mg twice daily in CY 5031, will continue with the down-titrated dose in CY 5032. Reldesemtiv should be taken twice daily, morning and afternoon (at least 8 hours apart).

At the end of 48 weeks, patients may transition to a reldesemtiv Managed Access Program (MAP). If the treating physician agrees to participate in the program, the treating physician's patient(s) may be eligible to transition from the OLE to the MAP.

Study Visits:

Patient visits will occur as follows (6 in-clinic, 2 remote lab visits, and 8 remote visits):

- Day 1 (will be dependent upon protocol approval at the site, can be Week 48 or Week 52 visit for CY 5031 or later when approval is received)
- End of Week 4 (remote visit)
- End of Week 6 (remote lab visit)
- End of Week 8 (remote visit)
- End of Week 12 (in clinic)
- End of Week 16 (remote visit)
- End of Week 18 (remote lab visit)
- End of Week 20 (remote visit)
- End of Week 24 (in clinic)
- End of Week 28 (remote visit)
- End of Week 32 (remote visit)
- End of Week 36 (in clinic)
- End of Week 40 (remote visit)
- End of Week 44 (remote visit)
- End of Week 48 (in clinic)
- FU: End of Week 52 (in clinic)

If a patient decides to discontinue reldesemtiv, the patient will come into the clinic for the Reldesemtiv Discontinuation Visit as soon as possible after the last dose was taken.

Remote Visits

Remote visits are defined as any contact with the patient at their home (or other location outside of the clinic) via telephone calls, telemedicine, and video contact. Day 1 visit must occur in-

clinic. 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 and approve the change.

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.

4.2. 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 and 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, the first dose on Day 1 may be administered. The site is to document the informed consent signature and the Day 1 date in the patient's medical record and in/on the case report form (CRF).

Prospective approval of a protocol deviation to recruitment and enrollment criteria, also known as a protocol waiver or exception, 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, but non-written consent is given, an impartial witness must sign the ICF form.
102. Completed dosing in CY 5031
103. 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 (as described in Appendix 3 [Section 10.3])
104. 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 (as described in Appendix 3 [Section 10.3]) and her male partner agrees 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)

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.

5.2. Exclusion Criteria

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

201. Has taken investigational study drug (other than reldesemtiv) prior to dosing, within 30 days or five half-lives of the prior agent, whichever is greater
202. Presence on Day 1 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.
203. Use of a strong cytochrome P450 (CYP) 3A4 inhibitor within 7 days prior to first dose of reldesemtiv in CY 5032 or a strong CYP3A4 inducer within 14 days prior to first dose of reldesemtiv in CY 5032 per Appendix 4 (Section 10.4)
204. Use of a medication that is an OCT1/OCT2 substrate within 7 days prior to first dose of reldesemtiv in CY 5032 per Appendix 4 (Section 10.4)
205. 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 Day 1. Patients also cannot be taking outside of a clinical trial certain investigational drugs (which includes drugs, supplements, and nutraceuticals) 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.

5.3. Lifestyle Considerations

Not applicable.

6. INVESTIGATIONAL PRODUCT

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

6.1. Study Drug Administered

Table 2: Study Drug

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

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

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 ensure that any discrepancies are reported and resolved before use of the IP.

Only patients enrolled 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. 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.

A patient who has lost the ability to swallow tablets may crush the 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 percutaneous endoscopic gastrostomy (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.

6.4. 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.

Riluzole, edaravone, and the combination product of sodium phenylbutyrate and taurursodiol are permitted in the countries in which they are approved for the treatment of ALS. Patients who start or stop edaravone, riluzole, or the combination product of sodium phenylbutyrate and taurursodiol following Day 1 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 induce 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.

6.5. 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 abnormal laboratory values, see Section 7.3.

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 a phone or video call 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.

Patients who experience a laboratory abnormality or adverse event requiring interruption of reldesemtiv while receiving 150 mg twice daily may resume reldesemtiv 150 mg twice daily once the laboratory value in question has returned to the threshold specified in the protocol for re-initiation of reldesemtiv; however, should the same laboratory abnormality requiring interruption of reldesemtiv recur, the patient must be permanently discontinued from reldesemtiv.

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

Cytokinetics plans to put in place a MAP for patients who complete 48 weeks of dosing in CY 5032. If the treating physician agrees to participate in the program, the treating physician's patient(s) may be eligible to transition from the OLE to the MAP.

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, treatment may be resumed at a lower dose as outlined in Section 7.3 (Renal Function Monitoring).

Patients who experience a laboratory abnormality or adverse event requiring interruption of reldesemtiv while receiving 150 mg twice daily may resume reldesemtiv 150 mg twice daily once the laboratory value in question has returned to the threshold specified in the protocol for re-initiation of reldesemtiv; however, should the same laboratory abnormality requiring interruption of reldesemtiv recur, the patient must be permanently discontinued from reldesemtiv.

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 a phone or video call 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.

    - 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 6.5 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. 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
- ALS progression
- Patient wants to enter another ALS trial or receive an experimental therapy for the treatment of ALS
- 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 via a phone or video call.

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.
- Patient agrees to a mix of remote and in-clinic visits to obtain study data
- Patient only agrees to allowing contact for determination of vital status
- Patient withdraws consent (see Section 7.6) and does not agree to any further study procedures or visits.

Assessments obtained at the early discontinuation (same as FU Visit at Week 52) 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

Reldesemtiv will be held if:

- Both $eGFR_{Cr}$ 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)

Reldesemtiv may be restarted at half the dose, or 1 tablet twice a day (150 mg BID) when:

- Both $eGFR_{Cr}$ 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, and $eGFR_{Cr}$ will be obtained. These renal related laboratory results will be reviewed by the local investigator and the study drug should be held or restarted in the event the above criteria are met.

Abnormal renal function tests meeting the above criteria will be repeated. The site investigator and medical monitor 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 for study drug to be resumed at a reduced dose.

1. If reldesemtiv is re-initiated, it must be at the lower dose of 150 mg BID,
   or
2. If the abnormal renal function test requiring interruption of reldesemtiv occurred during administration of 150 mg twice daily, reldesemtiv 150 mg twice daily may be resumed once the laboratory value in question has returned to the threshold specified in the

protocol for re-initiation of reldesemtiv; however, should the same abnormal renal function test requiring reldesemtiv interruption recur, the patient must be permanently discontinued from reldesemtiv.

To accomplish this, the medical monitor may direct the laboratory assessments (serum cystatin C, $eGFR_{CysC}$, serum creatinine, $eGFR_{Cr}$, and UPCR) to be repeated as often as twice a week until a final disposition is reached (ie, re-initiation of study drug at 150 mg BID or permanent discontinuation) is reached.

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 (and if available, direct) 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 as described below meet the criteria for permanent discontinuation of reldesemtiv. Patients who meet the criteria for permanent discontinuation must not be re-challenged.

Criteria for permanent discontinuation of reldesemtiv 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

If any of the criteria above are met, reldesemtiv must be permanently discontinued.

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

Confirmed abnormal liver function tests (LFTs) and INR 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, as warranted:
  - 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 hepatology consult, as warranted (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 may review public records as permitted by 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 10.1.7).

8. STUDY ASSESSMENTS AND PROCEDURES

There will be up to six clinic visits, two remote lab visits, and eight remote visits (that requires a 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 5032 Visit Windows

Visit	Visit Window
Start of Dosing (Day 1): clinic visit	
End of Week 4: remote visit	28 days ±4 days
End of Week 6: remote lab visit	42 days ±4 days
End of Week 8: remote visit	56 days ±4 days
End of Week 12: clinic visit	84 days ±4 days
End of Week 16: remote visit	112 days ±4 days
End of Week 18: remote lab visit	126 days ±4 days
End of Week 20: remote visit	140 days ±4 days
End of Week 24: clinic visit	168 days ±4 days
End of Week 28: remote visit	196 days ±4 days
End of Week 32: remote visit	224 days ±4 days
End of Week 36: clinic visit	252 days ±4 days
End of Week 40: remote visit	280 days ±4 days
End of Week 44: remote visit	308 days ±4 days
End of Week 48: clinic visit	336 days ±4 days
FU: End of Week 52: clinic visit	364 days ±4 days

Study procedures and their timing are summarized in the SoA (Section 1.3). If Day 1 in CY 5032 occurs more than 6-weeks after completion of the FU Visit (Week 52) in CY 5031, the initial dose of study drug will not be taken by the patient until their safety lab results are available and the $eGFR_{CysC} \geq 45$ ml/min/1.73m^2 and $eGFR_{Cr} \geq 45$ ml/min/1.73m^2, ALT/AST < 3 × ULN, and bilirubin is normal or if abnormal reported as non-clinically significant by the investigator.

Prospective approval of a protocol deviation to recruitment and enrollment criteria, also known as a protocol waiver or exception, is not permitted.

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.

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

Remote lab visits at Week 6 and Week 18 may occur in-clinic or by another method approved by the Sponsor if arrangements cannot be made for the home health vendor to draw lab samples at the patient's home.

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.

8.1.2. 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.

8.1.3. Hospitalizations

Hospitalizations experienced by a patient following enrollment in CY 5032 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 / radiologically inserted percutaneous gastronomy (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 electronic data capture (EDC) system. Hospitalizations that are for social reasons, or those that

were planned 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 on Day 1 if the patient enrolls in the OLE on the same day as the Week 48 visit in CY 5031. If a patient enrolls in the OLE at the follow-up visit in CY 5031, a physical exam does not need to be repeated on Day 1 of the OLE.

An abbreviated physical examination (consisting of an examination of general appearance, skin, lungs, cardiovascular and abdomen) will be performed at the Week 52 visit.

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 Day 1 visit. Height that was recorded in CY 5031 can be used to calculate the body mass index (BMI). 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. 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 on Day 1 if the patient enrolls in the OLE on the same day as the Week 48 visit in CY 5031. If a patient enrolls in the OLE at the follow-up visit in CY 5031, a neurological exam does not need to be repeated on Day 1 of the OLE. It will also be performed at the Week 52 visit as described in the Study Manual.

8.2.4. 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).

8.3. 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 (a condition that occurred before the patient was exposed to reldesemtiv) 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, electrocardiogram (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. Definition of Adverse Event of Special Interest

Adverse events of special interest (AESI) in the CY 5032 study are defined based on clinical and laboratory parameters.

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

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

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

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

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

- Manifestations of renal toxicity
- Both eGFRCr, $eGFR_{CysC} < 30.0$ ml/min/1.73m^2
- UPCR ≥ 3 mg protein/g creatinine (or ≥ 339 mg protein/mmol creatinine)

In addition, if reldsemtiv has been temporarily interrupted or permanently discontinued related to renal labs that don't meet the above criteria, this is also considered as Renal-Related AESIs.

8.3.1.4. 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 noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (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.

8.3.1.5. 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.

8.3.1.6. 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.

8.3.1.7. 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.

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

8.3.1.8. 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, are recorded in the AE CRF and immediately reported to Cytokinetics on an SAE Report Form (no later than 12 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: **CY5032DrugSafety@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 immediately reported to Cytokinetics (no later than 12 hours following knowledge of the new information). Cytokinetics Drug Safety may contact the investigator to obtain further information.

8.3.1.9. 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 adverse 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.

8.3.1.10. 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.

8.3.1.11. 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: CY5032DrugSafety@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.
- 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

No pharmacokinetic testing will be done for this trial.

8.6. Immunogenicity Assessments

No immunogenicity assessments will be done for this trial.

8.7. Sample Storage

The central laboratory will perform the standard safety testing described in this protocol. Any laboratory samples remaining after analysis may be temporarily stored for retesting and then will be destroyed. Laboratory samples will not be retained beyond the end of the study.

9. STATISTICAL CONSIDERATIONS

9.1. Populations for Analyses

The analysis populations are defined in Table 5. Efficacy comparisons will be based on the data collected during CY 5031 from the patients in the full analysis set (FAS) of CY 5031 plus the data collected during CY 5032 from the patients who were in the FAS of CY 5031 and enrolled into CY 5032. Safety comparisons will be based on the data collected during CY 5032.

To minimize bias, the randomized treatment assignments in CY 5031 for those in the Safety Analysis Set in CY 5032 will be remained blinded to the site staff until the patients complete or terminate from the OLE.

Table 5: Analysis Sets

Analysis Set	Description
Full Analysis Set	All enrolled patients who received any amount of study drug and have a baseline and at least one post baseline efficacy assessment during CY 5031, regardless of the enrollment status in the OLE.
Safety Analysis Set	All enrolled patients who received any amount of study drug in the OLE.

9.2. 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.

9.2.1. 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 early-start and delayed-start treatment groups in the planned analysis sets for all endpoints. For model-based analyses, least squares means, difference of least squares means between early-start and delayed-start treatment groups, their standard errors and 95% confidence intervals (CI), and two-sided p-values 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 the early-start and delayed-start treatment groups and the corresponding 95% CIs and p-values will also be presented. Analyses for comparisons will be conducted from baseline of CY 5031 through CY 5032 Week 48 and from Week 24 of CY 5031 through CY 5032 Week 48.

Comparisons between the delayed-start treatment group and the early-start treatment group will be presented using the nominal p-values at the two-sided 5% significance level.

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 and safety analyses will be performed on the full analysis set and safety analysis set respectively. Statistical analysis methods will be detailed in the SAP.

9.2.2. Primary Endpoint

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

9.2.3. Secondary Endpoint(s)

The secondary outcome endpoint(s) of the OLE are:

- 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 from baseline of CY 5031 through CY 5032 Week 48 and from Week 24 of CY 5031 through CY 5032 Week 48
- Time to the first occurrence of dependence on assisted ventilation or death from Day 1 in CY 5031 through CY 5032 Week 48
- Changes in ALSFRS-R total score from baseline of CY 5031 through CY 5032 Week 48 and from Week 24 of CY 5031 through CY 5032 Week 48
- Slopes of the changes in ALSFRS-R total score from baseline of CY 5031 through CY 5032 Week 48 and from Week 24 of CY 5031 through CY 5032 Week 48
- Time to first hospitalization from Day 1 in CY 5031 through CY 5032 Week 48
- Time to recurrent hospitalizations from Day 1 in CY 5031 through CY 5032 Week 48

The analyses of the secondary endpoints in the FAS are as follows:

9.2.3.1. Time-to Event Endpoints

Time to event endpoints, such as time to first occurrence of dependence on assisted ventilation or death, time to first hospitalization will be estimated using the Kaplan-Meier method. A proportional hazards Cox regression model will be used to estimate the hazard ratio between the early-start and delayed-start treatment groups. The model may adjust for baseline riluzole use and baseline edaravone use. If the proportionality assumption does not hold, the log rank test will be used. More details will be described in the SAP.

Time to recurrent hospitalizations will be assessed by a negative binomial regression where hospitalizations are considered as events, including terms for the stratification factors and treatment groups. Number of hospitalizations and total number of days in hospital will be summarized descriptively.

9.2.3.2. Change from Baseline Endpoints

Analyses for change from baseline of CY 5031 through CY 5032 Week 48 and from Week 24 of CY 5031 through CY 5032 Week 48 endpoints will be based on the data collected in CY 5031 in the FAS plus data collected during CY 5032 and performed with the methods below.

The estimand of the first secondary endpoint (combined assessment of change in ALSFRS-R total score, time to dependence on assisted ventilation, and survival time from baseline of CY 5031 through CY 5032 Week 48 and from Week 24 of CY 5031 through CY 5032 Week 48) is the stratified Mann-Whitney probability of a more favorable status at CY 5032 Week 48 in the early-start group compared to the delayed-start group in the FAS, based on the joint ranks of the

combined assessments collected up to Week 48 in CY 5032, and accounting for the intercurrent events of deaths, onset of dependence on assisted ventilation and decline in ALSFRS-R total score. The detailed ranking methods for missing data for all intercurrent events 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 the early-start and delayed-start groups while adjusting for baseline riluzole use and baseline edaravone use. Stratified Mann-Whitney probability as well as the p-value will be presented.

If data permit, the change from baseline endpoints will be analyzed using a MMRM based on a restricted maximum likelihood method (SAS® PROC MIXED default). The model terms will include the early-start and delayed-start treatment groups, CY 5031 baseline value, visit, riluzole use at baseline, edaravone use at baseline as well as baseline-by-visit and treatment-by-visit interactions. An unstructured variance-covariance matrix will be used in the model.

Observed data up to Week 48 of CY 5032 in the FAS will be included in the model. Assumptions for statistical models will be evaluated. If assumptions are substantially violated, alternative analysis methods will be considered. Missing data will not be imputed unless specified. Every attempt will be made to obtain ALSFRS-R measurements.

Slope endpoints will be analyzed using a mixed model which will include the early-start and delayed-start treatment groups, CY 5031 baseline value, time, riluzole use at baseline, edaravone use at baseline as well as interaction terms of the treatment-by-baseline and treatment-by-time, assuming random slope effect. The estimated slope, the slope difference and the corresponding standard errors, and 95% CIs and p-values will be presented.

9.2.4. Safety Analysis

Safety data collected on or after the date that reldesemtiv was first dispensed in the CY 5032 study up to the date of the last dose of reldesemtiv in the CY 5032 study will be summarized overall and by the early-start and delayed-start treatment groups in the safety analysis set, including all patients who take any amount of study drug.

9.2.4.1. Adverse Events

A treatment-emergent adverse event (TEAE) is an AE with an onset after initiation of study drug dosing in CY 5032, or an AE present at initiation of study drug dosing that worsens in severity after initiation of study drug dosing. 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. TEAEs will also be summarized by severity and relationship to study drug. AEs that led to early discontinuation from treatment or the trial and adverse events of special interest will be summarized. Listings will be presented for patients who discontinued due to TEAEs.

9.2.4.2. Serious Adverse Events

All SAEs will be summarized by system organ class, preferred term, the early-start and delayed-start treatment groups and overall, and by riluzole and edaravone use at baseline. Listings will be presented for patients who died and/or experienced serious AEs.

9.2.5. Patient Disposition

The number of patients who are enrolled, who complete the planned treatment, and who prematurely discontinue from the planned treatment and/or the trial will be presented by the early-start and delayed-start treatment groups and overall. Reasons for premature discontinuation as recorded on the termination page of the CRF will be summarized by the early-start and delayed-start treatment groups and overall.

9.2.6. Demographics and Other Baseline Characteristics

Patient demographics and other baseline characteristics will be summarized descriptively by the early-start and delayed-start treatment groups 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.

9.2.7. Investigational Product Exposure

IP exposure will be summarized by the early-start and delayed-start treatment groups and overall, 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.

9.2.8. Concomitant Medications

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

9.2.9. Clinical Laboratory Parameters

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

9.2.10. Vital Signs

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

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 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. 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, contract research organizations (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.

10.1.6. 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.

10.1.7. 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
- 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 6 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 6: Protocol-Required Safety Laboratory Assessments

Chemistry		Urinalysis	Other Assessments
Sodium	Total bilirubin[1]	Specific gravity	TSH
Potassium	Direct bilirubin[1]	pH	
Gamma-glutamyl transferase	Indirect bilirubin[1]	Blood	Serum Beta Human Chorionic Gonadotropin[2]
Chloride	CK	Protein	FSH[3]
Calcium	ALP[1]	Glucose	
Magnesium	LDH	Bilirubin	
Phosphorus	AST (SGOT)[1]	Microscopy	
Urea nitrogen	ALT (SGPT)[1]	UPCR	
Creatinine	Cystatin C		
$eGFR_{Cr}$ (calculated using the CKD-EPI creatinine equation)	$eGFR_{CysC}$ (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; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; TSH = Thyroid Stimulating Hormone; UPCR=urine protein creatinine ratio
Investigators must document their review of each laboratory report.
1=Additional remote clinical safety labs will be performed at Week 6 and Week 18 to include: ALP, ALT (SGPT), AST (SGOT), direct bilirubin, and total bilirubin. Remote clinical safety labs may be collected by a home health vendor in the patient's home, or in the clinic, or by another method approved by the Sponsor.
2=Pregnancy test is required for WOCBP (see Appendix 3 [Section 10.3]);
3=FSH only at Day 1 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:

Women 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).

Female participants of childbearing potential should refrain from donating ova during the trial and for at least 10 weeks after the last dose of reldesemtiv.

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
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALS	Amyotrophic lateral sclerosis
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
BID	Twice a day
BMI	Body mass index
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
DME	Durable medical equipment
EC	Executive Committee
ECG	Electrocardiogram
ED	Early Discontinuation
EDC	Electronic Data Capture

Abbreviation/Term	Explanation
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
FSH	Follicle stimulating hormone
FU	Follow-up
GCP	Good Clinical Practice
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
MedDRA	Medication Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
NIMP	Non-investigational medicinal product
NIV	Non-invasive ventilation
OCT	Organic cation transporter
OLE	Open Label Extension
PT	Preferred term
REB	Research Ethics Board
SAE	Serious adverse event

Abbreviation/Term	Explanation
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
WHO	World Health Organization
WOCBP	Women of childbearing potential

11. REFERENCES

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