PROTOCOL CY 5022

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

Product: CK-2127107

EudraCT Number: 2018-000586-37

Sponsor: Cytokinetics Inc.
280 East Grand Avenue
South San Francisco, California 94080

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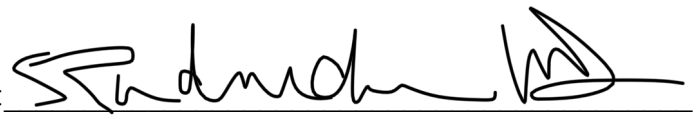
Sponsor (Medical Monitor) Signature: 

Lead Investigator Signature: 

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STUDY IDENTIFICATION

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Study Site	Multi-Center

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by Cytokinetics.
- Not to amend the protocol without agreement, prior review, and written approval from the Institutional Review Board (IRB)/Ethics Committee (EC) except where necessary to eliminate an immediate hazard to the patients.
- That I am thoroughly familiar with the appropriate use of the investigational product(s), as described in this protocol and any other information provided by the Sponsor including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document.
- That I am aware of, and will comply with, "Good Clinical Practices" (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the Cytokinetics investigational product(s) and of their study-related duties and functions as described in the protocol.
- That I have been informed that certain regulatory authorities require the Sponsor to obtain and supply, as necessary, details about the Investigator's ownership interest in the Sponsor or the investigational product, and more generally about his/her financial ties with the Sponsor. Cytokinetics will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply Cytokinetics with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children);
- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study; and
- Agree that Cytokinetics may disclose any information it has about such ownership interests and financial ties to regulatory authorities.

Investigator Name: _____

Investigator Signature: _____ Date: _____

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Explanation
AE	adverse event
ALP	alkaline phosphatase
ALSAQ-5	ALS Assessment Questionnaire Short Form
ALS	amyotrophic lateral sclerosis
ALSFRS-R	ALS Functional Rating Scale - Revised
ALT	alanine aminotransferase (alanine transaminase)
API	active pharmaceutical ingredient
AST	aspartate aminotransferase (aspartate transaminase)
AT	aminotransferase
AUC	area under the plasma concentration-time curve
BDI	Beck Depression Inventory
BMI	body mass index
CBC	complete blood count
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	clearance divided by fraction absorbed
C_{max}	maximum observed plasma concentration
C_{trough}	pre-dose plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	Cytochrome P450
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HHD	hand-held dynamometry

Abbreviation or Specialist Term	Explanation
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
LFT	liver function tests
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
OCT	organic cation transporter
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PKS	pharmacokinetics analysis set
PT	preferred term
QTc	corrected QT interval
R_{AC}	Accumulation ratio
REB	Research Ethics Board
SAE	serious adverse event
SAS	safety analysis set
SDD	spray dried dispersion
SOC	system organ class
SVC	slow vital capacity
$t_{½}$	apparent plasma terminal elimination half-life
TBL	total bilirubin
TDD	total daily dose
TEAE	treatment emergent adverse event
t_{max}	time where maximum concentration is reached
TSH	thyroid stimulating hormone
UA	urinalysis
ULN	upper limit of normal

Abbreviation or Specialist Term	Explanation
V/F	volume of distribution divided by fraction absorbed
WBC	white blood cells

1. INTRODUCTION

1.1. Background

CK-2127107 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. CK-2127107 selectively activates the fast skeletal muscle troponin complex by increasing its affinity for calcium. In intact rat skeletal muscle in vivo, CK-2127107 increases muscle force at sub-maximal nerve stimulation frequencies, increases muscle power, and decreases muscle fatigability. CK-2127107 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 CK-2127107 may provide benefit to patients with a wide variety of disorders characterized by muscle weakness and/or fatigue.

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, Vucic et al. 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, Sanofi-Aventis U.S. LLC) is the first medication approved for the treatment of ALS, and has a modest benefit on survival (Lacomblez, Bensimon et al. 1996). Two interventions that contribute greatly to the overall welfare and survival of ALS patients are the use of enteral feeding and ventilatory support.

Radicava (edaravone) was recently approved to treat patients with ALS in the United States in May 2017. The efficacy of Radicava 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 compared to those receiving a placebo (Writing Group on behalf of the Edaravone (MCI-186) ALS 19 Study Group. 2017).

To date, there are no available treatments that slow the decline of skeletal muscle function, and in particular, slow the decline of respiratory function. This clinical protocol is a double-blind, randomized, dose-ranging, placebo-controlled study to evaluate the efficacy, safety, and tolerability of CK-2127107 in patients with ALS.

1.2. Overview of CK-2127107 Nonclinical Studies

CK-2127107 was evaluated in a series of nonclinical safety studies in rat and monkey, including single- and repeat-dose (28 days and 13 weeks) toxicity studies, safety pharmacology studies, and a core battery of genotoxicity tests. CK-2127107 was formulated from a spray dried dispersion (SDD), which is a stabilized amorphous form of CK-2127107, to increase its absorption.

The toxicology studies conducted in rat and monkey with CK-2127107 demonstrated an acceptable safety profile, and supported Phase 1 clinical trials in healthy volunteers. Based on in vitro metabolism studies, the monkey was selected as the non-rodent toxicology species since the

metabolism of CK-2127107 in monkeys was qualitatively comparable to that in humans, in particular with respect to the production of CK-2127106, an identified inactive metabolite of CK-2127107. In definitive 28-day and 13-week repeat-dose toxicity and toxicokinetic studies, the no observed adverse effect level for CK-2127107 was 600 mg/kg/day, the highest dose level evaluated, in both rats and monkeys.

The core battery of safety pharmacology studies conducted with CK-2127107 indicated no functional changes in vital organs or systems which are likely to be of importance in clinical studies of CK-2127107.

The results of the bacterial reverse mutation, in vitro cytogenetic and in vivo rodent bone marrow micronucleus studies conducted with CK-2127107 indicated a lack of genotoxic hazard. CK-2127106 was equivocal in an in vitro cytogenetic assay conducted in human peripheral blood lymphocytes; in this assay, a statistically significant increase in the incidence of aberrant cells, compared to the vehicle control, was noted only at the highest CK-2127106 concentration evaluated (386 µg/mL) in the 21-hour regime.

Additional information concerning the pharmacology, pharmacokinetics (PK), and toxicology of CK-2127107 is available in the Investigator's Brochure (IB).

1.3. Overview of CK-2127107 Clinical Studies

Phase 1 Studies

CK-2127107 has been evaluated in five Phase 1 studies.

In a "first in human" study conducted in 35 healthy men (Study CY 5011), single oral doses of a SDD suspension (CK-2127107 ranging from 30 to 4000 mg were all well tolerated and no maximum tolerated dose was established.

In Study CY 5012, multiple dose administration of the CK-2127107 SDD suspension at 300 and 500 mg twice daily for either 10 or 17 days was well tolerated by 59 young and elderly healthy subjects and allowed the steady-state PK profile to be described.

A 4-way crossover, single dose PK/pharmacodynamic (PD) study (Study CY 5013) performed with placebo, 300 mg, 1000 mg and 3000 mg of the CK-2127107 SDD suspension demonstrated a dose- and concentration-dependent increase in the force-frequency relationship of the tibialis anterior muscle with transcutaneous electric stimulation of the deep fibular nerve.

Another study in 25 healthy men (Study CY 5014) was conducted to evaluate the relative oral bioavailability of a suspension of the crystalline form of CK-2127107, CK-2127107 active pharmaceutical ingredient (API), to the CK-2127107 SDD suspension dosed at 300 and 1000 mg.

Lastly, in Study CY 5015, the PK of a tablet formulated with CK-2127107 API was compared to CK-2127107 API suspension and found to have adequate bioavailability for use in future studies. The food effect of the tablet was also evaluated in Study CY 5015.

The terminal half-life ($t_{½}$) of CK-2127107 was generally around 12 hours with a time to maximum concentration (t_{max}) of 2-3 hours. The increase in exposure was largely dose-proportional although exposure was more variable at doses ≥3000 mg. There were no observed differences in PK parameters between young and elderly subjects but mean exposure was

slightly higher in women vs. men. A food effect was demonstrated with 2.6- and 1.6-fold increases in C_{max} and AUC_{∞}, respectively, following administration of the tablet formulation (500 mg as 2 x 250 mg tablets) with a high fat meal.

Exposure (C_{max} and AUC) to the inactive metabolite, CK-2127106, was higher after multiple doses of CK-2127107 compared to single doses. The geometric mean half-life of CK-2127106 ranged from 25.4 to 39.3 hours. Maximum concentrations (C_{max}) and area under the concentration-time curve (AUC) values increased somewhat greater than dose-proportionally following multiple dosing.

CK-2127107 was well tolerated at all dose levels with no serious adverse events (SAEs) or discontinuations due to an adverse event (AE). The most common (≥5%) AEs observed with CK-2127107 vs. placebo were dizziness, headache, nausea, and diarrhea. Dizziness, headache, and nausea appeared to be dose-related and their incidence increased at doses of 2250 mg and above. None of the AEs were classified as severe. Four subjects in the multiple dose study (one treated with placebo and three treated with CK-2127107 500 mg) had an AE of increased alanine aminotransferase (ALT)/hepatic enzymes; an additional three subjects (all treated with CK-2127107 500 mg) had at least one elevated liver enzyme during treatment with study drug that were not reported as an AE. Of these seven subjects, some of whom also had modest bilirubin elevations, none had values that met Hy's Law criteria. Other laboratory tests remained normal and consistent with baseline values following dosing with the exception of elevated serum creatinine values in most subjects treated with CK-2127107. This was observed consistently across all studies. CK-2127107 has been demonstrated to inhibit organic cation transporter (OCT) 2, a mediator of renal tubular secretion of creatinine in the human kidney, with a half maximal inhibitory concentration (IC_{50}) of 2.63 μM. Consequently, it is believed that inhibition of renal tubular OCT2 by CK-2127107 is the most likely reason for these generally small and reversible increases in serum creatinine during treatment with CK-2127107; inhibition of renal tubular secretion has also been observed with other drugs, such as cimetidine (Ducharme, Smythe et al. 1993). It is noted that a similar increase in creatinine has been observed in toxicology studies of CK-2127107 in monkey. In the 13-week monkey toxicology study, creatinine values returned to baseline after completion of dosing and there were no abnormalities in kidney histopathology noted, providing further support that this finding is not a reflection of renal toxicity.

Additional information on the Phase 1 clinical program can be found in the IB.

Ongoing Studies

There are 3 ongoing studies with CK-2127107.

3318-CL-3001 (NCT03065959) is a Phase 1b, double-blind, randomized, placebo-controlled, 2-period cross-over study of CK-2127107 of older healthy adults with limited mobility. Subjects are randomized (1:1) to placebo or 500 mg twice daily CK-2127107 for 14 days. The primary objective is to investigate the effect of CK-2127107 in tablet form on skeletal muscle fatigue assessed as change from baseline versus 14 days of treatment in sum of peak torque during isokinetic knee extensions.

CY 5021 (NCT02644668) is a Phase 2, double-blind, randomized, placebo-controlled, multiple-dose study of CK-2127107 in suspension form in two ascending dose cohorts of patients with spinal muscular atrophy ages 12 and older. The primary objective is to determine the potential

PD effects of CK-2127107 API suspension after multiple doses in patients with spinal muscular atrophy.

3318-CL-3002 (NCT02662582) is a Phase 2, randomized, double blind placebo-controlled, two period crossover study in patients with chronic obstructive pulmonary disease. The dose of CK-2127107 will be 500 mg twice daily and each period will be 14 days. The primary objective is to assess the effect of CK-2127107 in tablet form on physical function in subjects with chronic obstructive pulmonary disease.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to assess the effect of CK-2127107 versus placebo on respiratory function in patients with ALS.

2.1.1. Primary Efficacy Endpoint

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

2.2. Secondary Objectives

The secondary objectives of this study are:

- To assess the effect of CK-2127107 versus placebo on measures of skeletal muscle function
- To assess the effect of CK-2127107 versus placebo on global function
- To evaluate the safety and tolerability of CK-2127107 administered orally to patients with ALS
- To evaluate the exposure of CK-2127107 and its metabolites, when administered orally in tablet form to patients with ALS in the fed state

2.2.1. Secondary Endpoints

- Slope from baseline to Visit Week 12 in the mega-score of muscle strength measured by hand held dynamometry (HHD) and handgrip dynamometry
- Change from baseline to Visit Week 12 in the ALS Functional Rating Scale – Revised (ALSFRS-R)
- The incidence and severity of treatment-emergent adverse events (TEAEs)
- Plasma concentrations of CK-2127107 at the sampled time points during the study

2.3. Exploratory Objectives

The exploratory objectives of this study are:

- To assess the effect of CK-2127107 versus placebo on respiratory function self-assessments made at home by the patient with help as needed by the caregiver
- To assess the effect of CK-2127107 versus placebo on disease progression through measurement of speech production characteristics over time
- To assess the effect of CK-2127107 versus placebo on disease progression through measurement of handwriting abilities over time
- To assess the change from baseline to Visit Week 12 in quality of life (as measured by the ALS Assessment Questionnaire Short Form [ALSAQ-5]) and muscle strength in patients on CK-2127107 compared to placebo

- To assess the change in the slope of decline of measures of function in patients on CK-2127107 compared to placebo

2.3.1. Exploratory Endpoints

Endpoints assessed as a change from baseline include:

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

Endpoints assessed as a change in slope include:

- Slope of change from baseline to Visit Week 12 in the percent predicted SVC
- Slope of change from baseline to Visit Week 12 in the ALSFRS-R
- Slope of change from baseline to Visit Week 12 in percent predicted SVC measured at home
- Slope of change from baseline to Visit Week 12 in the components of voice analysis
- Slope of change from baseline to Visit Week 12 in the components of handwriting analysis
- Slope of change from baseline to Visit Week 12 in the ALSAQ-5

2.4. Pharmacokinetic / Pharmacodynamic Objective

The PK/PD objectives of this study are to characterize the PK of CK-2127107 following multiple doses in the fed state at three dose levels in ALS patients as well as to evaluate possible relationships between both dose and exposure of CK-2127107 and its PD effects following multiple oral doses in patients with ALS.

3. STUDY OVERVIEW

3.1. Study Design

This is a Phase 2, double-blind, randomized, placebo-controlled, dose ranging study of CK-2127107 in patients with ALS.

Approximately 445 eligible ALS patients will be randomized (1:1:1:1) to receive the following doses of CK-2127107 or placebo:

- 150 mg CK-2127107 twice a day for a 300 mg total daily dose (TDD)
- 300 mg CK-2127107 twice a day for a 600 mg TDD
- 450 mg CK-2127107 twice a day for a 900 mg TDD
- Placebo twice daily

Study medication should be taken twice daily, approximately 12 hours (± 2 hours) apart, and should be taken within the 2 hour period following a meal.

An overview of the randomized treatment groups is provided in Table 1:

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

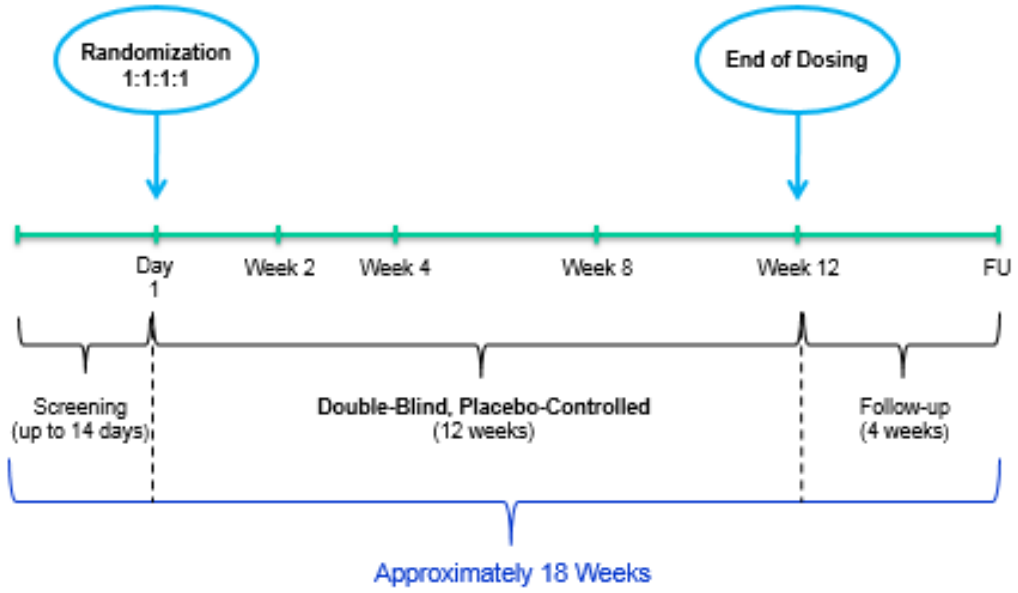
CK-2127107			**Placebo**
300 mg TDD 1 tablet (150 mg) of CK-2127107 and 2 placebo tablets twice daily for 12 weeks	600 mg TDD 2 tablets (150 mg) of CK-2127107 and 1 placebo tablet twice daily for 12 weeks	900 mg TDD 3 tablets (150 mg) of CK-2127107 twice daily for 12 weeks	3 placebo tablets twice daily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

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

There will be a total of seven study visits for each patient:

- Screening
- First Dosing Day (Day 1)
- Week 2
- Week 4
- Week 8
- Week 12
- Follow-Up Visit (4 weeks after last dose of study drug)

Figure 1: Patient Visit Diagram



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

3.2. Study Rationale

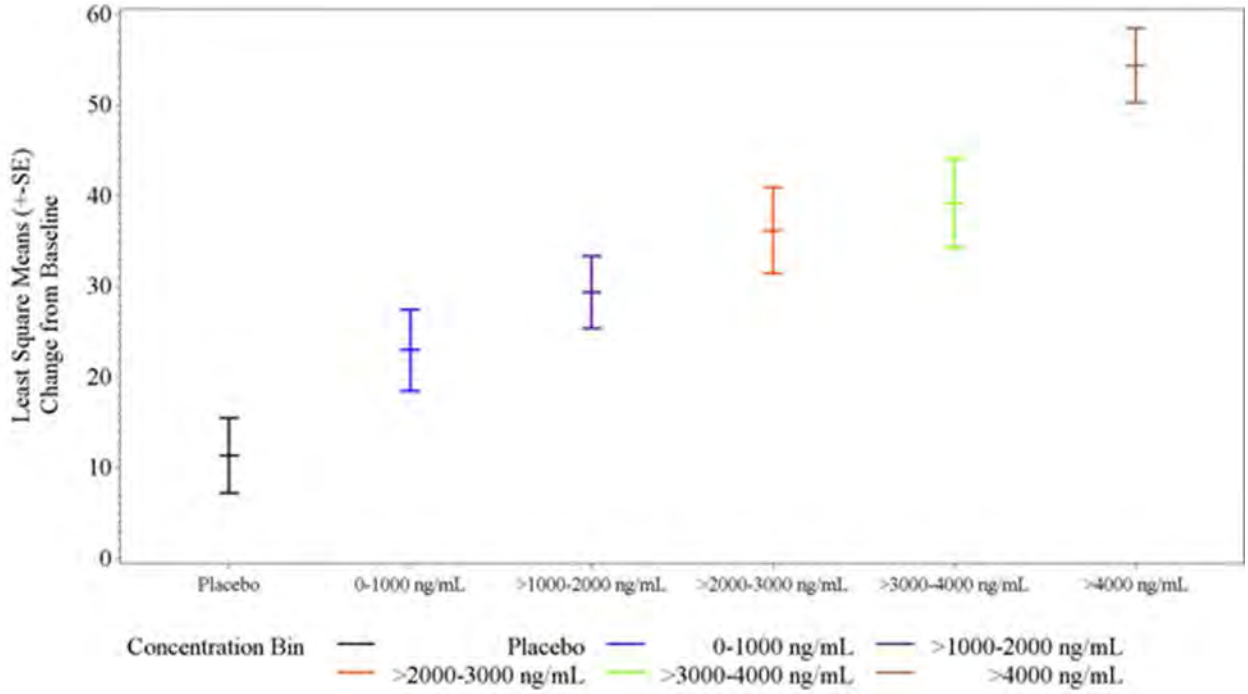
CK-2127107 is being investigated as a potential new therapy to slow the decline of skeletal muscle function, and in particular, slow the decline of respiratory function in patients with ALS. This is the first study being conducted in these patients with CK-2127107 and is designed to assess the effect of 12 weeks of its dosing on measures of muscle function in patients with ALS. The plasma concentration of CK-2127107 will be measured at selected time points during the course of dosing and the plasma concentrations obtained in this study may be used to conduct exposure-response analyses. A drug with a similar mechanism of action, tirasemtiv, is currently being investigated in a Phase 3 study in ALS (CY 4031, VITALITY-ALS) and in an open label extension study to CY 4031 (CY 4033, VIGOR-ALS). In a Phase 2b study (CY 4026, BENEFIT-ALS), patients on tirasemtiv had a reduction in the rate of decline in SVC compared to placebo.

3.3. Dose Rationale

CK-2127107 will be administered as 150 mg tablets, at doses of 300 mg/day, 600 mg/day, or 900 mg/day TDD in the fed state as described above in Table 1. Based on initial population PK modeling of the Phase 1 study data, these three doses yield predicted mean C_{max} values (%CV) ranging from approximately 1789 (44.1) to 5543 (35.9) ng/mL assuming exposures in ALS patients are similar to healthy volunteers. The doses selected in the current study should produce plasma concentrations that span the PD range observed in the healthy volunteer population in Study CY 5013.

In Study CY 5013, plasma concentrations were sampled at the time of nerve stimulation in order to understand the relationship between CK-2127107 plasma exposures and resulting changes from baseline force. Figure 2 shows that these plasma concentrations produce significant concentration-dependent increases in force at submaximal stimulation frequencies with the largest force increases at 10 Hz.

Figure 2: CY 5013: Increases in Force during Nerve Stimulation in Healthy Volunteers



Based on prior clinical experience, the doses selected for this study are expected to be well tolerated and potentially pharmacodynamically active. The information obtained in this study will guide the selection of doses for a potential Phase 3 clinical study of CK-2127107 in patients with ALS.

4. STUDY POPULATION

Approximately 500 patients with ALS will be screened in order to enroll at least 445 patients with ALS who fulfill the eligibility criteria.

4.1. Inclusion Criteria

Patients who meet all the following criteria may be included in the study:

1. Able to comprehend and willing to sign an Informed Consent Form (ICF)
2. Males or females between the ages of 18 and 80 years of age, inclusive
3. Diagnosis of familial or sporadic ALS (defined as meeting the possible, laboratory-supported probable, probable, or definite criteria for a diagnosis of ALS according to the World Federation of Neurology El Escorial criteria published in 2000 (Brooks, Miller et al. 2000) ≤ 24 months prior to screening
4. Upright SVC ≥ 60% of predicted for age, height and sex at screening
5. Able to swallow tablets
6. A caregiver (if one is needed)
7. Able to perform reproducible pulmonary function tests
8. Pre-study clinical laboratory findings within the normal range or, if outside the normal range, deemed not clinically significant by the Investigator
9. Male patients, who have not had a vasectomy and a confirmed zero sperm count, must agree after receiving the first dose of study drug until 10 weeks after the last dose to do either of the following:

    - use a condom during sexual intercourse with female partners who are of reproductive potential AND to have female partners use an additional effective means of contraception (e.g., diaphragm plus spermicide, or oral contraceptives)

    OR

    - abstain from sexual intercourse

10. Female patients must be post-menopausal (≥ 1 year) OR sterilized, OR if of childbearing potential (i.e., females who have had their first period unless they are anatomically and physiologically incapable to become pregnant), must:

    - not be breastfeeding,
    - have a negative pregnancy test,
    - have no intention of becoming pregnant during the course of the study, AND do either of the following:
        - use contraceptive drugs or devices as detailed in item number 9 from Screening until 10 weeks after the last dose of study drug AND require male partners to use a condom during sexual intercourse

    OR

- abstain from heterosexual intercourse from Screening until 10 weeks after the last dose of study drug

11. Patients must be either on riluzole for at least 30 days prior to screening or have not taken riluzole for at least 30 days prior to screening and not planning to start riluzole during the course of the study.
12. Patients on edaravone must have completed at least 2 cycles of dosing with edaravone at the time of screening or have not taken edaravone for at least 30 days prior to screening and not planning to start edaravone during the course of the study. Two cycles of dosing are defined as having completed Cycle 1 infusion, which is 14 consecutive days of intravenous (IV) edaravone followed by 14 days off edaravone, and Cycle 2, which is 10 out of 14 days of IV edaravone.

4.2. Exclusion Criteria

Any of the following will exclude potential patients from the study:

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

j. Cancer with metastatic potential (other than basal cell carcinoma, carcinoma in situ of the cervix, or squamous cell carcinoma of the skin excised with clean margins) diagnosed and treated within the last five years
k. Any other condition, impairment or social circumstance that, in the opinion of the Investigator, would render the patient not suitable to participate in the study
l. Patient judged to be actively suicidal or a suicide risk by the Investigator
m. Patient has estimated glomerular filtration rate (eGFR) less than 40 mL/min/1.73 m^2 calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) cystatin equation based on a cystatin C measurement at baseline

4. Has taken any investigational study drug within 30 days or five half-lives of the prior agent, whichever is longer, prior to dosing
5. Known to have received CK-2127107 or tirasemtiv in any previous clinical trial
6. Has received or is considering receiving during the course of the study any form of stem cell therapy for the treatment of ALS
7. Has received or is considering receiving during the course of the study any form of gene therapy for the treatment of ALS
8. Has received or is considering obtaining during the course of the study a diaphragmatic pacing system
9. History of substance abuse within the past 2 years
10. Use of a strong cytochrome P450 (CYP) 3A4 inhibitor within 7 days prior to first dose of study drug or a strong CYP3A4 inducer within 14 days prior to first dose of study drug
11. Use of a medication that is an OCT1/OCT2 substrate within 7 days (see Appendix B)

5. STUDY PROCEDURES

5.1. Screening

A signed ICF will be obtained from each patient prior to performing any study-specific procedures. A copy of the ICF will be retained in the study file and a copy will be provided to the patient.

The following screening procedures will be performed for all potential patients at a visit conducted within 14 days of study entry:

1. Demographic data
2. Medical history, including review of concomitant medications, tobacco and alcohol usage
3. Review of inclusion/exclusion criteria
4. Height, body weight, and calculation of body mass index (BMI)
5. Routine physical examination
6. Neurological examination
7. 12-lead ECG
8. Vital signs, including temperature, heart rate, blood pressure, and respiratory rate measured after the patient has been resting for at least 3 minutes
9. Clinical laboratory evaluations, including complete blood count (CBC) and white blood cells (WBC) with differential, serum chemistries, cystatin C, urinalysis (UA), and thyroid stimulating hormone (TSH)
10. Pregnancy test for all females of childbearing potential
11. SVC
12. Muscle strength measurements
13. ALSFRS-R
14. Voice recording
15. Fine motor measurement of handwriting and tracing of forms via an app (if the device is suitable for use in that region)
16. Ashworth score
17. ALSAQ-5
18. Beck Depression Inventory-Fast Screen (BDI-Fast Screen)

Once a patient is confirmed eligible to participate and before the first dose on Day 1, patients will be randomized to receive either CK-2127107 or placebo.

5.2. First Dosing Day (Day 1)

Prior to study drug dosing on Day 1, the following procedures will be performed:

1. Vital signs, including heart rate, blood pressure, and respiratory rate measured after the patient has been resting for at least 3 minutes
2. Weight and calculation of BMI
3. Clinical laboratory evaluations, including CBC and WBC with differential, serum chemistries, cystatin C and UA
4. PK blood sample
5. SVC
6. Muscle strength measurements
7. ALSFRS-R
8. Voice recording
9. Fine motor measurement of handwriting and tracing of forms via an app (if the device is suitable for use in that region)
10. Ashworth score
11. Falls assessment
12. ALSAQ-5
13. Record Health Economic Outcomes Measures
14. AE/SAE evaluation and concomitant medication assessment (since last visit)
15. BDI-Fast Screen

Patients will receive their first dose of study drug (CK-2127107 or placebo) within 2 hours of a meal.

The following assessment will be performed after the first dose of study drug is given:

16. PK blood sample at 1 hour post-dose

Training will also be provided to the patient for the measurements patients will perform at home.

- For patients who have access to a mobile device, the application will be downloaded to the device and instructions provided as detailed in the study manual on recording voice.
- All patients will be trained in performing SVC using a portable spirometer (if the device is suitable for use in that region) as detailed in the study manual.

Home voice recordings and SVC testing will be performed by the patient weekly for the duration of the study following Day 1.

Patients will be given an adequate supply of study drug (CK-2127107 or placebo) to take twice daily for 4 weeks. A dosing diary will be provided for patients to record the date and time of twice daily study drug administration.

5.3. Week 2 Visit

Prior to study drug dosing at the Week 2 Visit, the following procedures will be performed:

1. Vital signs, including heart rate, blood pressure, and respiratory rate measured after the patient has been resting for at least 3 minutes
2. Weight and calculation of BMI
3. PK blood sample
4. Clinical laboratory evaluations, including CBC and WBC with differential, serum chemistries, cystatin C and UA
5. SVC
6. Muscle strength measurements
7. ALSFRS-R
8. Voice recording
9. Fine motor measurement of handwriting and tracing of forms via an app (if the device is suitable for use in that region)
10. Ashworth score
11. Falls assessment
12. ALSAQ-5
13. Record Health Economic Outcomes Measures
14. AE/SAE evaluation and concomitant medication assessment (since last visit)
15. BDI-Fast Screen

Patients will receive their dose of study drug (CK-2127107 or placebo) within 2 hours of eating a meal. Patients should be reminded to bring their unused study drug with them to the clinic and that they will be taking their dose of study drug while at the clinic. The following assessment will be performed after the dose of study drug is given:

16. PK blood sample at 1 hour post-dose

Patients will have already been given their supply of study drug (CK-2127107 or placebo) to take twice daily at home until their next clinic visit at Week 4. A dosing diary will be provided for patients to record the date and time of twice daily study drug administration.

5.4. Week 4 Visit

Prior to study drug dosing at the Week 4 Visit, the following procedures will be performed:

1. 12-lead ECG
2. Vital signs, including heart rate, blood pressure, and respiratory rate measured after the patient has been resting for at least 3 minutes
3. Weight and calculation of BMI
4. PK blood sample
5. Clinical laboratory evaluations, including CBC and WBC with differential, serum chemistries, cystatin C and UA

6. SVC
7. Muscle strength measurements
8. ALSFRS-R
9. Voice recording
10. Fine motor measurement of handwriting and tracing of forms via an app (if the device is suitable for use in that region)
11. Ashworth score
12. Falls assessment
13. ALSAQ-5
14. Record Health Economic Outcomes Measures
15. AE/SAE evaluation and concomitant medication assessment (since last visit)
16. BDI-Fast Screen

Patients will receive their dose of study drug (CK-2127107 or placebo) within 2 hours of eating a meal.

Patients will be given an adequate supply of study drug (CK-2127107 or placebo) to take twice daily for 4 weeks at home until their next clinic visit at Week 8. A dosing diary will be provided for patients to record the date and time of twice daily study drug administration.

5.5. Week 8 Visit

Prior to study drug dosing at the Week 8 Visit, the following procedures will be performed:

1. Vital signs, including heart rate, blood pressure, and respiratory rate measured after the patient has been resting for at least 3 minutes
2. Weight and calculation of BMI
3. PK blood sample
4. SVC
5. Muscle strength measurements
6. ALSFRS-R
7. Voice recording
8. Fine motor measurement of handwriting and tracing of forms via an app (if the device is suitable for use in that region)
9. Ashworth score
10. Falls assessment
11. ALSAQ-5
12. Record Health Economic Outcomes Measures
13. AE/SAE evaluation and concomitant medication assessment (since last visit)

14. BDI-Fast Screen

Patients will receive their dose of study drug (CK-2127107 or placebo) within 2 hours of eating a meal.

Patients will be given an adequate supply of study drug (CK-2127107 or placebo) to take twice daily for 4 weeks at home. A dosing diary will be provided for patients to record the date and time of twice daily study drug administration.

5.6. Week 12 Visit

Prior to the last dose of study drug at the Week 12 Visit, the following procedures will be performed:

1. Vital signs, including heart rate, blood pressure, and respiratory rate measured after the patient has been resting for at least 3 minutes
2. Weight and calculation of BMI
3. PK blood sample
4. Clinical laboratory evaluations, including CBC and WBC with differential, serum chemistries, cystatin C and UA
5. SVC
6. Muscle strength measurements
7. ALSFRS-R
8. Voice recording
9. Fine motor measurement of handwriting and tracing of forms via an app (if the device is suitable for use in that region)
10. Ashworth score
11. Falls assessment
12. ALSAQ-5
13. Record Health Economic Outcomes Measures
14. AE/SAE evaluation and concomitant medication assessment (since last visit)
15. BDI-Fast Screen

Patients will receive their dose of study drug (CK-2127107 or placebo) within 2 hours of eating a meal. The following assessment will be performed after the last dose of study drug is given:

16. PK blood sample at 1 hour post-dose

5.7. Follow-Up Visit

The following procedures will be performed at a Follow-Up Visit 4 weeks after each patient's final dose of study drug:

1. 12-lead ECG

2. Vital signs including heart rate, blood pressure, and respiratory rate measured after the patient has been resting for at least 3 minutes
3. Weight and calculation of BMI
4. Abbreviated physical examination
5. Neurological examination
6. Clinical laboratory evaluations, including CBC and WBC with differential, serum chemistries, cystatin C, UA, and TSH
7. Pregnancy test for all females of childbearing potential
8. SVC
9. Muscle strength measurements
10. ALSFRS-R
11. Voice recording
12. Fine motor measurement of handwriting and tracing of forms via an app (if the device is suitable for use in that region)
13. Ashworth score
14. Falls assessment
15. ALSAQ-5
16. Record Health Economic Outcomes Measures
17. AE/SAE evaluation and concomitant medication assessment (since last visit)
18. BDI-Fast Screen

5.8. Early Termination Visit

If a patient decides to terminate early from the study, they should be seen in the clinic as soon as possible following discontinuation of study drug. The following procedures will be performed:

1. 12-lead ECG
2. Vital signs including heart rate, blood pressure, and respiratory rate measured after the patient has been resting for at least 3 minutes
3. Weight
4. Abbreviated physical examination
5. Neurological examination
6. Clinical laboratory evaluations, including CBC and WBC with differential, serum chemistries, cystatin C and UA
7. SVC
8. Muscle strength measurements
9. ALSFRS-R

10. Voice recording
11. Fine motor measurement of handwriting and tracing of forms via an app (if the device is suitable for use in that region)
12. Ashworth score
13. Falls assessment
14. ALSAQ-5
15. Record Health Economic Outcomes Measures
16. AE/SAE evaluation and concomitant medication assessment (since last visit)
17. BDI-Fast Screen

If a patient decides to terminate early from the study but does not wish to return to the clinic for an Early Termination Visit, they should be contacted by phone whenever possible and the following information should be collected:

1. ALSFRS-R
2. ALSAQ-5
3. Record Health Economic Outcomes Measures
4. Falls Assessment
5. AE/SAE evaluation and concomitant medication assessment (since last visit)

5.9. Visit Windows

To aid in scheduling patient visits, the following study visit windows are considered acceptable (Table 2). If a patient visit must be scheduled outside the visit window, the Medical Monitor should be contacted.

Table 2: Visit Windows

Visit	Visit Window
Screening	Up to 14 days prior to Day 1 visit (as per protocol)
Day 1	First day of randomized, double-blind dosing
Week 2 (Day 15)	± 2 days
Week 4 (Day 29)	± 2 days
Week 8 (Day 57)	± 4 days
Week 12 (Day 85)	± 4 days
Follow-Up	4 weeks after last dose of study drug ± 4 days

5.10. Diet Control

All doses of study drug should be taken within 2 hours following a meal.

Subjects will abstain from consuming grapefruit and Seville oranges along with foods or beverages containing them from Day 1 through the Follow-Up visit.

5.11. Concomitant Medications

All prescription drugs, over-the-counter medications, nutraceuticals and herbal remedies taken by the patient from the time of screening through the Follow-Up visit should be entered into the electronic case report form (eCRF). 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 (End of Week 8). 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 12). Please refer to Appendix B for 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 CK-2127107 may have the potential to inhibit OCT1 and OCT2-mediated transport. Please refer to Appendix B for OCT1/OCT2 substrates that should be avoided or used with caution.

5.12. Pharmacokinetic Sampling

Blood samples for analysis of CK-2127107, its metabolites, and riluzole will be collected from patients at the nominal time points listed in Table 3.

Table 3: Pharmacokinetic (PK) Samples

Day	Sample Time Points
Day 1	Pre-dose and 1 (±15 min) hour post-dose
Week 2	Pre-dose and 1 (±15 min) hour post-dose
Week 4	Pre-dose
Week 8	Pre-dose
Week 12	Pre-dose and 1 (±15 min) hour post-dose

If an indwelling catheter is used, saline flushes will be used. In some cases, sites may be unable to obtain the 6 hour timepoint at Week 2 or Week 12 for logistical reasons; these cases should be discussed with the medical monitor preferably ahead of time.

After completion of bioanalysis, remaining plasma samples will be retained consistent with the Sponsor's standard operating procedures. These samples will not be used for pharmacogenomic testing.

5.13. Clinical Safety Assessments

5.13.1. Clinical Laboratory Evaluations

Clinical laboratory evaluations will be collected at Screening, Day 1, Week 2 visit, Week 4 visit, Week 12 visit, and at the Follow-Up Visit as described in Appendix D.

5.13.2. 12-Lead Electrocardiograms

A 12-lead ECG, including ECG parameters of RR, PR, QRS, QT and QTc intervals as well as significant findings will be obtained at Screening, Week 4 visit, and at the Follow-Up Visit.

When 12-lead ECGs are scheduled at the same time as blood draws, the order of evaluation will be ECG, vital signs, and then blood draw.

5.13.3. 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 every visit. Temperature will also be obtained at the Screening visit. Height is obtained only at the screening visit. Weight will be obtained at each visit; and BMI will be calculated at screening and subsequent visits.

When vital signs are scheduled at the same time as blood draws, the order of evaluation will be ECG, vital signs, and then blood draw.

5.13.4. AE Assessments

Patients will be asked how they are feeling from the first administration of study drug through the Follow-Up visit (see Section 7.2). Patients will also be encouraged to voluntarily report any AEs they experience during the study.

5.13.5. Physical Examinations

A routine physical examination will be performed at Screening, and an abbreviated physical examination (consisting of an examination of general appearance, skin, lungs, cardiovascular and abdomen) will be performed at the Follow-Up Visit.

5.13.6. Neurological Examinations

A neurological examination will be administered at Screening and at the Follow-Up Visit as described in the Study Manual.

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

The BDI-Fast Screen will be assessed at all study visits as described in the Study Manual.

5.13.8. Falls Assessment

Falls assessment will be performed at each study visit except Screening as described in the Study Manual.

5.13.9. Ashworth Scale

The Ashworth scale to assess spasticity will be performed at each study visit. Further description of the Ashworth Scale can be found in the Study Manual.

5.14. Clinical and Pharmacodynamic Outcome Measures

5.14.1. Pulmonary Function Assessment

The pulmonary function assessment in this study will be SVC. Pulmonary function assessment will be performed at each study visit as described in the Study Manual. Patients will also perform home SVC assessments weekly through the course of the study following Day 1 (if the device is suitable for use in that region) as described in the Study Manual.

5.14.2. Hand-Held Dynamometry

Muscle strength measurements of selected muscles will be performed using HHD and hand grip dynamometry at each study visit as described in the Study Manual.

5.14.3. ALSFRS-R

The ALSFRS-R will be performed at each study visit as described in the Study Manual.

5.14.4. Voice Recording

Voice recording will be performed at each study visit and for patients who have access to mobile devices weekly at home as described in the Study Manual.

5.14.5. Fine Motor Assessments (Handwriting and Figure Tracing)

The handwriting and figure tracing assessments will be done at each study visit (if the device is suitable for use in that region) as described in the Study Manual.

5.14.6. ALSAQ-5

The ALSAQ-5 will be performed at each study visit as described in the Study Manual.

5.14.7. Health Economic Outcomes Measures

During the course of the study, if the patient is prescribed and agrees to receive any of the following, it will be recorded including the date prescribed:

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

5.15. Removal of Patients from Study Participation

Patients will be informed that they are free to discontinue study drug or withdraw from the study at any time and for any reason. The Investigator may discontinue study drug or withdraw a patient from the study if, in the Investigator's opinion, it is not in the best interest of the patient to continue the study. Patients may discontinue study drug or withdraw from the study due to the following:

a. A change in compliance with inclusion/exclusion criteria that is clinically relevant and/or affects patient safety, and/or study assessments/objectives, etc.
b. Occurrence of intolerable AEs
c. Changes in vital signs, ECGs, or clinical laboratory results that, in the opinion of the Investigator, pose a significant health risk
d. Intake of non-permitted concomitant medication that might affect patient safety or study assessments/objectives, etc.

e. eGFR calculated using the CKD-EPI cystatin equation (Inker, Schmid et al. 2012) shows a >25% decline compared to baseline (defined as Day 1 or Screening if Day 1 value is not available) as long as the decline is not related to dehydration or a superimposed reversible process such as infection or nausea.
f. Changes in liver function tests (LFTs) as outlined in Appendix C
g. Receiving any form of stem cell therapy for ALS either as part of a clinical trial or outside of a clinical trial
h. Having a diaphragmatic pacing system implanted either as part of a clinical trial or outside of a clinical trial
i. Initiating edaravone after screening.
j. Initiating riluzole after screening.
k. Initiating gene therapy for ALS either as part of a clinical trial or outside of a clinical trial after screening.

Patients should be strongly encouraged to perform the early termination visit as soon as possible following last dose of study drug taken, and the Follow-Up Visit should be performed 28 days after last dose taken of study medication. In addition, they should be encouraged to return for all remaining study visits and assessments (with the exception of 12-lead ECG, clinical laboratory and PK sampling) for the duration of the study following study drug discontinuation. These remaining study visits should be performed according to the original study visit windows.

Patients who decide to start or stop edaravone or riluzole after screening and before randomization, will no longer be eligible to be randomized and should not be followed subsequently. If a patient decides to start edaravone or riluzole after randomization, they will be terminated from taking study medication once that is known by the site. They should return to the clinic for their early drug termination visit as soon as possible following last dose of study drug taken and return 28 days after last dose taken for the Follow-Up Visit. They will not be followed thereafter.

For patients who terminate early from the study and do not want to return to the clinic for the visits as described in the above paragraph, phone call visits should be performed to collect the information if the patient is willing (see Section 5.8).

Notification of discontinuation will immediately be made to the Sponsor's Medical Monitor. In case of withdrawal of study participation, efforts will be made to perform Early Termination (Section 5.8) and Follow-Up visit assessments (Section 5.7). The date the patient is withdrawn from the study and the reason for discontinuation will be recorded on the patient's eCRF. All patients who prematurely discontinue from the study for AEs will be followed for up to 30 days, until the AE resolves, or until the unresolved AE is judged by the Investigator to have stabilized.

The primary reason for a patient prematurely withdrawing from the study should be selected from the following categories and documented in the source documents:

a. Patient Death
b. Adverse Event: One or more clinical or laboratory events which, in the medical judgment of the Investigator, are grounds for discontinuation even if the event does not appear to be related to study medication. The patient may withdraw because of an AE even if the Investigator does not feel that the event is grounds for discontinuation.
c. Protocol Violation: The patient's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements

d. Patient Withdrawal of Consent: Patient desires to withdraw from further participation in the study and reason for doing so.
e. Administrative/Other: Any cause of premature termination from the study other than the above, such as illness of investigator, loss of study drug, or termination of study by the Sponsor.

5.16. Assessment of Safety

An independent Data Monitoring Committee (DMC) will periodically assess patient safety in an unblinded manner during the course of the study. No unblinded data will be accessible to site staff, the Sponsor, study monitors, and personnel of the electronic data capture vendors before the database is locked. The specific activities and responsibilities of the DMC are defined in the DMC Charter for CY 5022.

Dosing of an individual will be stopped and not resumed if treatment-related AEs, changes in vital signs, ECGs, or clinical laboratory results are observed and these changes pose a significant health risk, in the opinion of either the Investigator or the Sponsor Medical Monitor. A blood sample for PK analysis should be collected at the time of the event or as close as possible to the time of the event.

In the event of a confirmed, marked hepatic abnormality as defined in Appendix C (Liver Safety Monitoring and Assessment), it is the Investigator's responsibility to ensure contact with the Sponsor immediately (i.e., within 24 hours of awareness or at the earliest possible time point). Patients with AEs of hepatic origin accompanied by LFT abnormalities should be carefully monitored.

5.17. Study Drug Interruption

Patients who do not take the total assigned daily dose of study drug due to conditions of hospitalization or other circumstances should be encouraged to return to treatment. The Medical Monitor should be contacted for a patient who has discontinued treatment for more than one week (prolonged study drug interruption).

If study drug interruption for more than one week has occurred, the Investigator should evaluate the patient in clinic to ensure that it is safe for the patient to resume study drug dosing and consult with the Medical Monitor for the appropriate course of action.

5.18. Study Discontinuation

The study may be discontinued by the Sponsor for the following reasons:

- Excessive rates of AEs
- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients
- A decision to cease or delay further development of the drug

6. INVESTIGATIONAL PRODUCT

6.1. Description of Investigational Product

This is a double-blind, placebo-controlled study. As such, the site pharmacy staff, the Investigator, the patient, remaining study site clinical staff, and the Sponsor will be blinded to treatment assignment.

CK-2127107 study drug is supplied as immediate release, white to off-white, modified capsule-shaped tablets at a dose strength of 150 mg of CK-2127107 per tablet, which are to be stored under secure conditions at ≤25°C (77°F) with excursions allowed up to 30°C (86°F).

Matching placebo tablets will be supplied and should also be stored at controlled room temperature under secure conditions.

Active CK-2127107 tablets contain 150 mg of CK-2127107 plus excipients. Placebo tablets contain excipients only.

Table 4: Study Drug

Study Drug	**CK-2127107**	**Placebo for CK-2127107**
Form	Tablet	Tablet
Supplier	Cytokinetics, Inc.	Cytokinetics, Inc.
Manufacturer	Patheon, Inc.	Patheon, Inc.

CK-2127107 and matching placebo tablets will be supplied to the clinical site in blister strips inside labeled wallets. Patients will receive one or more wallets of study drug, CK-2127107 or matching placebo at the appropriate visit. Each wallet is sufficient for one week of dosing, plus overage. Double-blind wallets will be labeled with a unique random kit number.

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

6.2. Dose Administration (CK-2127107 or Placebo)

This study drug will be administered orally as tablets to patients with ALS. Doses (CK-2127107 or placebo) for each of the treatment groups will be dispensed in accordance with the study randomization prior to the patient's first dose.

6.3. Dosing Diary

A dosing diary will be maintained by the patient to record date and time of twice daily study drug administration. The dosing diary should be returned at each clinic visit.

6.4. Randomization Schedule and Removal of Blind

An IWRS will provide patient randomization assignments for this study. The site pharmacist or other qualified person responsible for randomizing patients will receive the appropriate kit numbers through the IWRS and provide it to the site staff who will be distributing study drug to the patient. RANDOMIZATION INFORMATION MAY BE MADE AVAILABLE TO THE

INVESTIGATOR ONLY IN THE EVENT OF A MEDICAL EMERGENCY OR AN AE THAT NECESSITATES IDENTIFICATION OF THE STUDY DRUG (CK-2127107 or placebo) FOR THE WELFARE OF THAT PATIENT. Except in a medical emergency, the Investigator (or designee) and study site clinical staff will remain blinded during the conduct of the study and until such time that all discrepancies in the clinical database are resolved (i.e., at the time of the database lock). The date/initials and reason for study blind removal by the Investigator and/or clinical staff will be documented. The Investigator will contact the Sponsor as soon as possible before or immediately following the emergency unblinding of any patient.

6.5. Study Drug Accountability and Disposal

The site pharmacist or other qualified person responsible for managing study drug supplies will maintain an accurate record of the receipt of the investigational study drug as shipped by the Sponsor (or designee), including the kit number and date received. One copy of this receipt will be returned to the Sponsor when the contents of the investigational study drug shipment have been verified. An accurate drug disposition record will be kept, specifying the study drug provided to each patient and the dates of dose administration. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

The patient should be instructed to return all unused study drug to the designated clinical site staff at each study visit. Study drug accountability is to be conducted by the designated study staff member with the patient at each study visit. The dosing diaries should also be referenced when completing drug accountability.

All unused drug supplies will be returned to the Sponsor (or designee) or disposed of by the clinical research unit, per the Sponsor’s (or designee’s) instructions at the end of the study.

7. ADVERSE EVENTS

7.1. Definitions

7.1.1. Adverse Event

As defined by the International Conference on Harmonisation (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product, and which does not necessarily have to have a causal relationship with the investigational product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the investigational product.

Examples of an AE:

- Conditions newly detected or diagnosed after the administration of the investigational product, including conditions that may have been present but undetected prior to the start of the study
- Conditions known to have been present prior to the start of the study that increase in severity or frequency after the administration of the investigational product
- Signs, symptoms, or the clinical sequelae of a suspected drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose (overdose per se should not be reported as an AE term)
- Abnormal laboratory findings (e.g., clinical chemistry, hematology) or other abnormal assessments (e.g., ECGs, vital signs, etc.) that are considered by the Investigator as a clinically significant change after the first dose of the investigational product. The Investigator will exercise his/her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is a clinically significant change after the first dose of the investigational product.

Issues Not Considered AEs:

- Medical or surgical procedures (e.g., appendectomy). The AE is the condition that leads to the procedure (e.g., appendicitis) if it qualifies according to the definition above.
- Hospitalizations where an untoward medical occurrence did not occur. Examples include:
  - hospitalization for social reasons such as unavailability of a caregiver outside of the hospital due to living situation, OR
  - hospitalization for percutaneous endoscopic gastrostomy placement prior to signing the ICF
- Fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not represent a clinically significant change after the first dose of the investigational product.

- Abnormal laboratory or test findings that are not assessed by the Investigator as a clinically significant change after the first dose of the investigational product.

7.1.2. Serious Adverse Event

A serious adverse event (SAE) is any AE that:

a. Results in death

NOTE: Death is selected as a seriousness criterion ONLY when the event is the cause of death. Death is an outcome and the event which led to the death should be the reported event term.

b. 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 that hypothetically might have caused death if it were more severe, prolonged, or untreated.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE: Hospitalization signifies that the subject has been admitted to the hospital as an in-patient for any length of time. Emergency room treatment does not qualify for this category, but may be appropriately included in category f (see below). If a complication prolongs the hospitalization or fulfills any other seriousness criterion or criteria, the complication will be considered an additional SAE. When in doubt as to whether 'hospitalization' occurred, consult the Medical Monitor.

Hospitalization should not be considered an AE term in itself. It will be considered an outcome of an AE. For example, hospitalization for an elective treatment of a pre-existing condition that did not worsen after the first dose of the investigational product will not be considered an AE.

d. Results in disability/incapacity

NOTE: The term disability means a substantial or permanent disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) that may temporarily interfere with or prevent everyday life functions but do not constitute a substantial or permanent disruption.

e. Is a congenital anomaly/birth defect

f. Is an important medical event

NOTE: Medical and scientific judgment should be exercised in deciding if an event should be reported as serious. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition may be considered serious. Examples of such events are 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. If in doubt as to whether or not an event qualifies as an "important medical event", consult the Sponsor's Medical Monitor.

7.2. Collection of AEs/SAEs

During each scheduled visit, ask about potential AEs or SAEs using the following standard questions:

1. Have you had any medical problems since your last visit?
2. Have you taken any new medications since your last visit?

7.3. Recording and Reporting of AEs/SAEs

7.3.1. Recording and Reporting of AEs

Events occurring between the Screening Visit and just prior to the first dose of the investigational product on Day 1 should be recorded in the Medical History eCRF unless the event is related to a protocol-mandated procedure. If the event is deemed related to a protocol-mandated procedure (e.g., hematoma at the puncture site) and deemed clinically significant by the Investigator, the event should be reported as an AE or an SAE (if applicable).

AEs will be documented from the first administration of the investigational product through the Follow-Up Visit. The Investigator will review all documentation (e.g., hospital progress notes, laboratory and diagnostic reports) relevant to the event. A diagnosis will then be determined based on signs, symptoms, and/or other clinical information. The diagnosis and not the individual signs/symptoms should be reported as the AE term.

ALS progression and signs/symptoms that are expected as part of ALS progression (see Section 7.4.3) will not be collected as AEs unless they meet seriousness criteria and should be recorded as SAEs.

7.3.2. Recording and Reporting of SAEs

If an AE meets any of the seriousness criteria (see Section 7.1.2), it must be reported using the SAE report form **within 24 hours of the site's knowledge**. At a minimum, the following information should be included:

- Patient number
- Event term, including an onset date and stop date, if applicable, and a brief description
- Seriousness criterion/criteria
- Causality assessment in relation to the investigational product

If all information regarding the SAE is not initially available, the site should still report the SAE within 24 hours of awareness/discovery. Additional information should be reported when it becomes available and no later than 24 hours after receipt of such information.

7.4. Evaluating AEs and SAEs

7.4.1. Assessment of Severity

The Investigator should assess the severity of each AE/SAE. The severity of AEs/SAEs will be assessed by assigning a Grade of 1, 2, 3, 4 or 5 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, except for ALT, AST, and TBL levels as described in Appendix C.

When an AE/SAE cannot be graded by CTCAE, the following severity grade may be used:

- Grade 1 (Mild): Aware of sign or symptom, but easily tolerated and intervention is not indicated
- Grade 2 (Moderate): Discomfort enough to cause interference with usual activity, local or non-invasive intervention is indicated
- Grade 3 (Severe): Incapacitating with inability to work or do usual activity, not immediately life-threatening; hospitalization or prolongation of hospitalization may be indicated
- Grade 4 (Life-Threatening): Refers to an event in which the patient was, in the view of the Investigator, at risk of death at the time of the event. (This category is not to be used for an event that hypothetically might have caused death if it were more severe.); urgent intervention is indicated
- Grade 5 (Fatal): Death related to AE

Severity should not be confused with seriousness. Severity is a category for rating the intensity of an event, and an event becomes serious when it meets one of the outcomes described in Section 7.1.2 “Serious Adverse Event”.

7.4.2. Assessment of Causality

The Investigator will assign causality to each SAE (related or unrelated). When assessing relationship to study drug, the Investigator will consider the following factors:

- Temporal association between the administration of the investigational product and the event
- Cessation of the AE following discontinuation of dosing
- Recurrence of the AE with reintroduction of study drug, if performed
- Similarity to known class effects
- Alternative causes, such as:
  - Known effects of concomitant medications
  - Pre-existing risk factors
  - Concurrent illnesses

The assessment of causality will be based on the information available, and may be changed upon receipt of additional information.

7.4.3. Assessment of Expectedness

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 events, in addition to death due to ALS progression, are anticipated to occur in the study population as signs/symptoms of ALS progression which may or may not lead to hospitalization.

Table 5: MedDRA Preferred Terms

MedDRA Preferred Term[a]	MedDRA Preferred Term[a]
Dysarthria	Muscle spasticity
Dysphagia	Muscle weakness
Dyspnoea	Pneumonia aspiration
Gait disturbance	Respiratory failure
Muscle contractions involuntary	Weight decreased/Abnormal loss of weight
Muscle spasms	

[a] MedDRA Version 19.1

7.5. Follow-Up of AEs and SAEs

After the initial recording of an AE/SAE, the Investigator should proactively follow the patient. Non-serious AEs that are still ongoing at the end of the study should be reviewed by the Investigator to determine if further follow up is required. The Investigator will document on the AE eCRF any/all ongoing non-serious AEs that will not be followed up further after the patient exits the study. If in doubt, the Investigator should consult the Medical Monitor.

All SAEs should be followed until resolution, until the condition stabilizes, or until the patient is lost to follow-up. Once the seriousness criterion no longer applies to the SAE (e.g., patient was discharged), the corresponding AE eCRF page should be updated. All relevant additional information collected regarding an SAE, including laboratory test reports, consultation reports from other health care professionals, discharge summaries, or other information should be transmitted to Cytokinetics with the follow-up SAE report form **within 24 hours of receipt or awareness**.

Cytokinetics may request the Investigator to perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of any AE/SAE.

If a patient dies during participation in the study or during the follow-up period, the Investigator will provide Cytokinetics with a copy of any post-mortem findings, including an autopsy report if obtainable.

7.6. Post-Study AEs/SAEs

A post-study AE/SAE is defined as any event that occurs outside of the AE detection period defined in Section 7.3.1.

Investigators are not obligated to actively solicit AEs from former study participants. However, if the Investigator learns of an SAE that he/she considers reasonably related to the investigational product at any time after a patient has been terminated from the study, the Investigator will promptly notify Cytokinetics.

7.7. Pregnancy

Pregnancy is not an AE; however, information on pregnant female patients and partners of male patients will be collected if the pregnancy occurs after the patient receives the first dose of the investigational product until 10 weeks after the last dose. The pregnancy information and its outcome will be collected using the Pregnancy Report Form. If the pregnancy occurs in a partner of a male patient, the partner's consent will be obtained before collecting information regarding the pregnancy and its outcome.

If the pregnancy test (urine or serum) is positive, the pregnancy should be immediately reported to the Investigator and the Sponsor. Any female patient who becomes pregnant during the study is not eligible to continue the study and should complete the study procedures as soon as possible.

If a partner of a male patient becomes pregnant during the study, the male patient may opt to continue his participation but must use barrier method (condom) to prevent fetal exposure.

Accidental, therapeutic, or spontaneous abortions and congenital anomalies or birth defects will be reported as SAEs.

8. STATISTICAL METHODS

8.1. General Considerations

8.1.1. General Approach

All pre-specified hypothesis tests will be 2-sided with a significance level of 0.05. Descriptive statistics for categorical variables will include frequency and percentage, and for continuous variables will include number of patients, mean, median, standard deviation, standard error, minimum and maximum. Baseline is defined as the last available measurement taken before the first dose of study medication unless otherwise specified. Missing data will not be imputed unless otherwise specified.

8.1.2. Sample Size and Randomization

Approximately 445 patients will be randomized to receive either one of the three CK-2127107 doses (300 mg/day, 600 mg/day and 900 mg/day TDD) or matching placebo tablets in a ratio of 1:1:1:1. Randomization will be stratified by riluzole use/non-use and edaravone use/non-use. The dropout rate at Visit Week 12 is estimated to be 10%, thus approximately 400 patients are expected to complete 12 weeks of double-blind treatment. The effect of CK-2127107 on the change from baseline to Week 12 in percent predicted SVC will be analyzed using a mixed model for repeated measures (MMRM) with the contrast (-5, -1, 3, 3) to reflect the assumed relationship for the placebo, 300 mg/day, 600 mg/day and 900 mg/day dose groups. The analysis is estimated to provide 90% power to detect 2.75, 5.5 and 5.5 percentage points advantage over placebo for the 300 mg/day, 600 mg/day and 900 mg/day CK-2127107 dose groups, respectively, in change from baseline of percent predicted SVC, at the end of the double-blind treatment (Visit Week 12). This calculation is based on a two-sided test with alpha set at 0.05 and a common standard deviation of 14 percentage points.

8.2. Analysis Sets

8.2.1. Full Analysis Set (FAS)

The FAS will consist of all randomized patients who receive at least one dose or portion of a dose of study drug and who have a baseline and at least one post-baseline efficacy assessment during the double-blind treatment.

8.2.2. Safety Analysis Set (SAS)

The SAS will consist of all randomized patients who receive at least one dose or portion of a dose of study drug.

8.2.3. Pharmacokinetics Analysis Set (PKS)

The PKS will consist of all randomized patients who have at least one evaluable plasma concentration of CK-2127107, provided they have no major protocol violations that could affect the PK of CK-2127107.

8.3. Endpoints

8.3.1. Efficacy Endpoints

8.3.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline to Visit Week 12 in the percent SVC.

8.3.1.2. Secondary Efficacy Endpoints

- Slope from baseline to Visit Week 12 in the mega-score of muscle strength measured by HHD and handgrip dynamometry
- Change from baseline to Visit Week 12 in the ALSFRS-R

8.3.1.3. Exploratory Efficacy Endpoints

Change from Baseline Endpoints

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

Slope Endpoints:

- Slope of change from baseline to Visit Week 12 in the percent predicted SVC
- Slope of change from baseline to Visit Week 12 in the ALSFRS-R
- Slope of change from baseline to Visit Week 12 in percent predicted SVC measured at home
- Slope of change from baseline to Visit Week 12 in the components of voice analysis
- Slope of change from baseline to Visit Week 12 in the components of handwriting analysis
- Slope of change from baseline to Visit Week 12 in the ALSAQ-5

8.3.2. Safety Endpoints

The safety endpoints are listed in the following:

- The incidence and severity of TEAEs
- Clinically important changes in safety assessment results [including, as appropriate, vital signs, clinical laboratory tests, ECGs, Ashworth score, falls assessment, physical and neurological examinations, BDI-Fast Screen and suicidality assessment].

8.3.3. Pharmacokinetic Measurements

The plasma concentrations of CK-2127107 and possible metabolites will be measured at the sampled time points during the study.

8.4. Statistical Analysis

8.4.1. Patient Disposition

The number and percentage of patients randomized, receiving any study drug, completing the study, prematurely discontinuing treatment and prematurely discontinuing from the study will be summarized by dose group, treatment and overall. Reasons of premature discontinuation will also be summarized.

8.4.2. Demographics and Other Baseline Characteristics

Patient demographics and other baseline characteristics will be summarized by dose group, treatment and overall using descriptive statistics.

8.4.3. Prior and Concomitant Medications

Prior and concomitant medications will be classified using the World Health Organization Drug dictionary, and summarized by drug class and preferred term (PT).

8.4.4. Efficacy Analysis

Efficacy analyses will be conducted for the FAS.

8.4.4.1. Primary Efficacy Analysis

The hypothesis for the primary efficacy analysis is that there is a positive treatment difference (CK-2127107 minus placebo) in change from baseline to Week 12 in the percent predicted SVC.

The effect of CK-2127107 on the change from baseline to Week 12 in percent predicted SVC will be analyzed using a MMRM with the contrast (-5, -1, 3, 3) to reflect the assumed relationship for the placebo, 300 mg/day, 600 mg/day and 900 mg/day dose groups. The response variable in the model will be the change in the percent predicted SVC from baseline to each post-baseline visit. The model will include the terms of treatment, baseline value, pooled site, visit, randomization stratification factors of riluzole use/non-use and stratified edaravone use/non-use, as well as treatment-by-visit and baseline-by-visit interactions. An unstructured variance-covariance structure will be used to model the within-subject errors.

8.4.4.2. Secondary Efficacy Analysis

Slope from baseline in the mega-score of muscle strength will be analyzed using a MMRM. The response variable will be the change from baseline to each post-baseline visit. The model will include the terms of treatment, the baseline value, pooled site, time, randomization stratification factors of riluzole use/non-use, and stratified edaravone use/non-use as well as treatment-by-baseline and treatment-by-time interactions. A random slope effect will be assumed in the model. Change from baseline in the ALSFRS-R will be analyzed using the same method as for the primary efficacy analysis.

8.4.4.3. Exploratory Efficacy Analysis

Exploration of the dose-response relationship will come from model-based analyses that will use various assumptions of an implicit dose-response relationship. In addition, placebo will be tested against each dose group of CK-2127107 for specified endpoints and the 600 mg/day and 900 mg/day dose groups combined.

8.4.4.4. Multiplicity

The global null hypothesis for the primary and secondary efficacy endpoints will be tested in a pre-specified order using a closed testing procedure. This procedure will maintain the family-wise error rate at two-sided significance level of 0.05 for all hypotheses tested in a confirmatory sense. Details of the procedures will be provided in the Statistical Analysis Plan.

Hypotheses other than the primary and secondary efficacy endpoints will also be tested with a significance level of 0.05. However, no adjustments for multiple comparisons will be made for these tests.

8.4.5. Safety Analysis

Safety analyses will be conducted for the SAS. Safety data will be summarized by dose group, treatment and overall using descriptive statistics.

8.4.5.1. Study Drug Exposure

The amount of study drug received and duration of study drug exposure will be summarized.

8.4.5.2. Adverse Event

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by system organ class (SOC) and PT. Individual events (PT) within each SOC will be presented in order of descending frequency.

An AE (or SAE) will be regarded as treatment emergent if it starts or worsens (e.g., increases in severity or frequency) during or after the first dose of study drug. TEAEs will be summarized by maximum severity, and by relationship to the study treatment. All AEs will be listed.

8.4.5.3. Serious Adverse Event

Treatment emergent SAEs will be summarized by maximum severity, and by relationship to the study treatment. All SAEs will be listed.

8.4.5.4. Clinical Laboratory Parameters

For each laboratory parameter, the number and percentage of subjects with alert values or values outside the normal range during the study will be tabulated. All laboratory evaluations identified as outside the normal range or as alerts by the central laboratory will be listed. The value and change from baseline in continuous laboratory parameters will be summarized at each scheduled visit where laboratory measurements are taken.

8.4.5.5. Vital Signs

For each measurement of heart rate, blood pressure, respiratory rate, and BMI, the number and percentage of subjects with clinically relevant abnormalities during the study will be tabulated. All measurements identified as clinically relevant abnormalities will be listed. The value and change from baseline in heart rate, blood pressure, respiratory rate and BMI will be summarized at each scheduled visit where vital signs are taken.

8.4.5.6. ECGs

For each ECG measurement, the number and percentage of subjects with clinically relevant abnormalities during the study will be tabulated. ECG measurements identified as clinically relevant abnormalities will be listed. The value and change from baseline in ECG measurements will be summarized at each scheduled visit where measurements are taken.

8.4.5.7. Physical and Neurological Examinations

The number and percentage of subjects deemed by the investigators to have clinically significant abnormalities will be tabulated by type of exam at each scheduled visit where physical or neurological examinations are taken. All measurements identified as clinically relevant abnormalities will be listed.

8.4.5.8. Ashworth Score

Ashworth score will be determined bilaterally at the elbows and knees with the results summarized at each body location.

8.4.5.9. Falls Assessments

The number and percentage of subjects with falls will be tabulated at each scheduled visit where falls assessments are taken. Activities engaged at the time of the fall, physical symptoms experienced immediately preceding the fall, and if the fall resulted in injury will also be summarized.

8.4.5.10. Beck Depression Inventory-Fast Screen

The total score of the BDI-Fast Screen is determined by summing the scores from the 7 questions, and can range from 0 to 21, with higher scores indicating greater depression severity. The value and change from baseline in the total score of the BDI-Fast Screen will be summarized at each scheduled visit where scores are taken.

8.4.6. Exposure-Response Analysis

The relationship of drug exposure with efficacy and safety endpoints of interest will be explored. Graphical and tabular presentations will be provided as appropriate.

8.4.7. Pharmacokinetic Analysis

PK analyses will be conducted using the PKS. All of the PK samples collected, including those obtained at Hour 3 on Day 1 as well as Hour 3 and Hour 6 at Week 2 and Week 12 from patients enrolled prior to Amendment 03, will be used for PK analyses. PK parameters such as t_{max}, C_{max},

C_{trough}, AUC_{0-24}, AUC_{∞}, CL/F, V/F, $t_{½}$ and R_{AC} will be summarized by dose group using descriptive statistics as appropriate. Nominal sample times will be presented in all statistical and graphical summaries.

The observed plasma concentrations of CK-2127107 and its metabolites (if applicable) and riluzole at planned sampling time points will be summarized and listed. The potential for drug-drug interaction between CK-2127107 given alone and in the presence of riluzole will also be assessed.

The PK parameters with and without co-administration of riluzole will also be summarized. Box-whiskers-plots of AUC and C_{max} at Visit Week 12 with and without co-administration of riluzole will be presented.

8.5. Interim Analysis

After the last patient completes dosing, an interim analysis may be conducted by the Sponsor.

8.6. Statistical Software

Statistical analyses will be performed using SAS® version 9.4 or greater.

8.7. Changes in Statistical Methods

All changes in statistical methods that are described in the statistical analysis plan will be documented in the clinical study report.

9. ADMINISTRATIVE ASPECTS

9.1. Change in Protocol

There will be no alterations in the protocol without agreement between the Sponsor and the Investigator. There will be no alterations in the protocol without the express written approval of the Sponsor, Investigator, and the Institutional Review Board (IRB)/Research Ethics Board (REB)/Ethics Committee (EC) and regulatory authorities, as applicable.

9.2. Initiation Visit

Prior to the start of the clinical study at each site, the representative(s) of the Sponsor will meet with the Investigator(s) and appropriate clinical staff to familiarize the Investigator and clinical staff with the materials necessary for conducting the clinical study.

9.3. Disclosure

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Investigator agrees not to disclose such information in any way without prior written permission from the Sponsor.

Any publication of the results, either in part or in total (e.g., articles in journals or newspapers, oral presentations, abstracts, etc.) by the Investigator(s) or their representative(s), shall require prior notification and review, within a reasonable time frame, by the Sponsor, and cannot be made in violation of the Sponsor's confidentiality restrictions or to the detriment of the Sponsor's intellectual property rights.

9.4. Monitoring

The Sponsor will designate site monitors who will be responsible for monitoring this clinical trial. The site monitor will monitor the study conduct, proper eCRF and source documentation completion and retention, and accurate study drug accountability. To this end, the monitor will visit the study site at suitable intervals and be in frequent contact through verbal and written communication. It is essential that the site monitor have access to all documents (related to the study and the individual participants) at any time these are requested. In turn, the site monitor will adhere to all requirements for patient confidentiality as outlined in the ICF. The Investigator and other study personnel will be expected to cooperate with the site monitor, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

9.5. Institutional Review Board/Research Ethics Board/Ethics Committee

In accordance with the US Code of Federal Regulations (CFR), 21 CFR 56, the protocol, subject recruitment advertisements (if applicable), and ICF will be submitted to the IRB/REB/EC for review and subsequent written approval by the IRB/REB/EC must be received before proceeding. The Sponsor will supply relevant material for the Investigator to submit to the IRB for the protocol's review and approval. Verification of the IRB/REB/EC unconditional approval of the protocol and the written ICF statement will be transmitted to the Investigator.

The IRB/REB/EC will be informed by the Investigator of subsequent protocol amendments and of serious and unexpected AEs. Approval for protocol amendments will be transmitted in writing to the Investigator. If requested, the Investigator will permit audits by the IRB/REB/EC and regulatory inspections by providing direct access to source data/documents.

The Investigator will provide the IRB/REB/EC with progress reports at appropriate intervals (not to exceed one year) and a Study Progress Report following the completion, termination, or discontinuation of the Investigator's participation in the study.

9.6. Informed Consent

Before protocol-specific procedures are carried out, written informed consent for the study will be obtained from patients. The ICF generated by the Investigator (or designee) will be approved (along with the protocol) by the IRB/REB/EC and will be acceptable to the Sponsor.

The Investigator (or designee) will explain the nature of the study and the action of the test product. The patients will be informed that participation is voluntary and that patients can withdraw from the study at any time. In accordance with 21 CFR 50, informed consent shall be documented by the use of a written ICF approved by the IRB/REB/EC and will be signed by the patient prior to protocol-specific procedures being performed. A copy of the signed consent, and the original will be maintained with the patient's records. A copy of the IRB/REB/EC approved ICF must be sent to the Sponsor (or designee).

9.7. Records

The results from data collected during the study will be recorded in the patient's eCRF. To maintain confidentiality, the patient will be identified only by a unique identification number.

The completed eCRFs will be transferred to the Sponsor or designee. All source documents, records, and reports will be retained by the study site in accordance with 21 CFR 312.62(c). All primary data, or copies thereof (e.g., laboratory records, source documents, correspondence, photographs, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report, will be retained in the study site archives.

9.8. Reference to Good Clinical Practices (GCP)

The study procedures outlined in this protocol will be conducted in accordance with the CFR governing Protection of Human Subjects (21 CFR 50), Financial Disclosure by Clinical Investigators (21 CFR 54), IRBs (21 CFR 56), Investigational New Drug Application (21 CFR 312), and Applications for FDA Approval to Market a New Drug (21 CFR 314), as appropriate. As such, these sections of U.S. Title 21 CFR, along with the applicable ICH Guidelines, are commonly known as Good Clinical Practices (GCP).

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APPENDIX A. SCHEDULE OF EVENTS

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

[a] Complete physical examination at Screening Visit, abbreviated physical examination at FU visit
[b] Temperature only at Screening
[c] TSH only at Screening and Follow-Up Visit
[d] Serum pregnancy test only for females of childbearing potential
[e] PK sampling on Day 1 visit, Week 2 visit, Week 4 visit, Week 8 visit, and Week 12 visit; refer to Table 3 in protocol
[f] If the device is suitable for use in that region

Schedule of Events for Home Testing

SVC*	To be done every Saturday (± 1 day) independent of day of first dose
Voice recording	To be done every Saturday (± 1 day) independent of day of first dose

*if the device is suitable for use in that region

APPENDIX B. 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:	**Moderate Inducers:**
erythromycin	bosentan
diltiazem	efavirenz
verapamil	etravirine
suboxone	modafinil
	nafcillin
	nevirapine
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	

APPENDIX C. LIVER SAFETY MONITORING AND ASSESSMENT

Any patient enrolled in a clinical study with active drug therapy who reveals an increase of serum aminotransferase (AT) to > 3 x ULN or bilirubin > 2 × ULN, should undergo detailed testing for liver enzymes (including at least ALT, AST, alkaline phosphatase [ALP], and TBL). Testing should be repeated within 48-72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central laboratory regarding moderate and severe liver abnormality to inform the Investigator, study monitor and study team. Patients should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe as follows:

	ALT or AST		**Total Bilirubin**
Moderate	> 3× ULN	or	> 2× ULN
Severe	> 3× ULN	and	> 2× ULN

In addition, the patient should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8× ULN
- ALT or AST > 5× ULN for more than 2 weeks
- ALT or AST > 3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)

The investigator may determine that abnormal LFTs, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. Patients with confirmed abnormal LFTs should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2-3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the patient is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology, may be considered an important medical event and may be reported as a SAE. The Sponsor should be contacted and informed of all patients for whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new onset-diseases should be recorded as ‘adverse events’ on the AE

page of the eCRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Non-alcoholic steatohepatitis is seen in obese hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating aminotransferase levels. The investigator should ensure that the medical history form captures any illness that pre-dates study enrollment that may be relevant in assessing hepatic function.

- Obtain a history of concomitant drug use (including non-prescription medication, complementary and alternative medications), alcohol use, recreational drug use, and special diets. Medications, including dose, should be entered on the concomitant medication page of the eCRF.
- Obtain a history of exposure to environmental chemical agents.
- Based on the patient's history, other testing may be appropriate including:
  - acute viral hepatitis (A, B, C, D, E or other infectious agents)
  - ultrasound or other imaging to assess biliary tract disease
  - other laboratory tests including international normalized ratio (INR), direct bilirubin
- Consider gastroenterology or hepatology consultations

Patient Discontinuation

In the absence of an explanation for increased LFTs, such as viral hepatitis, pre-existing or acute liver disease or exposure to other agents associated with liver injury, the patient may be discontinued from the study. The investigator may determine that it is not in the patient's best interest to continue study enrollment. Discontinuation of treatment should be considered if:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks
- ALT or AST > 3 × ULN and TBL > 2 × ULN
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)

In addition, if close monitoring for a patient with moderate or severe hepatic laboratory tests is not possible, drug should be discontinued.

Hy's Law Definition - Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10–50% mortality (or transplant) (Temple 2006; FDA 2009).

The three "requirements" for Hy's Law are:

1. Patients with ALT or AST ≥ 3 × ULN compared to placebo, AND
2. For patients with AT elevations (often much greater than 3 × ULN), elevation of serum TBL > 2 × ULN, without initial findings of cholestasis (elevated serum ALP), AND

3. No other reasons can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

APPENDIX D. CLINICAL LABORATORY EVALUATIONS

<table>
<tr><td colspan="4">All Visits:</td></tr>
<tr><td>TBL</td><td>Urea nitrogen</td><td>Globulin</td><td>Magnesium</td></tr>
<tr><td>Direct bilirubin</td><td>Creatinine</td><td>Triglycerides</td><td>Cystatin C</td></tr>
<tr><td>Indirect bilirubin</td><td>Glucose</td><td>Cholesterol</td><td>UA</td></tr>
<tr><td>ALP</td><td>Uric acid</td><td>Creatine kinase</td><td rowspan="2">CBC with differential</td></tr>
<tr><td>ALT</td><td>Calcium</td><td>Sodium</td></tr>
<tr><td>AST</td><td>Phosphorus</td><td>Potassium</td><td rowspan="3">eGFR (calculated by CKD-EPI Cystatin C equation)</td></tr>
<tr><td>Gamma-glutamyl transferase</td><td>Total protein</td><td>Bicarbonate</td></tr>
<tr><td>Lactate dehydrogenase</td><td>Albumin</td><td>Chloride</td></tr>
<tr><td colspan="4">Screening and Follow-Up only:</td></tr>
<tr><td colspan="4">TSH</td></tr>
<tr><td colspan="4">Serum Beta Human Chorionic Gonadotropin</td></tr>
</table>