# 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)

Published: 04-06-2018
Last updated: 11-04-2024

Main objective: To assess the effect of CK-2127107 versus placebo on respiratory function in patients with ALS.

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Neuromuscular disorders |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON45879

**Source**
ToetsingOnline

**Brief title**
CY 5022 / FORTITUDE-ALS

### Condition

- Neuromuscular disorders

**Synonym**
Amyotrophic Lateral Sclerosism (ALS), Motor Neuron Disease

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Cytokinetics, Inc.
**Source(s) of monetary or material Support:** de sponsor of the study

## Intervention

**Keyword:** ALS, CK 2127107, Phase 2, Placebo-controlled

## Outcome measures

### Primary outcome

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

### Secondary outcome

* 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

# Study description

### Background summary

Protocol section 1.1, page 13

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.

**Study objective**

Main objective: To assess the effect of CK-2127107 versus placebo on respiratory function in patients with ALS.

**Study design**

Protocol, section 3.1, page 19 and 20

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.

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)

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.

**Intervention**

Patient will need to take the study medication as tablets, and will be randomized to receive the following doses of study medication 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.

**Study burden and risks**

In general, study participants may experience physical or psychological discomfort from the study tests, study procedures and questionnaires; and each study participant may have a different experience. In addition, study particpants may experience side effects from the study medication.

Please note that the numbers below are maximum numbers, based on the schedule

of events table from the protocol.

Number of visits: 7

Physicial examination: 2

Neurological Examination: 2

ECG: 3

Blood draws (including pregnancy tests): 6

Pulmonary Function Test, Slow Vital Capacity (SVC): 7

Ashworth Score: 7

Muscle Strength Test: 7

Maximum Handgrip Test: 7

Health Economic Outcome Measurements: 6

Voice Recording: 7

Fine Motor Assessment: 7

Falls Assessment: 6

Questionnaire ALSFRS-R: 7

Questionnaire ALSAQ-5: 7

Questionnaire BDI-Fast Screen: 7

# Contacts

**Public**
Cytokinetics, Inc.

East Grand Avenue 280
South San Francisco, CA 94080
US
**Scientific**
Cytokinetics, Inc.

East Grand Avenue 280
South San Francisco, CA 94080
US

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

1. Able to comprehend and willing to sign an Informed Consent Form (ICF);2. Males or females between the ages of 18 and 80 years of age, inclusive;3. Diagnosis of familial or sporadic ALS (defined as meeting the possible, laboratory-supported probable, probable, or definite criteria for a diagnosis of ALS according to the World Federation of Neurology El Escorial criteria published in 2000 (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 and 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 heterosexual 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.

## Exclusion criteria

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 m2 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

# Study design

## Design

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|---|---|
| Study phase: | 2 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 24-08-2018 |
| Enrollment: | 6 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Reldesemtiv |
| Generic name: | Reldesemtiv |

# Ethics review

Approved WMO

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|---|---|
| Date: | 04-06-2018 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |

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|---|---|
| Approved WMO Date: | 15-08-2018 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2018-000586-37-NL |
| ClinicalTrials.gov | NCT03160898 |
| CCMO | NL65920.041.18 |

# Study results

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| Date completed: | 25-02-2019 |
| Actual enrolment: | 11 |

**Summary results**
Trial is onging in other countries