A Phase 3, Multi-National, Double-Blind, Randomized, Placebo-Controlled, Stratified, Parallel Group, Study to Evaluate the Safety, Tolerability and Efficacy of Tirasemtiv in Patients with Amyotrophic Lateral Sclerosis (ALS)

Published: 30-11-2015
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Protocol version Amendment 1, 31-Jul-2015, paragraph 2.1, page 28:Primary objective:The primary objective is to assess the effect of tirasemtiv versus placebo on respiratory function in patients with ALS.Secondary objectives:* Evaluation of...

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

Summary

ID

NL-OMON44882

Source
ToetsingOnline

Brief title
CY 4031

Condition

- Neuromuscular disorders

Synonym
ALS, Amyotrophic Lateral Sclerosism

Research involving

Human

Sponsors and support

Primary sponsor: Cytokinetics, Inc.
Source(s) of monetary or material Support: Cytokinetics;Inc.

Intervention

Keyword: ALS, Amyotrophic Lateral Sclerosis, CK-2017357, Tirasemtiv

Outcome measures

Primary outcome

Protocol synopsis:

To evaluate the safety, tolerability and effect of Tirasemtiv in patients with Amyotrophic Lateral Sclerosis (ALS).

Secondary outcome

The following secondary endpoints will be analyzed in a closed testing procedure if the primary efficacy analysis is met as defined in the protocol.

- Change from baseline in the ALSFRS-R score of the three respiratory items of the ALSFRS-R (i.e., the sum of items 10, 11 and 12) at the end of 48 weeks of double-blind, placebo-controlled treatment

- Slope of mega-score of muscle strength during the 48 weeks of double-blind, placebo-controlled treatment

- Time to the first occurrence of a decline from baseline in percent predicted

SVC *20 percentage points or the onset of respiratory insufficiency or death at the end of the 48 weeks of double-blind, placebo-controlled treatment

- Time to the first occurrence of a decline in SVC to *50% predicted or the onset of respiratory insufficiency or death at the end of the 48 weeks of double-blind, placebo-controlled treatment

- Change from baseline in the ALSFRS-R total score to the end of 48 weeks of the double-blind, placebo-controlled treatment

- Time to the first use of mechanical ventilatory assistance or death during all 48 weeks of double-blind, placebo-controlled treatment

Study description

Background summary

Protocol version Amendment 1, 31-Jul-2015, paragraph 1.1 & 1.2, page 13:

No curative therapies for ALS exist. Rilutek® (riluzole, Sanofi-Aventis U.S. LLC) is one of two medications approved for the treatment of ALS, and has a modest benefit on survival (Lacomblez, Bensimon et al. 1996). The other approved medication, Nuedexta, has a specific effect on emotional lability, a symptom experienced by a minority of ALS patients.
Two interventions that contribute greatly to the overall welfare and survival of ALS patients are the use of enteral feeding and ventilatory support.

To date, there are no available treatments that can improve skeletal muscle function, and in particular respiratory function.

Tirasemtiv (formerly CK-2017357) is a novel small molecule activator of fast skeletal muscle troponin, intended to improve skeletal muscle function in

disease states associated with muscular weakness or fatigue, including amyotrophic lateral sclerosis (ALS), without affecting the structure of muscle itself. It may be useful in the treatment of patients with ALS.

Study objective

Protocol version Amendment 1, 31-Jul-2015, paragraph 2.1, page 28:

Primary objective:
The primary objective is to assess the effect of tirasemtiv versus placebo on respiratory function in patients with ALS.

Secondary objectives:
* Evaluation of alternative methods to assess the effect of tirasemtiv versus placebo on percent predicted SVC in patients with ALS
* Assessment of the effect of tirasemtiv versus placebo on other clinical measures related to the progressive decline in respiratory function in patients with ALS
* Assessment of the effect of tirasemtiv versus placebo on measures of skeletal muscle function in patients with ALS

Safety objective:
To assess the safety of tirasemtiv

Study design

Protocol version Amendment 1, 31-Jul-2015, paragraph 3, page 31-34:

A Phase 3, Multi-National, Double-Blind, Randomized, Placebo-Controlled, Stratified, Parallel Group Study, including the Double-Blind, Randomized and Placebo-Controlled Withdrawal phase.

Intervention

Protocol version Amendment 1, 31-Jul-2015, paragraph 6.1 and 6.2, page 69 and 70

CK-2017357 (tirasemtiv) study drug is supplied as immediate release, white, modified oval tablets at a dose strength of 125 mg of tirasemtiv per tablet. This study drug will be administered orally as tablets to patients with ALS. Doses (tirasemtiv or placebo) for each of the treatment groups will be dispensed in accordance with the study randomization prior to the patient*s first dose.

Study burden and risks

Protocol version Amendment 1, 31-Jul-2015, paragraph 1.4, pages 15-19:

Phase 2b Clinical Trial in Patients with ALS (CY 4026; BENEFIT-ALS):
The most common SAE was respiratory failure, which occurred in one patient on tirasemtiv and three patients on placebo, while confusional state and delirium occurred in two patients on tirasemtiv and no patients on placebo.
Adverse events (AEs) more common on tirasemtiv than on placebo (> 10% difference) were dizziness (50.8% vs. 19.7%), fatigue (33.2% vs. 14.2%), and nausea (21.9% vs. 7.8%).
Patients on tirasemtiv lost more weight than patients on placebo (change from baseline to Week 12: -1.70 kg vs. -0.79 kg; p = 0.006).

For the side effects related to this study I refer to Section E9 of this form.

Contacts

Public
Cytokinetics, Inc.

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

East Grand Avenue 280
South San Francisco 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. Male or female 18 years of age or older;3. A 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) * 24 months prior to screening;4. Upright SVC * 70 % of predicted for age, height and sex;5. Able to swallow tablets without crushing, and in the opinion of the Investigator, is expected to continue to be able to do so during the trial;6. A caregiver if one is needed;7. Clinical laboratory findings within the normal range or, if outside the normal range, deemed not clinically significant by the Investigator
8. Male patients must agree for the duration of the study and 10 weeks after the end of the study to use a condom during sexual intercourse with female partners who are of childbearing potential (i.e., following menarche until post-menopausal if not anatomically and physiologically incapable of becoming pregnant) and to have female partners use an additional effective means of contraception (e.g., diaphragm plus spermicide, or oral contraceptives) or the male patient must agree to abstain from sexual intercourse during and for 10 weeks after the end of the study, unless the male patient has had a vasectomy and confirmed sperm count is zero
9. Female patients must be post-menopausal (* 1 year) or sterilized, or, if of childbearing potential, not be breastfeeding, have a negative pregnancy test, have no intention to become pregnant during the course of the study, and use effective contraceptive drugs or devices while requiring male partner to use a condom for the duration of the study and for 10 weeks after the end of the study
10. Patients must be either on a stable dose of riluzole 50 mg twice daily for at least 30 days prior to screening or have not taken riluzole for at least 30 days prior to screening and are willing not to begin riluzole use until they complete study drug dosing.

Exclusion criteria

1. At the time of screening, any use of non-invasive positive pressure ventilation (NIPPV, e.g. continuous positive airway pressure [CPAP] or bi-level positive airway pressure [BiPAP]) for any portion of the day, or mechanical ventilation via tracheostomy, or on any form of oxygen supplementation;2. Patients with a diaphragm pacing system (DPS) at study entry or who anticipate DPS placement during the course of the study;3. BMI of 20.0 kg/m2 or lower;4. Unwilling or unable to discontinue tizanidine and theophylline-containing medications during study participation;5. Serum chloride outside the normal reference range;6. Neurological impairment due to a condition other than ALS, including history of transient ischemic attack within the past year;7. Presence at screening of any medically significant cardiac, pulmonary, GI, musculoskeletal, or psychiatric illness that might interfere with the patient*s ability to comply with study procedures or that might confound the interpretation of clinical safety or efficacy data, including, but not limited to:;a. Poorly controlled hypertension;b. NYHA Class II or greater congestive heart failure;c. Chronic obstructive pulmonary disease or asthma requiring daily use bronchodilator medications;d. GI disorder that might impair absorption of

study drug;e. History of significant liver disease defined by bilirubin > 2 times the upper limit of normal (ULN) or ALT or AST > 3 times the ULN on repeat testing;f. Poorly controlled diabetes mellitus;g. History of vertigo within three months of study entry;h. History of syncope without an explainable or treated cause;i. History of untreated intracranial aneurysm or poorly controlled seizure disorder;j. Amputation of a limb;k. Cognitive impairment, related to ALS or otherwise, sufficient to impair the patient*s ability to give informed consent and to understand and/or comply with study procedures;l. 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 two years;m. 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;n. Patient judged to be actively suicidal or a suicide risk by the Investigator;8. Has taken any investigational study drug within 30 days or five half-lives of the prior agent, whichever is greater, prior to dosing;9. Prior participation in any form of stem cell therapy for the treatment of ALS;10. Previously received tirasemtiv in any previous clinical trial

Study design

Design

Study phase:	3
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):	15-04-2016
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Tirasemtiv
Generic name:	Not known yet

Ethics review

Approved WMO Date:	30-11-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	06-04-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	03-06-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-08-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	18-10-2017
Application type:	Amendment
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	EUCTR2014-005413-23-NL
ClinicalTrials.gov	NCT02496767
CCMO	NL54137.041.15