A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBOCONTROLLED, PARALLEL STUDY TO ASSESS THE EFFICACY, SAFETY, TOLERABILITY, PK, AND BIOMARKER EFFECTS OF PTC857 IN ADULT SUBJECTS WITH AMYOTROPHIC LATERAL SCLEROSIS (CARDINALS)

Published: 11-10-2022
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This study has been transitioned to CTIS with ID 2023-510317-26-00 check the CTIS register for the current data. To evaluate the efficacy of PTC857 in reducing disease progression in subjects with amyotrophic lateral sclerosis (ALS)

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Movement disorders (incl parkinsonism)
Study type	Interventional

Summary

ID

NL-OMON53503

Source
ToetsingOnline

Brief title
CARDINALS

Condition

- Movement disorders (incl parkinsonism)

Synonym
Lou Gehrig's disease, Motor neurone disease

Research involving
Human

Sponsors and support

Primary sponsor: PTC THERAPEUTICS, INC.
Source(s) of monetary or material Support: Sponsor

Intervention

Keyword: AMYOTROPHIC LATERAL SCLEROSIS, Neurodegenerative disease, PTC857, small molecule

Outcome measures

Primary outcome

The primary endpoint is the change from baseline in ALS Functional Rating Scale-Revised (ALSFRS-R) in the Intent-To-Treat 1 (ITT1) Analysis Set after 24 weeks of treatment.

Secondary outcome

The secondary endpoints of the study are the following:

1. Change from baseline in ALSFRS-R in the Intent-to-Treat 2 (ITT2) Analysis Set after 24 weeks of treatment

2. Safety and tolerability of PTC857 as measured by the severity and number of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs), and change in clinical laboratory tests, physical examination, vital signs, Columbia-Suicide Severity Rating Scale (C-SSRS), and 12-lead electrocardiograms (ECGs) during the Treatment Period

3. Change from baseline in respiratory function as assessed by pulmonary function tests (PFTs) after 24 weeks of treatment

4. Change from baseline in motor/limb and bulbar function as assessed by the

Modified Norris Scale after 24 weeks of treatment

5. Change from baseline in neuropsychological function as assessed by the ALS Cognitive Behavioral Screen (ALS CBS) after 24 weeks of treatment

6. Survival as assessed by rate of and length of time to needing respiratory support/intubation and/or death

7. Survival and functional change as assessed by the Combined Assessment of Function and Survival (CAFS) after 24 weeks of treatment

8. Quality of life as assessed by ALSAQ-40 after 24 weeks of treatment

9. Plasma PK and cerebrospinal fluid (CSF) exposure of PTC857

Study description

Background summary

Currently, there is no cure for amyotrophic lateral sclerosis (ALS), and treatment of patients with ALS is largely limited to management of symptoms. The only approved treatments, in some countries, for ALS are riluzole (Rilutek, administered orally; Tiglutik, oral solution; and Exservan, oral film) and edaravone (Radicava, administered intravenously). As these existing approved therapies are limited in efficacy of altering disease progression, there remains a high unmet medical need for new treatments for ALS. PTC857 (also known as utreloxastat) is an orally bioavailable small molecule (a proprietary cyclohexadiene-dione compound) being developed by PTC Therapeutics, Inc. for the treatment of neurological diseases characterized by high levels of oxidative stress and mitochondrial pathology, including ALS. In diseases characterized by high levels of oxidative stress, reactive oxygen species (ROS) production outstrips the available supply of glutathione, resulting in depletion of glutathione and ROS-mediated cell injury and cell death. PTC857 functions as an inhibitor of the oxidoreductase 15-lipoxygenase (15-LO) enzyme to reduce oxidative stress and spare reduced glutathione. This study is intended to assess the efficacy, safety, tolerability, pharmacokinetic (PK), and biomarker effects of PTC857 in adult male and female subjects diagnosed with ALS. PTC857 was evaluated in Study PTC857-CNS-001-PD, a 3-part, Phase 1, single-center, double-blind, randomized, placebo-controlled, single- and multiple-ascending-dose, as well as food effect study of PTC857 in healthy volunteers. There were no treatment-emergent serious adverse events (TESAEs),

no treatment-emergent adverse events (TEAEs) leading to discontinuation of PTC857, and no TEAEs leading to death. PTC857 was also evaluated in Study PTC857-CNS-002-HV, a Phase 1, 2-period, crossover, relative bioavailability study of 2 formulations in healthy volunteers. There were no TESAEs, no TEAEs leading to discontinuation of PTC857, and no TEAEs leading to death. Exposure to PTC857 in Studies PTC857-CNS-001-PD and PTC857CNS002-HV included 84 subjects (healthy volunteers) at doses ranging from 100 to 1000 mg. The longest treatment duration was 14 days. The clinical safety data suggest that PTC857 is safe and well tolerated. No TESAEs were reported.

Study objective

This study has been transitioned to CTIS with ID 2023-510317-26-00 check the CTIS register for the current data.

To evaluate the efficacy of PTC857 in reducing disease progression in subjects with amyotrophic lateral sclerosis (ALS)

Study design

This is a Phase 2, randomized, double-blind, placebo-controlled, parallel study to assess the effects of PTC857 treatment in adult male and female subjects diagnosed with ALS. The study consists of 5 periods: Screening, Treatment, LTE, Continued LTE, and Follow-Up.

Intervention

Subjects will receive 1 of 2 treatment regimens during the 24-week Treatment Period:
• PTC857 (250 mg) administered orally BID for 24 weeks
• Matching placebo (250 mg) administered orally BID for 24 weeks
All subjects will receive open-label PTC857 250 mg BID during the 28-week LTE Period and during the 108-week Continued LTE Period.

Study burden and risks

Drugs that work through the brain and nervous system can potentially cause changes in mood and thoughts, including suicidal feelings
The lumbar puncture procedure could cause headache, nausea and vomiting, dizziness, double vision, and ringing ears.
It is possible that the subject might experience new side effects that have not been observed in the prior animal or human studies. For example, allergic reactions or interactions with another medication could occur.
Reversible changes in the lipid profile were observed with short-term exposure in healthy human volunteers but not observed in the monkey toxicology studies at exposure multiples 11.8× clinical exposures.

Few cases of breast adenocarcinoma were observed in female rats in a 6-month toxicity study. However, there were no mammary gland findings in the 9-month toxicity study in monkeys. The clinical relevance of the findings is yet to be established and will be further investigated in nonclinical studies. Based on the likely non-genotoxic mechanism of action, safety margin to the clinical dose, and low incidence of findings seen, an adequate risk-benefit is present for subjects with ALS in this study.

Benefit - Overall, PTC857 has been safe and well tolerated in subjects in the 2 studies of healthy volunteers. There is no guarantee that ALS subjects will receive personal benefit from participating in this study. But based on the in-vitro studies, the protective activity and potency of PTC857 against ferroptotic cell death in human astrocytes were demonstrated. In an ALS mouse model study, PTC857 was demonstrated to protect innervation of the neuromuscular junction within the lumbar spinal cord. Due to the benefits demonstrated by PTC857 in these pathways for ALS, further studies with PTC857 are warranted in subjects with ALS to understand its potential clinical benefits in this population.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Males or females aged between 18 and 80 years at the time of the initial Screening Visit
2. ALS with preserved function, defined as:
a. Onset of the first symptom leading to the diagnosis of ALS < 24 months at the time of the initial Screening Visit
b. Revised EL Escorial criteria of either:
(i) Clinically definite ALS
(ii) Clinically probable ALS
3. A total ALSFRS-R score of at least 34 at the start of the Screening Period
4. No significant respiratory compromise as evidenced by slow vital capacity 60% at the start of the Screening Period
5. Subjects or their designee (ie, legal authorized representative or caregiver) must understand the nature of the study and must provide signed and dated written informed consent prior to conducting any study-related procedures
6. year (cessation of menses for 12 consecutive months) or surgically sterile (having undergone tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 6 months or, if of childbearing potential and not abstinent, willing to use a highly effective method of contraception from the start of the Screening Period through 90 days after the last dose of study drug. Females who are abstinent will not be required to use a contraceptive method unless they become sexually active
12. Female subjects must have a negative breast cancer imaging screening status (not considered clinically abnormal and/or requiring further evaluation/treatment) within 6 months prior to the Screening Visit or during the Screening Period.
13. Standard-of-care therapy for the treatment of ALS (riluzole, edaravone, or sodium phenylbutyrate/taurursodiol) should be stable and unchanged from 30 (-3) days prior to the start of the Screening Period and intend to remain stable and unchanged throughout the course of the study

Exclusion criteria

1. History of allergies or adverse reactions to any of the excipients in the study drug formulation
2. Females who are pregnant or nursing or plan to become pregnant during the study

3. Subjects with clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular/ischemic disease or any other condition that, in the opinion of the investigator, would jeopardize the safety of the subject or impact the validity of the study results
4. Any clinically significant medical or psychiatric condition or medical history that, in the opinion of the investigator or the medical monitor, would interfere with the the risk of participation for that subject.
Note: The lumbar puncture may be skipped for an individual subject if the investigator deems it appropriate, and after discussion with the medical monitor. Subjects with a contraindication to lumbar punctures, such as but not limited to space occupying lesion with mass effect, increase of intracranial pressure due to increased CSF pressure, posterior fossa mass, Arnold-Chiari malformation, anticoagulation medication use, coagulopathy, uncorrected bleeding diathesis, congenital spine abnormality, previous adverse event associated with a lumbar puncture or skin infection at the puncture site, should not undergo the lumbar punctures as listed in the Schedule of Events. These subjects may still enroll in the study and should undergo all other study procedures.
5. Hepatic insufficiency, defined as liver function tests (LFTs) (ie, AST and/or ALT) >=3× the upper limit of normal (ULN), or bilirubin >=1.5× the ULN (except in the case of Gilbert*s disease).
6. Moderate or worse renal insufficiency, defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min
7. Current participation in any other investigational study with an investigational product or participation within 30 days prior to the start of the Screening Period or 5 half-lives of the previously taken investigational drug, whichever is longer
12. For female subjects, any past medical history of breast cancer, regardless of remission status, or any first degree relative with history of breast cancer

Study design

Design

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:	Recruiting
Start date (anticipated):	02-10-2023
Enrollment:	10
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	PTC857
Generic name:	2,3,5-trimethyl-6-nonyl-2,5- cyclohexadiene-1,4-dione

Ethics review

Approved WMO Date:	11-10-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	06-04-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	21-05-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-06-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-11-2023

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-02-2024
Application type:	Amendment
Review commission:	METC NedMec

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
EU-CTR	CTIS2023-510317-26-00
EudraCT	EUCTR2021-006511-29-NL
ClinicalTrials.gov	NCT05349721
CCMO	NL81540.041.22