An open label, cross over pilot study to evaluate the effect of a single dose of TW001 on the oxidative stress and pharmacokinetics with and without food in patients with amyotrophic lateral sclerosis

Published: 24-02-2015
Last updated: 16-04-2024

The aim of this study is to evaluate the effect of a single oral dose of TW001 on oxidative stress and pharmacokinetics with and without food. Dosing with an oral solution is considered to have major advantages over iv dosing in a chronic condition...

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

Summary

ID

NL-OMON42324

Source
ToetsingOnline

Brief title
Pilot phase IB study with TW001

Condition

- Neuromuscular disorders

Synonym
ALS, muscle disease

Research involving

Human

Sponsors and support

Primary sponsor: Treeway B.V.
Source(s) of monetary or material Support: sponsor

Intervention

Keyword: Amyotrophic Lateral Sclerosis, Food effect, Oxidative stress, Pharmacokinetics

Outcome measures

Primary outcome

1. To establish the pharmacokinetic profile of a single dose TW001

2. To evaluate the effect of single dose TW001 on oxidative stress parameters

in CSF (3NT) and blood (3NT, calcium, albumin, creatinine)

3. To evaluate the effect of food on the PK of TW001 and oxidative stress

Secondary outcome

1. To evaluate the safety and tolerability of TW001

2. To investigate the PK/PD relationship

Study description

Background summary

Amyotrophic lateral sclerosis is a devastating neurodegenerative disorder characterised by progressive weakness of limb, bulbar and respiratory muscles. ALS is caused by loss of motor neurons in the spinal cord, brainstem and motor cortex and can occur at any time in adulthood. Median survival is three years after symptom onset. Recently performed trials failed to show a beneficial effect on disease course and the mainstay of ALS care remains symptomatic.

Study objective

The aim of this study is to evaluate the effect of a single oral dose of TW001 on oxidative stress and pharmacokinetics with and without food. Dosing with an

oral solution is considered to have major advantages over iv dosing in a chronic condition like ALS. Moreover, an oral solution is expected to have additional benefits in ALS patients as it has been reported that swallowing may become difficult over time when the disease progresses.

This study will be performed in patients, both male and female, diagnosed with ALS since a primary aim of this study is to evaluate the effect on oxidative stress markers, which have been reported to be elevated in ALS patients. No differences in pharmacokinetics have been reported between males and females. Therefore, both genders are allowed to enroll. The study will also investigate the PK/PD relationship of TW001 levels with oxidative stress markers such as 3NT. This measurement will be used to characterize the time course of the marker and the relationship between 3NT and TW001 levels. The relation between the 3NT concentrations measured in the CSF and the levels measured in plasma will also be investigated.

Study design

All subjects will complete a screening visit. Prior to the day of dosing, eligible subjects will receive an iv cannula for blood sampling and will stay overnight in the hospital as it is controlled for fasting conditions.
Subjects will be allocated based on their study number for the order of the food conditions, which are :
- treatment A: 4.5 mL of TW001 solution (20 mg/mL), fasted
- treatment B: 4.5 mL of TW001 solution (20 mg/mL), fed
the sequence order will be A-B or B-A, depending on their study number

For each subject in treatment A, administration of TW001 is taken with 100 mL water. No intake of water is allowed the hour prior to and one hour post administration of the drug. Next four hours, the subject will abstain from food intake. The food intake will be standardised for all patients during 12 hours post dose.

On the day of dosing, subjects in treatment B will take a high fat, high calorie meal (50 % of the caloric intake of 800-1000 kcal) on site. The drug is administered 30 min after the start of the food intake and the meal should be completed within this 30 minutes time frame. No intake of water is allowed the hour prior to and one hour after the administration of the drug. Drug will be taken with 100 mL water and subjects will abstain from food intake the following four hours. The food intake will be standardised for all patients during twelve hours post dose.

An evaluation will be performed after the first dosing to assess the concentrations of TW001 reached in human and based on the results the second dose will be provided or not.

Both administrations will be separated by a washout period of at least three

days between the dosing of the 1st period and the 2nd period. Safety will be monitored throughout the study by repeated clinical and laboratory evaluations. During each treatment period, blood samples will be obtained pre-dose and at selected time points post-dose for determination of plasma concentrations of TW001. The duration of the study is approximately 14 days, including pre-study and post-study evaluation.

Intervention

TW001 is an oral solution with a concentration of 20 mg/mL in polytethyleneglycol (PEG) 400. The solution is viscous and clear. The administration will be performed by aspiration of TW001 with a syringe. The filled syringes will be emptied in the subject's mouth by the study nurse with face validity. The procedure will be performed twice, once in a fasted condition and once in a fed condition. The administrations will be separated by a washout period of at least 3 days.

Study burden and risks

Since this will be a single dose study in patients, the subjects participating are not expected to benefit from any of the treatments given. The subjects may experience AEs associated with the study drugs or study procedures.
In conclusion, the risk for the patients in this study is deemed acceptable in comparison to the potential benefit for future patients through the further characterisation of the effect on oxidative stress, PK and food effects of TW001.

Contacts

Public
Treeway B.V.

Sevillaweg 142
Rotterdam 3047 AL
NL
Scientific
Treeway B.V.

Sevillaweg 142
Rotterdam 3047 AL
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Provision of written informed consent and compliance with study procedures
2. Diagnoses of definite, probable or possible ALS according to the El Escorial criteria, supported by laboratory values and confirmed by a trained and qualified expert physician
3. Aged between 18 and 70 years of age (both inclusive)
4. Women must not be able to become pregnant (post-menopausal for at least a year, surgically sterile or practicing adequate birth control methods) for the duration of the study
5. Women of childbearing potential must have a negative serum pregnancy test at screening and be non-lactating
6. Vital capacity equal to or more than 70% predicted normal value for gender, height and age at screening
7. No clinically significant abnormality on 12-lead ECG performed at screening

Exclusion criteria

1. Other causes of neuromuscular weakness have not been excluded
2. Significant cognitive impairment, clinical dementia or psychiatric illness
3. Diagnosis of other neurodegenerative disease
4. Significant pulmonary disorder not attributed to ALS, requirement of treatment complicating evaluation of ALS on respiratory function
5. History of known sensitivity or intolerability of edaravone or to any related compound
6. Severe disturbance of consciousness
7. Hepatic impairment as indicated by Child-Pugh Class B or C (moderate to severe hepatic insufficiency)
8. Renal impairment as indicated by a creatinine clearance of less than 50 mL/min as calculated by the Cockcroft Gault equation using serum creatinine.
9. Serious difficulty swallowing and/or inability to eat high-fat high-calorie meal
10. Tracheostomy or non-invasive ventilation

11. Administration of antibiotics, CYP3A4 and or PgP inhibitors
12. Smoking
13. Advanced cancer
14. Exposure to any investigational drug within 30 days of the screening visit
15. Malnourishment based on laboratory data, dehydration or on a sodium free diet
16. Presence of any of the following clinical conditions:
a. Substance abuse within the past year
b. Uncontrolled cardiac, pulmonary, renal, hepatic, endocrine, hematologic or active infectious disease
c. AIDS or AIDS related disease, hepatitis B virus (HBV) or hepatitis C virus (HCV)
d. Unstable psychiatric illness defined as psychosis, untreated major depression within 90 days of the screening visit

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-05-2015
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Edaravone
Generic name:	Edaravone

Ethics review

Approved WMO

Date:	24-02-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	18-05-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	04-06-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-06-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-06-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	30-06-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	24-07-2015
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	EUCTR2015-000685-64-NL
CCMO	NL52559.041.15