Safety and efficacy of tauroursodeoxycholic acid (TUDCA) as add-on treatment in patients affected by amyotrophic lateral sclerosis (ALS)

Published: 06-06-2019
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The primary objective of the study is:To assess the efficacy of TUDCA in slowing disease progression in patients with ALS during the treatment period compared to the lead-in phase), as measured by ALSFRS-R.

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

Summary

ID

NL-OMON55527

Source
ToetsingOnline

Brief title
TUDCA-ALS

Condition

- Neuromuscular disorders

Synonym
ALS

Research involving
Human

Sponsors and support

Primary sponsor: Humanitas Mirasole SpA

Source(s) of monetary or material Support: European Commission grant

Intervention

Keyword: ALS

Outcome measures

Primary outcome

The primary objective of the study is:

* To assess the efficacy of TUDCA in slowing disease progression in patients

with ALS during the treatment period compared to the lead-in phase), as

measured by ALSFRS-R.

Secondary outcome

The secondary objectives of this study are:

* To assess the efficacy of TUDCA in slowing disease progression and functional

impairment in patients with ALS, as measured by the survival time, the ALSAQ-40

questionnaire, FVC, the EQ-5D, and muscle force

* To assess the long term safety and tolerability of TUDCA for up to 18 months

in patients with ALS

Study description

Background summary

Amyotrophic lateral sclerosis (ALS) is a chronic non-communicable neu-rodegenerative rare disease, affecting some 40,000 individuals in Eu-rope, and causing around 11,000 death. Although much has been achieved over the last two decades in understanding the disease com-plexity in ALS, there is a pressing need to find disease-modifying thera-pies that will slow disease progression and enable patients to gain any length in survival. Although this is a formidable challenge, there is one drug (riluzole) that slightly prolongs survival in ALS and is still the only agent with a *disease modifying* effect.

The effect of riluzole on surviv-al in ALS is modest, but indicates that modifying disease progression is a realistic goal in ALS. Nonetheless, all subsequent ALS drugs tested have failed to deliver advances in patient care.

We propose a novel therapeutic approach to overcome the current therapeutic impasse. The *Tauroursodeoxycholic in ALS* (TUDCA-ALS) study will take advantage of the results of a recent proof-of-concept / proof-of-mechanism phase IIb study showing that, in patients who re-ceived TUDCA in addition to riluzole, the per-year decline rate of ALS disease functional rating scale revised (ALSFRS-R) was of about 7 points smaller (on a 0-48 score) compared to riluzole only. This corresponds to a prolongation of median survival by 4-5 months. In keeping with this observation, an independent phase IIa study showed that ursodeoxy-cholic acid (UDCA) penetrates into the cerebrospinal fluid (CSF) of pa-tients with ALS. This strong indication of efficacy is further supported by the evidence that TUDCA has cytoprotective properties in animal mod-els of neurodegenerative diseases. Therefore, a large-scale, phase III, clinical trial is needed to confirm and further measure the efficacy of TUDCA as a disease modifier in ALS. We have also selected solid biomarkers related to disease progression and cytoprotective activity to test during the 18-month treatment period. We have therefore assem-bled a consortium composed of leading European centres with estab-lished experience in ALS and a strong catching capability on this patient population.

Study objective

The primary objective of the study is:

To assess the efficacy of TUDCA in slowing disease progression in patients with ALS during the treatment period compared to the lead-in phase), as measured by ALSFRS-R.

Study design

This is a Phase III, multicenter, randomised, double-blind, placebo-controlled, parallel-group study.

Intervention

Tauroursodeoxycholic

Study burden and risks

Previous studies have shown that TUDCA is safe and well tolerated. However, all medicines can (not) advertise. The most complex side effects of TUDCA are: occasional nausea, vomiting, soft stools or mild diarrhea, gallstone calcareous deposits and itching. Keep in mind that you can not experience any of these

side effects.
To date, no interactions with other drugs have been reported. At this moment we do not know any contraindications for the use of TUDCA.
Treatment with TUDCA should be avoided:
* Substances that limit the absorption of bile acids [such as colestyramine (Questran) from colestipol (Colestid)];
* Gastric acid inhibitors containing aluminum hydroxide and / or smectites (aluminum oxide) (such as Maalox);
* estrogens (such as oestradiol estriol);
* Medications that lower plasma cholesterol from the removal of cholesterol by the gallbladder (estrogens, hormonal contraceptives, single statins and fibrates), and
• Hepatogenic drugs, that are drugs that affect the leg.
The use of TUDCA

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. laboratory-supported, probable, or definite ALS diagnosis, as defined by El Escorial Revised ALS diagnostic criteria
2. Disease duration <= 18 months
3. No swallowing difficulty (4 at ALSFRS-R swallowing subscore)
4. Able to perform reproducible pulmonary function tests
5. Forced vital capacity >=70% of normal
6. Stable on riluzole treatment for 3 months in the lead-in period
7. Signed informed consent

All patients who entered and completed the TUDCA-ALS clinical trial can be included in the open-label TUDCA-ALS Extension.
Inclusion criteria:
1. Completion of the visit M18 (Month 18) of the TUDCA-ALS clinical trial.
2. Signed informed consent for participation in the TUDCA-ALS Extension sub-study.

Exclusion criteria

1. Treatment with edaravone or other unaccepted concomitant therapy (substances inhibiting the intestinal absorption of bili-ary acids, antacids containing aluminium hydroxide and/or smectites, estrogens and drugs acting by lowering plasmatic cholesterol; drugs increasing biliary clearance of cholesterol, hepatolesive drugs)
2. Other causes of neuromuscular weakness
3. Presence of other neurodegenerative diseases
4. Significant cognitive impairment, clinical dementia or psychiat-ric illness
5. Severe cardiac or pulmonary disease
6. Other diseases precluding functional assessments
7. Other life-threatening diseases
8. At the time of screening, any use of non-invasive ventilation for any portion of the day, or mechanical ventilation via tracheost-omy, or on any form of oxygen supplementation
9. Gastrointestinal disorder that is likely to impair absorption of study drug from the gastrointestinal tract
10. Has taken any investigational study drug within 30 days or five half-lives of the prior agent, whichever is longer, prior to dosing
11. Any clinically significant laboratory abnormality
12. Other concurrent investigational medications
13. Active peptic ulcer
14. Previous surgery or infections of small intestine
15. Patients unable to easily swallow the treatment pills at time of enrolment

16. Occurrence of frequent biliary colic, biliary infections, severe pancreatic abnormalities
17. Subjects who weigh 88 lbs (40 kg) or less at screening
18. Sieric Aspartate aminotransferase or alanine aminotransferase concentrations more than 3 times the upper limit of normal
19. Creatinine clearance 50 ml/min or less
20. Any clinically significant neurological, haematological, autoim-mune, endocrine, cardiovascular, neo-plastic, renal, gastroin-testinal, or other disorder that, in the Investigator's opinion, could interfere with the subject's participation in the study, place the subject at increased risk, or confound interpretation of study results
21. Consideration by the investigator, for any reason, that the sub-ject is an unsuitable candidate to receive TUDCA or that the subject is unable or unlikely to comply with the dosing schedule or study evaluations
22. The patient is sexually active and is not willing to use highly ef-fective contraception during the study and up to 90 days after the day of last dose

Exclusion criteria:
1. Treatment with edaravone or other unaccepted concomitant therapy (as per section 8 of the main TUDCA-ALS clinical trial protocol)
2. Consideration by the investigator, for any reason, that the subject is an unsuitable candidate to re-ceive TUDCA or that the subject is unable or unlikely to comply with the dosing schedule or study evaluations
3. The patient of reproductive potential is sexually active and is not willing to use highly effective con-traception during the study and up to 90 days after the day of last dose (see Contraceptive Guidance in Appendix A)
4. The patient is pregnant or breast feeding

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:	Completed
Start date (anticipated):	11-12-2019
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tauroursodeoxycholic acid
Generic name:	Tauroursodeoxycholic acid

Ethics review

Approved WMO Date:	06-06-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	21-11-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	02-04-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-05-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-12-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	27-08-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-09-2021
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
EudraCT	EUCTR2018□002722□22-NL
ClinicalTrials.gov	NCT03800524
CCMO	NL69414.041.19