A Multi-arm, Adaptive, Group-sequential trial NETwork to evaluate drug efficacy in patients with Amyotrophic Lateral Sclerosis (ALS)

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This study has been transitioned to CTIS with ID 2024-516559-41-00 check the CTIS register for the current data. To investigate the efficacy and safety of drugs for patients with ALS.

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

Summary

ID

NL-OMON54016

Source
ToetsingOnline

Brief title
MAGNET

Condition

- Neuromuscular disorders

Synonym
ALS, MND

Research involving
Human

Sponsors and support

Primary sponsor: Stichting TRICALS Foundation
Source(s) of monetary or material Support: Stichting ALS Nederland (the

Netherlands);Fight MND (Australia);FWO (Belgium);MNDA (United Kingdom);Thierry Latran Foundation (European Union);Ulla-Carin Lindquist Foundation (Sweden)

Intervention

Keyword: Amytrophic lateral sclerosis, Neurodegenerative disease

Outcome measures

Primary outcome

The primary endpoint is overall survival, defined as time to death from any cause or respiratory insufficiency (DRI; defined as tracheostomy or the use of non-invasive ventilation for >=22 h per day for >=10 consecutive days). Secondary endpoints will be functional decline, respiratory function, quality of life, tolerability and safety.

Open Label Extension: idem.

Secondary outcome

• To assess the effect of each drug versus placebo on a combined assessment of survival and measures of daily functioning (ALS functional rating scale [ALSFRS-R])

• To assess the effect of each drug versus placebo on ALSFRS-R

• To assess the effect of each drug versus placebo on respiratory function (SVC)

• To assess the effect of each drug versus placebo on plasma creatinine

• To assess the effect of each drug versus placebo on the time to reach advanced disease stages

• To evaluate the safety and tolerability of each drug administered orally to patients with ALS

• To assess the effect of each drug versus placebo on change in urinary P75ECD

• To assess the effect of each drug versus placebo on change in plasma neurofilament light and heavy chain

• To assess the effect of each drug versus placebo on change in cognitive functioning (ECAS & ALS-FTD-Q)

• To assess the effect of each drug versus placebo on change in quality of life (EQ-5D)

Lithium specific (UMC Utrecht only):

To determine the value of the compound muscle action potential (CMAP) scan to monitor disease progression

Open Label Extension:

- Composite endpoint evaluating daily functioning and survival based on the joint model framework of survival and longitudinal ALSFRS-R total scores during the open label phase.
- Daily functioning, defined as mean change from baseline in ALSFRS-R total score during the open label phase.
- Long-term safety of lithium carbonate during the open label phase
- Quality of life during the open label phase (EQ5D).

Study description

Background summary

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease leading to death within three years. Over 60 drugs have been tested, but despite significant efforts from scientists, patients, and promising early signals, none of the treatments made it to the patient*s home. We propose an innovative and adaptive multi-arm trial design to investigate multiple treatments simultaneously. The study protocol acts as an overarching umbrella for multiple individual sub-studies and harmonizes their randomization, outcomes, visiting schemes, procedures and infrastructure. We implement innovation in inclusion criteria, statistical analysis and biomarker development. The study protocol doubles the number of patients that can participate, allows for a rapid screening for treatment benefit and provides the evidence required for market approval and patient access. The protocol is optimized in order to minimize patient burden and time on placebo, while maximizing the collection of information on safety and treatment benefit. As more drugs will become available in the near future, the study protocol can be adapted seamlessly to rapidly evaluate their value and speed-up the development of effective treatments for ALS.

Lithium specific:
Lithium interferes with transmembrane sodium exchange in nerve cells by affecting sodium, potassium-stimulated adenosine triphosphatase (Na+, K+-ATPase); alters the release of neurotransmitters; affects cyclic adenosine monophosphate (cAMP) concentrations; and blocks inositol metabolism resulting in depletion of cellular inositol and inhibition of phospholipase C-mediated signal transduction. Lithium has been shown to have neuroprotective effects in a number of models of neurodegeneration through a variety of mechanisms (please refer to protocol appendix 1A).

Study objective

This study has been transitioned to CTIS with ID 2024-516559-41-00 check the CTIS register for the current data.

To investigate the efficacy and safety of drugs for patients with ALS.

Study design

A confirmatory, multi-arm, group-sequential, double-blind placebo-controlled trial in 14 sites in Europe, UK and Australia.

Open Label Extension: An open label, non-randomized, extension study in 14 sites in Europe, UK and Australia.

Intervention

Randomization will be stratified by genotype and patients will be randomly

allocated in a 2:1 fashion to either active treatment or a matched placebo for a maximum duration of 24 months. Other active arms may be added in the future. Initial sample size is 171 patients with ALS.

Lithium specific:
The treatment is lithium carbonate capsules or placebo (2:1). Capsules will be taken once daily, starting with one capsule (400 mg daily) initially titrated up to two or three capsules daily over the first four weeks of treatment, depending on blood lithium levels. The lithium levels will be titrated to a blood plasma level between and including 0.4 to 0.8 mmol/L.
In the exceptional case when plasma lithium levels exceed 0.8 mmol/l on two consecutive occasions while on the minimum dose of 1 capsule per day (400mg per day), this will be accepted if concentrations remain <= 1.0 mmol/l (for patients 65 years or older) or <= 1.5 mmol/l (for patients >= 18 - < 65 years). If values exceed these limits the investigational product must be permanently discontinued. Additionally, when patients display symptoms of a lithium intoxication (as evaluated by the unblinded lithium physician and based on changes in LiSERS questionnaire outcome), the investigational product will also be permanently discontinued. Patients cannot be rechallenged.

Open Label Extensie: idem to lithium specific intervention without a placebo treatment. In other words: all patients will receive lithium carbonate.

Study burden and risks

All treatment modalities have been proven to be safe and well tolerated. Side effect profiles are expected to be mild. Patients will need to attend for genotyping, screening and every three months for follow-up visits, where blood (30 ml) and urine samples (20 ml) will be collected. At follow-up visits a number of neurological examinations and questionnaires on physical functioning and quality of life will be assessed. All study medication will be provided orally. For patients with a gastrostomy, all study medication can be administered through the feeding tube. There is no anticipated discomfort with any of the physical or behavioral assessments. Given the favorable AE profiles of study medications and their potential beneficial effect on disease progression, the potential benefits are considered to outweigh the burden of participation.

Contacts

Public
Stichting TRICALS Foundation

Goeman Borgesiuslaan 77
Utrecht 3515 ET
NL
Scientific
Stichting TRICALS Foundation

Goeman Borgesiuslaan 77
Utrecht 3515 ET
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Age >= 18 years at the time of screening.
2. Diagnosis of ALS according to the revised El Escorial criteria (possible, probable-laboratory supported, probable or definite).
3. Capable of providing informed consent and complying with trial procedures, including randomization to sub-studies.
4. TRICALS risk profile >= -6.0 and =< -2.0 **
5. The use of riluzole will be permitted during the study. Subjects taking riluzole must be on a stable dose for at least 30 days prior to the baseline visit, or stopped taking riluzole at least 30 days prior to the baseline visit.
6. Women of childbearing potential* must have a negative pregnancy test at baseline and be non-lactating.
7. Men must agree to practice contraception for the duration of the trial and for at least 3 months after last dose of study drug.
8. Men must not plan to father a child or to provide sperm for donation for the duration of the trial and 3 months after the last dose of study drug.
9. Women must not be able to become pregnant (e.g. post-menopausal***, surgically sterile or using effective birth control methods) for the duration of the study. Effective contraceptives are defined as having a failure rate of

less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label, including: abstinence, hormonal contraception, intrauterine device in place for >= 3 months (Appendix 1). Women of childbearing potential must have a negative pregnancy test at baseline, and be non-lactating. Women who are pregnant or are actively seeking to become pregnant, and women of reproductive potential who are not using effective contraceptives are excluded.

For the Open Label Extension:
Inclusion criteria:
1. Completion of the end of study visit (month 24) in the MAGNET lithium study, while on study medication
2. Signed informed consent for participation in the lithium extension
3. Capable of providing informed consent and complying with trial procedures
4. The same inclusion criteria of the MAGNET master protocol and MAGNET lithium subprotocol apply, with the exception of the TRICALS risk profile.

Exclusion criteria

1. Safety Laboratory Criteria at baseline:
o ALT >= 5 times upper limit of normal (ULN)
o AST >= 3 times ULN
o Bilirubin >= 1.5 times ULN (Gilbert syndrome is accepted)
o Estimated glomerular filtration rate (eGFR) Creatinine clearance < 50 mL / min (Cockroft-Gault) based on Cystatin C, if not available eGFR can also be calculated based on creatinine clearance.
o Platelet concentration of < 100 x109 per L
o Absolute neutrophil count of < 1x109 per L
o Haemoglobin < 100 g/L (<6.2 mmol/L)
o Both amylase & lipase >= 2 times ULN (suspected pancreatitis)
o Lactate >= 2 times ULN (suspected lactate acidosis)

2. Moderate to severe hepatic impairment according to Child-Pugh classification (Class B or higher; score >= 7). Child-Pugh classification is based on bilirubin, albumin, International Normalized Ratio (INR) and presence of encephalopathy or ascites.
3. Participation in any other investigational drug trial or using any investigational drug (beginning within 30 days prior to baseline). Only in the exceptional circumstance that an investigational product is available through an EAP, CUP or similar AND for which a clear clinical benefit has been demonstrated in phase 3 study can an exception be made after discussion with the PI and TRICALS.
4. Hypothyroidism unresponsive to thyroid hormone supplementation.
5. Subjects using non-invasive ventilation (NIV, >=22 h per day) or having a tracheostomy.

6. [No longer applicable since protocol version 3.2]
7. Clinically significant history of unstable or severe cardiac (e.g. congestive heart failure, coronary insufficiency and arrhythmias), oncological, hepatic or renal disease, neuromusculair diseases, significant pulmonary disorder or other medically significant illness.
8. Drug or alcohol abuse.
9. Unstable psychiatric illness defined as psychosis or untreated major depression within 90 days of the screening visit. This exclusion criterion is based on a prior psychiatric diagnosis that is unstable as determined by the subject*s treating Psychiatrist.
10. Presence of frontotemporal dementia which prevents informed consent.

Lithium subprotocol specific criteria:
1. Patients heterozygous or homozygous for the A-allele of rs12608932 (UNC13A)
2. Known allergy or hypersensitivity to lithium, or its excipients, or to the components of the placebo.
3. Brain injury with posttraumatic epilepsy or neurologic deficit, excluding a concussion in the medical history. Brain infarction is an exclusion criterion, a transient ischemic attack is not.
4. Addison disease.
5. Patients with the following co-medication: antipsychotics, digoxin and calcium antagonists, carbamazepine, methyldopa, verapamil and diltiazem.
6. Brugada Syndrome or family history of Brugada Syndrome.
7. Plasma sodium <120 mmol/L

For the Open Label Extension:
1. Judgement by the investigator that the patient is an unsuitable candidate, or that the patient is unable or unlikely to comply with the dosing schedule or study evaluations
2. The same exclusion criteria of the MAGNET master protocol and MAGNET lithium subprotocol apply

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:	Recruiting
Start date (anticipated):	09-08-2021
Enrollment:	28
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Lithium Carbonate
Generic name:	Lithium Carbonate
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	29-03-2021
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	25-06-2021
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	29-07-2021
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO

Date:	03-08-2021
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO

Date:	07-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-05-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-11-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-12-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-05-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-06-2024
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	CTIS2024-516559-41-00
EudraCT	EUCTR2020-000579-19-NL
CCMO	NL76763.041.21