ISRCTN15671139 https://doi.org/10.1186/ISRCTN15671139

An international multi-center clinical trial to investigate the efficacy of multiple drug compounds in patients with amyotrophic lateral sclerosis

Submission date
21/05/2022

Recruitment status
No longer recruiting

Registration date
21/09/2022

Overall study status
Completed

Last Edited
09/05/2023

Condition category
Nervous System Diseases

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Amyotrophic lateral sclerosis (ALS) is a progressive nervous system disease that affects nerve cells in the brain and spinal cord, causing loss of muscle control. The aim of this study is to simultaneously investigate the effectiveness and safety of multiple drugs for ALS. We do this by using so-called 'study arms'. Each study arm investigates the effectiveness and safety of one drug or a combination of drugs. Once it is clear which arm of the study they are participating in, participants will be assigned a drug or placebo by drawing lots. A placebo is a substance without an active substance, a 'fake substance'. Currently one arm is active that investigates the effect of lithium carbonate vs placebo in ALS. Lithium is a substance currently registered for use in bipolar disorders. This is a psychiatric disease that causes severe mood swings. Lithium affects multiple biological mechanisms involved in ALS. Previous research has shown that the drug is not effective in all patients with ALS, but may be beneficial in patients with a variation in the UNC13A gene (1 in 6 patients has this variation). Lithium is not currently being prescribed for ALS outside of this study.

Who can participate?
Patients aged 18 years and over with ALS

What does the study involve?
The participants will be randomly allocated to either placebo or an active drug and are required to visit the clinic every 3 months for a maximum duration of 24 months. Patients are required to take the study medication orally on a daily basis. During each hospital visit the patient is required to undergo blood tests, provide a urine sample, undergo an interview and lung function testing. Electrocardiography and neurological examinations will be performed every 12 months.

What are the possible benefits and risks of participating?
Participants receiving the study medication may benefit from a delay in loss of function due to ALS. The blood tests require a single needle to be placed into the arm to draw blood. This may

cause some discomfort. The risks following blood collection are bruising, bleeding or infection from the site. Participants should maintain pressure on the site for at least 5 minutes and not use the affected arm to lift anything heavy for 24 hours after the blood test. There is no potential harm involved with the other medical assessments (e.g. urine sample, questionnaires, lung function). Administration of lithium carbonate for this study is not anticipated to induce any potential risk other than the potential side-effects as have been listed previously but may benefit subjects participating in this study. Note that lithium may interact with other medications. In the previous studies, lithium carbonate was relatively well-tolerated by patients with ALS. Perhaps in part due to the fact that the target dose was relatively low. Given the fact that the side effects were modest and that the potential survival benefit is very large, there is sufficient evidence to proceed with a confirmatory trial, which is the objective of this study.

Where is the study run from?
Stichting TRICALS Foundation (Netherlands)

When is the study starting and how long is it expected to run for?
January 2021 to June 2026

Who is funding the study?
Stichting TRICALS Foundation (Netherlands)

Who is the main contact?
Prof. Leonard van den Berg, magnet@tricals.org

Contact information

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Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2020-000579-19

Integrated Research Application System (IRAS)
1005268

Central Portfolio Management System (CPMS)
53777

Study information

Scientific Title
A Multi-arm, Adaptive, Group-sequential trial NETwork to evaluate drug efficacy in patients with amyotrophic lateral sclerosis

Acronym
MAGNET

Study objectives
The primary objective of this study is to assess the efficacy of each drug versus placebo on overall survival, defined as death from any cause or respiratory insufficiency, in patients with amyotrophic lateral sclerosis (ALS).

The secondary objectives of this study are to assess:
1. The effect of each drug versus placebo on a combined assessment of survival and measures of daily functioning (ALS functional rating scale [ALSFRS-R])
2. The effect of each drug versus placebo on ALSFRS-R
3. The effect of each drug versus placebo on respiratory function (SVC)
4. The effect of each drug versus placebo on plasma creatinine
5. The effect of each drug versus placebo on the time to reach advanced disease stages
6. The safety and tolerability of each drug administered orally to patients with ALS

7. The effect of each drug versus placebo on change in urinary P75EDC
8. The effect of each drug versus placebo on change in plasma neurofilament light and heavy chain
9. The effect of a drug versus placebo on change in plasma pharmacodynamic markers (e.g. HERV-K expression)

Lithium specific (UMC Utrecht only):
To determine the value of the compound muscle action potential (CMAP) scan to monitor disease progression

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 27/07/2022, East of England - Cambridge Central Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA, UK; +44 (0)207 104 8384; cambridgecentral.rec@hra.nhs.uk), ref: 22/EE/0132

Primary study design
Interventional

Study design
Double-blind randomized placebo-controlled parallel-group trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Amyotrophic lateral sclerosis (ALS)

Interventions
Lithium carbonate or placebo are supplied as white hard gelatin capsules size 00 filled with white to off-white powder. Each capsule contains 400 mg of lithium carbonate or placebo. 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 4 weeks of treatment, depending on blood lithium levels. For patients on placebo, dose sham adjustments will be made. Lithium carbonate will be titrated to a blood plasma level between and including 0.4 to 0.8 mmol/l. Study medication will be provided orally. For patients with a gastrostomy, all study medication can be administered through the feeding tube. Patients are treated for a maximum duration of 24 months.

Follow-up:
Patients will visit the site at 3-monthly intervals. After a patient completes the 24-month follow-up period, patients will be offered to enroll in an open-label extension phase of the respective sub-study as described in each sub-study protocol, or if applicable and meeting the inclusion criteria, re-randomized to other sub-studies. All patients, also those stopped prior to month 24, will be monitored for survival data (i.e. living status or date of death) until the master protocol is terminated.

Randomization:
Randomization consists of two steps: (1) randomization to sub-study and (2) randomization to treatment arm (i.e. active or placebo). Based on genotype, patients are eligible for a given

number of sub-studies. Patients are randomly allocated to the eligible sub-studies with equal allocation probabilities. A second randomization takes place within each sub-study, where patients will be randomly allocated in a 2:1 ratio to receive active treatment or a matched placebo until the sub-study reaches its target sample size. Randomization sequences in each sub-study will be in random block sizes of 4 – 6, and stratified for trial site and risk category (high vs. low risk [i.e. low-risk TRICALS risk profile defined as ≤ -4.5). Randomization will be done using a centralized online response system (Research Online, Utrecht, the Netherlands), which assigns each randomized participant a unique identification number that will be used throughout the study.

Intervention Type
Drug

Phase
Phase III

Primary outcome(s)
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).

For each sub-study, there is one pre-planned, event-driven, interim analysis when approximately 60% of the required events are available. If the trial cannot be terminated early, the trial continues until the required number of events is reached or until 24 months after the last enrolled patient, whichever occurs first. Patients are required to visit the clinic every 3 months for a maximum duration of 24 months. In case of the lithium sub-study, if treatment is futile, the trial can be stopped after an average of 28.0 months since first enrolled patient with an average sample size of 137 patients. In this scenario, the probability for individual patients to remain in the trial for 18 months or more is 11.3% and to complete 24 months of follow-up is 1.8%.

Key secondary outcome(s)
1. Composite endpoint evaluating daily functioning and survival based on the joint model framework of survival and longitudinal ALSFRS-R total scores, measured quarterly for a maximum duration of 24 months
2. Daily functioning, defined as mean change from baseline in ALSFRS-R total score, measured quarterly for a maximum duration of 24 months
3. Respiratory function, defined as mean change from baseline in SVC (% predicted of normal according to the GLI-2012 reference standard), measured quarterly for a maximum duration of 24 months
4. Quality of life, defined as change from baseline on the Visual Analogue Scale (single-item scale) and EQ-5D, measured quarterly for a maximum duration of 24 months
5. Neuropsychological status, defined as change from baseline on the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) and Amyotrophic Lateral Sclerosis-Frontotemporal Dementia-Questionnaire (ALS-FTD-Q), measured yearly
6. Clinical disease stage, defined as mean time spent in each stage of the King’s and ALS Milano-Torino staging systems, measured quarterly for a maximum duration of 24 months
7. Change from baseline in laboratory parameters:
7.1. Urinary P75ECD, measured quarterly for a maximum duration of 24 months
7.2. Neurofilament light and heavy chain, measured quarterly for a maximum duration of 24 months
7.3. Plasma creatinine, measured quarterly for a maximum duration of 24 months

8. Tolerability, defined as time-to-discontinuation of the assigned treatment since randomization, continuously for a maximum duration of 24 months
9. Safety based on the safety assessments including physical neurological examinations, clinical laboratory evaluations, vital signs and frequency of adverse events (AEs) or serious adverse events (SAEs). (S)AEs will be categorized according to the Common Terminology Criteria for Adverse Events and will be rated for severity and association with the study drug, continuously for a maximum duration of 24 months

Completion date
30/06/2026

Eligibility

Key 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.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex

All

Key exclusion criteria
For all subjects:
1. Safety Laboratory Criteria at baseline:
1.1. ALT ≥5 times upper limit of normal (ULN)
1.2. AST ≥3 times ULN
1.3. Bilirubin ≥1.5 times ULN
1.4. Creatinine clearance <50 ml/min (Cockroft-Gault) based on Cystatin C
1.5. Platelet concentration of < 100 x109 per L
1.6. Absolute neutrophil count of < 1x109 per Lo Haemoglobin <100 g/L (<6.2 mmol/L)
1.7. Amylase & lipase ≥2 times ULN (suspected pancreatitis)
1.8. 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 investigational drug (within 30 days prior to screening)
4. Hypothyroidism unresponsive to thyroid hormone supplementation
5. Subjects using non-invasive ventilation (NIV, ≥22 h per day) or having a tracheostomy
6. Subjects taking edaravone within 30 days prior to screening. Edaravone is approved by the FDA, but remains an investigational product in Europe and Australia
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

For lithium carbonate:
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

Date of first enrolment
15/06/2021

Date of final enrolment
30/09/2025

Locations

Countries of recruitment
United Kingdom

England

Australia

Belgium

Ireland

Netherlands

Spain

Sweden

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Study participating centre
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Study participating centre
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Sponsor information

Organisation
Stichting TRICALS Foundation

Funder(s)

Funder type
Research organisation

Funder Name
Stichting TRICALS Foundation

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No