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EXPErimental medicine Route To Success in Amyotrophic Lateral Sclerosis (EXPERTS-ALS)

Submission date
21/02/2024

Recruitment status
Recruiting

Registration date
15/04/2024

Overall study status
Ongoing

Last Edited
18/11/2025

Condition category
Nervous System Diseases

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

Plain English summary of protocol

Background and study aims
Amyotrophic lateral sclerosis (ALS), the most common form of motor neuron disease (MND), is a fatal disease affecting 1 in 300 people. ALS causes muscle wastage that gets worse over time, leading to loss of the ability to walk, talk, eat and eventually breathe. There is no cure or highly effective disease-slowing therapy for ALS.
Historically, drug trials for ALS have been unsuccessful. A process that can quickly screen drugs in people with ALS, rather than in cells or animal models, is believed will be better at selecting treatments for the large Phase III trials that are needed. EXPERTS-ALS is a UK multicentre study that will screen drugs for their potential to slow the progression of ALS, by looking at changes in blood test markers. Higher blood levels of a marker known as neurofilament light chain (NFL), a building block of nerve cells, are associated with faster rates of ALS disability. A drug will be recommended to go forward into Phase III trials if a large and important reduction in blood NFL levels is seen.

Who can participate?
Patients with a diagnosis of ALS aged at least 18 years old and over at the time of consent

What does the study involve?
EXPERTS-ALS is an adaptive trial, meaning that drugs can be added, assessed and removed as the trial is ongoing. Drugs will be selected for the study based on explicit criteria agreed upon by a group of experts. The data generated throughout the study will be analysed, and if a drug does not meet the team's pre-agreed criteria, it will be removed from the study. There will be no placebo/dummy drug. Participants will know what drug they are receiving and will take it for a maximum of 6 months. The study aims to test between 9-12 drugs over 5 years.

What are the possible benefits and risks of participating?
The results of this study will help to prioritise drugs for testing in larger clinical trials to inform the treatment of future patients with ALS. By taking part in the study, participants are directly helping to do this.

Taking part in EXPERTS-ALS will require participants to attend additional hospital appointments. Travel costs to EXPERTS-ALS appointments will be reimbursed if required. To try and minimise

the burden, it will be possible for participants to attend the week 4 and week 8 study appointments remotely (via telephone or video call) unless there are drug-specific safety assessments required.

The study drugs are all repurposed medications which are used widely in other settings however participants may experience side effects from taking the study drugs. Possible side effects will be listed in the drug-specific PISs, and information on who to contact if side effects are experienced will be included. Participants will also be asked about any side effects experienced at their routine study visits. Depending on the drug, it may be possible to reduce the dose taken if a participant is struggling with side effects. Local study teams will review participants' treatment regularly and may decide to pause or stop the medication if needed.

Fasting blood samples will be required at three time points, one before randomisation (at either the screening or baseline visit), one at week 12 and one at week 24. Participants will be required not to eat anything from 8.30 pm the night before their appointment and to drink only water. These appointments will be scheduled to take place in the morning to minimise inconvenience for participants.

Where is the study run from?
Royal Hallamshire Hospital, UK

When is the study starting and how long is it expected to run for?
February 2024 to September 2028

Who is funding the study?
EXPERTS-ALS is funded by the Efficacy and Mechanism Evaluation (EME) Programme, a Medical Research Council (MRC) and National Institute for Health and Care Research (NIHR) partnership.

Who is the main contact?
experts-als@sheffield.ac.uk

Contact information

Type(s)
Scientific

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Type(s)
Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1007791

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
EXPERTS-ALS, IRAS 1007791, CPMS 55939

Study information

Scientific Title
A multi-centre, Bayesian phase II, open label, randomised drug prioritisation platform trial using blood neurofilament light (NFL) chain levels as a surrogate outcome for biological efficacy in patients with ALS

Acronym
EXPERTS-ALS

Study objectives
Current study objectives as of 18/11/2025:
To determine:
- Whether a candidate drug is associated with a relevant decrease in mean group neurofilament light chain (NFL) level from baseline.
- How a candidate drug ranks compared with concurrently or previously randomised competitor drugs on its effect on mean NFL levels.

Secondary objectives:
- To evaluate the safety and tolerability of candidate drugs in patients with ALS.
- To assess the effect of candidate drugs on standard clinical measures of daily functioning (e.g. ALS revised functional rating scale ALSFRS-R) and clinical (King's) stage.
- To create an ALS sample bioresource for further research.

Exploratory objectives:
- To explore survival without tracheostomy or non-invasive ventilation and compare it with the

median prediction of survival without tracheostomy or non-invasive ventilation from the European Network for the Cure of ALS (ENCALS) survival prediction model.
- To explore the effect of candidate drugs on disability and quality of life.
- To explore respiratory function assessments and determine the feasibility and validity of remote, unsupervised respiratory function assessment as compared with supervised assessments.
- To explore participant and site staff (Principal Investigators, Research Nurses) understanding and experience of the EXPERTS-ALS platform trial design, including barriers and enablers for recruitment and retention.

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Exploratory objectives:
- To explore survival without tracheostomy or non-invasive ventilation and compare it with the median prediction of survival without tracheostomy or non-invasive ventilation from the European Network for the Cure of ALS (ENCALS) survival prediction model.
- To explore the effect of candidate drugs on disability and quality of life.
- To explore respiratory function assessments and determine the feasibility and validity of remote, unsupervised respiratory function assessment as compared with supervised assessments.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 08/04/2024, London - Harrow Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8154, (0)207 104 8357; harrow.rec@hra.nhs.uk), ref: 24/LO/0205

Study design
Randomized open-label parallel-group adaptive platform trial

Primary study design
Interventional

Study type(s)
Efficacy, Safety

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

Interventions
The EXPERTS-ALS protocol describes an overarching trial design to evaluate the effect of candidate drugs on blood NFL levels in patients with ALS receiving usual standard of care. The protocol is deliberately flexible, allowing:
- as broad a range of ALS patients to be recruited;
- participant randomisation between only those treatment arms that are not believed by the enrolling doctor to be contraindicated (e.g. by particular co-morbid conditions or concomitant medications); and
- treatment arms to be added or removed according to the emerging evidence from within the trial.

The current treatment arms are metformin, nifedipine and ropinirole.

Metformin: Where possible, prolonged-release tablets should be used. The starting dose is 500mg once daily, taken with the evening meal. After 14 days the dose should be increased to 1000mg once daily.

Nifedipine: LA/XL versions of nifedipine formulated for once-daily dosing will be used where possible. The starting and target dose is 30mg LA/XL once daily. As a precaution against potential hypotension, it is recommended that the dose be taken at bedtime.

Ropinirole: Where possible, prolonged-release tablets should be used. Ropinirole HCl extended-release in a starting dose of 2mg once per day and building up by 2mg per day at weekly intervals to a dose of 16mg per day.

Randomisation is completed by a member of the local study team by accessing a web-based randomisation system provided by the University of Sheffield Clinical Trials Research Unit.

Follow-up visits are completed at week 4*, week 8*, week 12, week 18 and week 24 post-randomisation. *May be completed remotely by telephone call.

Survival status will be collected at 12 months post-randomisation via a review of medical records.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Metformin, nifedipine, ropinirole

Primary outcome(s)
Change in blood neurofilament light chain (NFL) levels measured using automated immunoassay analysed via the SIMOA HD-X instrument (Quanterix) from baseline to weeks 18 and 24

Key secondary outcome(s))
Current secondary outcome measures as of 14/03/2025:

Secondary outcomes:
1. Change in daily functioning measured using the ALS revised functional rating scale (ALSFRS-R)

score from baseline to weeks 12 and 24
2. Progression in the clinical stage by 1 stage or more measured using King's staging system from baseline to week 24
3. Adverse events and serious adverse events measured using data recorded at each study visit during the trial

Exploratory outcomes:
1. To explore survival at 12 months without non-invasive ventilation >22 hr/day or invasive ventilation, and compare it with the median prediction of survival without non-invasive ventilation >22 hr/day or invasive ventilation from the European Network for the Cure of ALS (ENCALS) survival prediction model.
2. Change in WHO Disability Assessment Schedule (WHODAS 2.0) and Quality of Life (WHOQOL-Bref) from baseline to 24 weeks (or early discontinuation of treatment) against a natural history cohort
3. In-person forced vital capacity (FVC) and peak cough flow (PCF), compared with remote FVC (rFVC) and remote PCF (rPCF) where readings are available within +/- 7 days of each other (FVC and PCF measured at screening, baseline, week 12 and week 24 post randomisation)

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Previous secondary outcome measures:

Secondary outcomes:
1. Change in daily functioning measured using the ALS revised functional rating scale (ALSFRS-R) score from baseline to weeks 12 and 24
2. Progression in the clinical stage by 1 stage or more measured using King's staging system from baseline to week 24
3. Adverse events and serious adverse events measured using data recorded at each study visit during the trial

Exploratory outcomes:
1. Survival without tracheostomy or non-invasive ventilation at 12 months, compared with the ENCALS median prediction of survival without tracheostomy or non-invasive ventilation
2. Change in WHO Disability Assessment Schedule (WHODAS 2.0) and Quality of Life (WHOQOL-Bref) from baseline to 24 weeks (or early discontinuation of treatment) against a natural history cohort
3. In-person forced vital capacity (FVC) and peak cough flow (PCF), compared with remote FVC (rFVC) and remote PCF (rPCF) where readings are available within +/- 7 days of each other (FVC and PCF measured at screening, baseline, week 12 and week 24 post randomisation)

Completion date
30/09/2028

Eligibility

Key inclusion criteria
1. Diagnosis of ALS according to Gold Coast criteria.
2. Age at least 18 years at the time of consent.
3. ENCALS prognosis risk score of -6.0 to -2.0 as calculated from the results of the screening visit.
4. Those taking riluzole must be on a stable dose for at least 30 days prior to the baseline visit or must have chosen not to take it for the study duration.

5. Must be able to be randomised to at least two of the open arms after reviewing contraindications, current medication and the IMP-specific eligibility criteria as detailed in the IMP-specific appendices.
6. Fertile persons must use adequate contraception if required by the IMPs (see protocol Section 5.8 and IMP-specific appendices for details).
7. Persons of childbearing potential must have a negative pregnancy test prior to randomisation.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
100 years

Sex
All

Total final enrolment
0

Key exclusion criteria
Current exclusion criteria as of 14/03/2025:

1. Clinically significant history of unstable or severe cardiac, oncological, hepatic or renal disease or other medically significant illness which, in the opinion of the local investigator*, is a contraindication to participation.
2. Presence of an active disorder (other than ALS) which is known to independently raise NFL levels.
3. Treatment with IMP in any other investigational drug trial within 30 days prior to screening.
4. Pre-existing use of current EXPERTS-ALS IMPs or drugs in the same class as current EXPERTS-ALS IMPs that would result in the patient not being able to be randomised between a minimum of two arms.
5. Contraindications to IMPs that would result in the patient not being able to be randomised between a minimum of two arms. Refer to IMP-specific appendices for details.
6. Use of non-invasive ventilation >22 hr/day or invasive ventilation.
7. Pregnant or breastfeeding
8. Unable to comply with trial procedures.

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1. Clinically significant history of unstable or severe cardiac, oncological, hepatic or renal disease or other medically significant illness which, in the opinion of the local investigator*, is a contraindication to participation.
2. Presence of an active disorder (other than ALS) which is known to independently raise NFL levels.
3. Participation in any other investigational drug trial within 30 days prior to screening.
4. Pre-existing use of current EXPERTS-ALS IMPs or drugs in the same class as current EXPERTS-ALS IMPs that would result in the patient not being able to be randomised between a minimum of two arms.
5. Contraindications to IMPs that would result in the patient not being able to be randomised between a minimum of two arms. Refer to IMP-specific appendices for details.
6. Use of non-invasive ventilation >22 hr/day or tracheostomy ventilation.
7. Pregnant or breastfeeding
8. Unable to comply with trial procedures.

Date of first enrolment
18/11/2024

Date of final enrolment
31/03/2028

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
Royal Hallamshire Hospital
Glossop Road
Sheffield
England
S10 2JF

Study participating centre
Oxford Radcliffe Hospital NHS Trust
The John Radcliffe
Headley Way
Headington

Oxford
England
OX3 9DU

Study participating centre
The Anne Rowling Regenerative Neurology Clinic
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Study participating centre
Royal Devon University Healthcare NHS Foundation Trust
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SE5 9RS

Study participating centre
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Study participating centre
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Heath Park
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University College Hospital
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NW1 2BU

Study participating centre
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Newcastle MND Care and Research Centre, Queen Victoria Road
Newcastle upon Tyne
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NE1 4LP

Sponsor information

Organisation
Sheffield Teaching Hospitals NHS Foundation Trust

ROR
https://ror.org/018hjpz25

Funder(s)

Funder type
Government

Funder Name
Efficacy and Mechanism Evaluation Programme

Alternative Name(s)
NIHR Efficacy and Mechanism Evaluation Programme, Efficacy and Mechanism Evaluation (EME), EME

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

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?
Study website	Study website	11/11/2025	11/11/2025	No	Yes