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Assessing the effect of Triumeq in amyotrophic lateral sclerosis

Submission date	Recruitment status	[X] Prospectively registered
22/02/2021	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
14/12/2021	Ongoing	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
07/08/2024	Nervous System Diseases	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Amyotrophic lateral sclerosis (ALS) is a progressive motor neuron disease. Unfortunately, there are limited medications available for ALS. The only available treatment is riluzole, which tends to provide only minimal benefit. Therefore, there is a high need for further research using other medications, to help improve the options for treatment for this disease.
There has been laboratory research that suggests that a virus called an endogenous retrovirus may be the cause or trigger for ALS in some people. This virus may be of the same family (although quite different) to the virus that causes HIV (also called 'AIDS'). Researchers are intending to test if an anti-viral medication that is a very effective treatment for HIV, may also be effective for people who have ALS.
Triumeq, commonly prescribed for HIV treatment, is an antiviral medication that is a combination of three medications: dolutegravir 50 mg, abacavir 600 mg, and lamivudine 300 mg. Triumeq is approved by the Therapeutic Goods Administration (TGA) to treat HIV patients. However, it is not approved to treat ALS. Therefore, it is an experimental treatment for ALS.
The aim of this study is to determine whether Triumeq is effective at delaying the progression of ALS, and whether it is safe and well-tolerated in patients with ALS. The Lighthouse study demonstrated Triumeq to be safe and well tolerated in people with ALS.

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

What does the study involve?
The entire study will last for around 2 years. Participation is voluntary. Participation in this study will involve up to 10 visits (about 2 hours each) roughly every 3 months, and as many telephone calls as participants would like, to make sure they are comfortable with the research process. Participants will be assessed throughout the project using assessment scales to determine if it is suitable for them to continue the medication.
Participants will be randomly allocated to receive either Triumeq or a matching placebo (dummy drug) once daily in addition to standard care. The random allocation will be done using a computer maintained by the King's Clinical Trials Unit. Two thirds of research participants will receive active Triumeq and one third will receive matched placebo capsules. A placebo is a medication with no active ingredients and so has no medical benefit. It looks like the real thing,

but it is not. The study is a 'double-blind' study. This means that neither participants nor the study doctor will know which treatment they are receiving. However, in certain circumstances the study doctor can find out which treatment participants are receiving. This study has been designed to make sure the researchers interpret the results fairly without any bias and avoids study doctors or participants jumping to conclusions.
There are a number of procedures and reviews that will be carried out at different times over the 24 months:
1. Demographics
2. Review of medical history
3. Physical examination/vital signs
4. Neurological exam
5. Blood collection
6. Urine collection
7. Throat or nasal swab: the doctor/nurse/research coordinator will perform either a throat or nasal swab to check for COVID-19 infection
8. Spirometry (breathing) test
9. Questionnaire completion
10. ECG test

What are the possible benefits and risks of participating?
The researchers cannot guarantee or promise that participants will receive any benefits from this research; however, possible benefits may include some relief of ALS symptoms. The tests provided may help participants learn about their general health. This study may assist doctors and scientists to help people suffering from symptoms with ALS in the future.
Medical treatments often cause side effects. Participants may have none, some or all of the effects listed below, and they may be mild, moderate or severe. There may be side effects that the researchers do not expect or do not know about and that may be serious. Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long-lasting or permanent. If a severe side effect or reaction occurs, the study doctor may need to stop the treatment.
The following side effects have been experienced by people taking Triumeq:
Common side effects (occur in 1 out of 10 people): fever, not feeling well, discouragement, nausea, rash, irritability, loss of interest and/or pleasure, trouble concentrating and/or sleeping.
Uncommon side effects (occur in 1 out of 100 people): neuropathy (tingling in fingers and toes), anxiety, difficulty moving, weight loss, itching and hair loss as well as high blood sugar.
Rare side effects (occur in 1 out of 10, 0000 people): abnormal liver function tests, low blood pressure dizziness or light-headedness, fainting or lack of concentration or fatigue, acute inflammation of the pancreas, nausea, fever and a swollen and or tender abdomen and hepatitis, joint pain, abdominal pain and yellowing of the skin.

Where is the study run from?
King's College London (UK)

When is the study starting and how long is it expected to run for?
January 2020 to August 2026

Who is funding the study?
1. National Institute for Health Research (NIHR) (UK)
2. FightMND (Australia)
3. Motor Neurone Disease Research Institute of Australia (Australia)
4. Treatment Research Initiative to Cure ALS (TRICALS)

Who is the main contact?
Sylvia Wilczynska
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Study website
https://www.mndcsg.org.uk/healthcare-research/studies/lighthouse-ii

Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
2020-005069-15

IRAS number
271218

ClinicalTrials.gov number
NCT05193994

Secondary identifying numbers
IRAS 271218

Study information

Scientific Title
Randomized double-blind placebo-controlled Phase III trial of Triumeq in amyotrophic lateral sclerosis

Acronym
Lighthouse II

Study objectives

Activation of a human endogenous retrovirus is a key component of the pathogenesis of amyotrophic lateral sclerosis (ALS), and blocking its lifecycle with antiretroviral therapy will therefore provide an effective treatment.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 01/02/2022, London - Westminster Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA, UK; +44 (0)207 104 8066, +44 (0)207 104 8236, +44 (0)207 104 8283; westminster.rec@hra.nhs.uk), ref: 22/LO/0059

Study design
Double-blind (participant, investigators) 2:1 randomized placebo-controlled international multi-centre trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Amyotrophic Lateral Sclerosis (ALS)

Interventions
Lighthouse II is an international, phase III, multi-centre, parallel-group, placebo-controlled, blinded (participant, investigators, analyst) randomised controlled trial of Triumeq (abacavir 600 mg, lamivudine 300 mg and dolutegravir 50 mg) or matched placebo, once daily in addition to standard care, in a 2:1 treatment/placebo allocation ratio in participants with ALS, in order to determine the superiority of treatment versus placebo. If the trial is not terminated at a planned interim analysis, the trial will continue until 24 months after the last enrolled participant or a minimum of 212 events have occurred, whichever is first.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)

Abacavir, lamivudine, dolutegravir

Primary outcome measure
Overall survival, defined as time to mortality from any cause. This will be recorded and reported on an ongoing basis from the participant randomisation. The primary outcome timepoint is at 24 months.

Secondary outcome measures
1. Combined assessment of survival and measures of daily functioning using the ALSFRS-R total score (CAFS) at baseline, 3, 6, 9, 12, 15, 18, 21 and 24 months
2. Daily functioning is measured by using the ALSFRS-R total score at baseline, 3, 6, 9, 12, 15, 18, 21 and 24 months
3. Respiratory function is measured by slow vital capacity (SVC) (% predicted of normal according to the GLI-2012 reference standard) at baseline, 3, 6, 9, 12, 15, 18, 21 and 24 months
4. Plasma creatinine levels are measured using safety blood test at baseline, 3, 6, 9, 12, 15, 18, 21 and 24 months
5. Clinical disease stage, defined as mean time spent in each stage of the King's Staging Scale and the ALS Milano-Torino staging systems (MITOS, derived from ALSFRS-R) at baseline, 3, 6, 9, 12, 15, 18, 21 and 24 months
6. Safety based on safety assessments including:
6.1. Physical examinations at baseline, 3, 6, 9, 12, 15, 18, 21 and 24 months
6.2. Clinical laboratory evaluations at baseline, 3, 6, 9, 12, 15, 18, 21 and 24 months
6.3. Vital signs at baseline, 3, 6, 9, 12, 15, 18, 21 and 24 months
6.4. Frequency of adverse events (AEs) or serious adverse events (SAEs) – ongoing from participant randomisation
7. Tolerability measured by medication discontinuation – ongoing from participant randomisation
8. Cognitive function measured by using Edinburgh Cognitive and Behavioural ALS Screen (ECAS) at baseline, 12 and 24 months
9. Quality of life, defined as total scores on the Visual Analogue Scale (single-item scale) and EQ-5D-5L questionnaire at baseline, 3, 6, 9, 12, 15, 18, 21 and 24 months
10. Laboratory parameters, e.g. urine P75ECD, plasma neurofilament light and heavy chain, HERVK expression and genotyping (UNC13a / C9orf72), measured by blood and urine tests at baseline, 3, 6, 9, 12, 15, 18, 21 and 24 months

Overall study start date
01/01/2020

Completion date
01/08/2026

Eligibility

Key inclusion criteria
Current inclusion criteria as of 13/02/2024:
1. Age ≥ 18 years at the time of screening
2. Diagnosis of ALS according to the Gold Coast Criteria
3. Capable of providing informed consent and complying with trial procedures
4. TRICALS risk profile > -6.0 and < -2.0
5. Those taking Riluzole must be on a stable dose for at least 30 days prior to the baseline visit or must have stopped taking Riluzole at least 30 days prior to the baseline visit
6. Women must not become pregnant (e.g., post-menopausal, surgically sterile, using highly

effective birth control methods or not having potentially reproductive sex) for the duration of the study plus five days. Highly effective methods of birth control are those with a failure rate of < 1% per year when employed consistently and correctly, e.g. combined (oestrogen and progestogen containing) hormonal contraception or progestogen-only hormonal contraception
7. Women of childbearing potential must have a negative serum pregnancy test at screening and be non-lactating. Patients will be advised regarding appropriate contraception. A menstruation history will be taken at each visit. Women of childbearing potential are defined as females who are fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy
8. For participants taking antacids (regularly or as required), the participant is willing and able to avoid taking antacids for at least 6 hours before and 2 hours after Triumeq
9. Participants taking taurursodiol supplements (TUDCA) can participate in this trial if the supplement does not contain sodium phenylbutyrate.
10. Participants taking taurursodiol supplements (TUDCA) that also contain sodium phenylbutyrate must be willing to stop supplementation 30 days prior to randomisation.

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2. Diagnosis of ALS according to the Gold Coast Criteria
3. Capable of providing informed consent and complying with trial procedures
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5. Those taking Riluzole must be on a stable dose for at least 30 days prior to the baseline visit or must have stopped taking Riluzole at least 30 days prior to the baseline visit
6. Women must not become pregnant (e.g., post-menopausal, surgically sterile, using highly effective birth control methods or not having potentially reproductive sex) for the duration of the study. Highly effective methods of birth control are those with a failure rate of < 1% per year when employed consistently and correctly, e.g. combined (oestrogen and progestogen containing) hormonal contraception or progestogen-only hormonal contraception
7. Women of childbearing potential must have a negative serum pregnancy test at screening and baseline and be non-lactating. Women of childbearing potential are defined as females who have experienced menarche and are not surgically sterilised (e.g. hysterectomy or bilateral salpingectomy) or post-menopausal (defined as at least 1 year since last regular menstrual period)
8. For participants taking antacids (regularly or as required), participant is willing and able to avoid taking antacids for at least 2 hours before and 6 hours after Triumeq

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
390

Key exclusion criteria

Current exclusion criteria as of 13/02/2024:
1. People who are HLA-B*5701 positive
2. Known hypersensitivity to dolutegravir, abacavir or lamivudine, or to any of the excipients
3. Safety Laboratory Criteria at screening:
3.1. ALT ≥ 5 times upper limit of normal (ULN)
3.2. AST ≥ 3 times ULN
3.3. Bilirubin ≥ 1.5 times ULN with clinical indicators of liver disease
3.4. Creatinine clearance < 30 ml/min
3.5. Platelet concentration of < 100 x109 per l
3.6. Absolute neutrophil count of < 1x109 per l
3.7. Haemoglobin < 100 g/l
3.8. Amylase ≥ 2 times ULN
3.9. Lactate ≥ 2 times ULN
4. Moderate to severe hepatic impairment, as defined by local clinical guidelines
5. Presence of HIV antibodies at screening
6. Presence of Hepatitis C antibodies at screening unless participants have had effective treatment for Hepatitis C
7. Presence of Hepatitis B core or surface antigen at screening
8. Participation in any other investigational drug trial or using investigational drug within 30 days prior to screening
9. Use of NIV ≥22 h per day or having a tracheostomy
10. Edaravone dose within 30 days prior to screening. Edaravone is approved by the FDA and in Japan, but remains an investigational product in Europe and Australia
11. Clinically significant history of unstable or severe cardiac, oncological, psychiatric, hepatic, or renal disease or other medically significant illness
12. Taking medication contraindicated with Triumeq: dofetilide or fampridine (dalfampridine)
13. Taking Tofersen within 3 months prior to screening.

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11. Clinically significant history of unstable or severe cardiac, oncological, psychiatric, hepatic, or renal disease or other medically significant illness
12. Taking medication contraindicated with Triumeq: dofetilideor fampridine (dalfampridine)

Date of first enrolment
31/01/2022

Date of final enrolment
29/09/2024

Locations

Countries of recruitment
Australia

England

Ireland

Netherlands

New Zealand

Slovenia

Spain

Sweden

United Kingdom

Study participating centre
King's College Hospital
King's College Hospital NHS Foundation Trust
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
Royal Hallamshire Hospital
Sheffield Teaching Hospitals NHS Foundation Trust
Glossop Road
Sheffield
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S10 2JF

Study participating centre
John Radcliffe Hospital
Oxford University Hospitals NHS Foundation Trust
Headley Way
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OX3 9DU

Study participating centre
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L9 7LJ

Study participating centre
Royal Preston Hospital
Royal Preston NHS Trust
Sharoe Green Lane
Fulwood
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PR2 9HT

Study participating centre
University College London
National Hospital London MND Care Centre
Queen Square
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WC1N 3BG

Study participating centre
The Perron Institute
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Nedlands
Australia
WA 6009

Study participating centre
MQ Health Neurology
MQ Health Neurology
Suite 204, Level 2, F10A Building
2 Technology Place
Sydney
Australia
NSW 2109

Study participating centre
Launceston General Hospital
274-280 Charles St
Launceston
Australia
TAS 7250

Study participating centre
The University of Sydney - Brain and Mind Centre
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94 Mallett Street
Camperdown
Sydney
Australia
NSW 2050

Study participating centre
Flinders Medical Centre
Flinders Drive
Bedford Park
South Australia
Australia
SA 5042

Study participating centre
Royal Brisbane and Women's Hospital
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4029

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UMC Utrecht
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Netherlands
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Study participating centre
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Dublin
Ireland
D09V2N0

Study participating centre
Karolinska University Hospital
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476 Kooyong Rd, Caulfield
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Study participating centre
Christchurch Hospital
2 Riccarton Avenue, Christchurch Central City
Christchurch
New Zealand
4710

Study participating centre
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Spain
08003

Study participating centre
Dunedin Hospital
201 Great King Street, Central Dunedin
Dunedin
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9016

Study participating centre
Derriford Hospital
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Plymouth
United Kingdom
PL6 8DH

Study participating centre
Royal Stoke University Hospital
Newcastle Road
Stoke-on-trent
United Kingdom
ST4 6QG

Study participating centre
St George's Hospital
Blackshaw Rd
London
United Kingdom
SW17 0QT

Study participating centre
UMC Ljubljana
Zaloška cesta 7
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1000

Study participating centre
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Queensland
Australia
4575

Study participating centre
Tauranga Hospital
829 Cameron Road, Tauranga South
Tauranga
New Zealand
3112

Study participating centre
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Edinburgh
United Kingdom
EH16 4SB

Study participating centre
Wellington Hospital
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Wellington
New Zealand
6021

Study participating centre
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Avinguda de Fernando Abril Martorell, 106, Quatre Carreres
Valencia
Spain
46026

Study participating centre
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Sponsor type
University/education

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ROR
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Sponsor details
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Sponsor type
University/education

Website
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Stichting TRICALS Foundation

Sponsor details
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Utrecht
Netherlands
3515 ET
+31 (0)88 75 554 94
operations@tricals.org

Sponsor type
Research organisation

Website
https://www.tricals.org/about/

Funder(s)

Funder type
Government

Funder Name
Efficacy and Mechanism Evaluation Programme

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

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
FightMND

Alternative Name(s)
Fight MND

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Australia

Funder Name
Motor Neurone Disease Research Institute of Australia

Alternative Name(s)
MND Research Institute of Australia, MND Research Institute, MNDRIA

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
Australia

Funder Name
Treatment Research Initiative to Cure ALS (TRICALS)

Results and Publications

Publication and dissemination plan
The primary and secondary outcomes will be published in a peer-reviewed open-source medical journal within 12 months of the end of trial. Recruiting sites will be informed of the results and will be asked to disseminate the findings to participants. Patient groups will be informed of the results for dissemination among their members. The sharing dataset will be passed to the UK Chief Investigator by the analyst and all future data sharing will be managed by the TRICALS consortium and Macquarie University.

Intention to publish date
31/01/2027

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a repository.

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
	version 2.6				

Protocol file	version 4.0	20/10/2021	26/01/2023	No	No
Protocol file		19/10/2023	23/02/2024	No	No