Targeting metabolic flexibility in ALS (MetFlex); safety and tolerability of trimetazidine for the treatment of ALS;An investigator initiated and conducted, multicentre, international, open-label Phase 2a trial to determine the safety and tolerability of trimetazidine for the treatment of amyotrophic lateral sclerosis/motor neuron disease (ALS/MND)

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The objectives of this study are to determine:• The safety and tolerability of trimetazidine in patients with ALS/MND• The change from baseline in oxidative stress markers in patients with ALS/MND after the initiation of trimetazidine• The change...

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

Summary

ID

NL-OMON52162

Source
ToetsingOnline

Brief title
MetFlex

Condition

- Neuromuscular disorders

Synonym
amyotrophic lateral sclerosis (ALS), motor neuron disease (MND)

Research involving
Human

Sponsors and support

Primary sponsor: University of Queensland
Source(s) of monetary or material Support: FightMND

Intervention

Keyword: Amyotrophic Lateral Sclerosis, Energy expenditure, Metabolism, Trimetazidine

Outcome measures

Primary outcome

The primary endpoints are safety and tolerability of trimetazidine, and the

change from baseline of oxidative stress markers.

The safety and tolerability of trimetazidine will be determined by examining

the toxicities and AEs that are attributable to treatment. The safety

parameters will include an assessment of clinical signs and symptoms from the

history and physical exam, vital signs, AEs, and laboratory findings (e.g.

liver and kidney function).

The change from baseline of oxidative stress markers will be determined by

quantitative analyses of plasma and/or serum samples by liquid chromatography-

mass spectrometry/mass-spectrometry (LC-MS/MS) and/or multiplex analysis of

selected targets of interest: IL-6, MDA, 8-OhdG.

Secondary outcome

The secondary endpoints are:

• Change from baseline in energy expenditure, based on a composite outcome of body composition and predicted energy expenditure, and measured energy expenditure, following administration of trimetazidine.

• Pharmacodynamic properties of oxidative stress markers (IL-6, MDA, and 8-OhdG) following administration of trimetazidine

Study description

Background summary

ALS/MND is classified as either familial or sporadic. Approximately 10% of cases are classified as familial, with the remaining 90% as sporadic. Familial cases are defined by their heritability, whereby most cases are autosomal dominant mutations in a heterogeneous set of genes. Sporadic cases of the disease are characterised by disease incidence in the absence of an identified inherited mutation. From a clinical and neuropathological standpoint, however, familial and sporadic cases are indistinguishable, and a number of commonly observed familial ALS/MND associated mutations are observed in sporadic ALS/MND patients.
Current treatment options for ALS/MND are limited. While a number of therapeutic candidates have demonstrated efficacy in pre-clinical models of the disease, these outcomes have not translated into viable treatments for people living with ALS/MND. To date, only two drugs have received US Food and Drug Administration (FDA) approval, Riluzole and Edaravone, both of which have limited efficacy.

The maintenance of optimal energy balance and body composition is critically dependent on balancing energy intake with energy expenditure. In healthy individuals, dietary intake and nutrient absorption are theoretically in balance with resting and activity-associated energy expenditure. This balance underpins the capacity to maintain relatively stable energy stores.
Evidence of metabolic dysfunction in ALS/MND arose in the 1980s. Since that time, a growing number of studies have indicated that impairments in whole body physiology and energy balance are common presentations in the disease. Of the metabolic changes that occur in ALS/MND, hypermetabolism (defined by an increase in resting energy expenditure) has been observed in multiple patient cohorts. While reports of hypermetabolism in ALS/MND have increased over the years, and a study by Jesus and colleagues in 2018 hinted at a potential

negative role of hypermetabolism in the disease, the majority of studies to date have identified hypermetabolism using predictions of resting energy expenditure that are based on the Harris-Benedict equation, which fails to correct for muscle atrophy in the disease. In 2017, we published data to show that predictions of resting energy expenditure in ALS/MND are impacted by fat-free mass. Thus, most reports of the prevalence and impact of hypermetabolism in ALS/MND have been confounded by incorrect estimates of predicted resting energy expenditure.
In 2018, we published an influential and fundamental case-control study investigating the prevalence and impact of altered energy expenditure in ALS/MND. Our study was the first to correct predictions of resting energy expenditure in patients relative to fat free mass, and therefore the only study to consider the impact of the disease on muscle mass as a factor in identifying hypermetabolism. Generating a metabolic index for each patient (MI; measured resting energy expenditure as a % of predicted resting energy expenditure), we confirmed that hypermetabolism (where MI >120%) was more prevalent in ALS/MND patients when compared to age- and sex-matched controls. Moreover, we were able to highlight the clinical significance of hypermetabolism in ALS/MND, demonstrating that hypermetabolic patients have an aggressive disease that is associated with faster progression of disability (i.e. faster decline in ALSFRS-R) and increased risk for earlier death [13]. Using skeletal muscle and plasma samples from ALS/MND patients, we have also generated published data to show that metabolic perturbations are widespread, and that this is characterised by increased expression of metabolic proteins (e.g. pyruvate dehyrodenase kinase 4 (PDK4) and adipokines/ cytokines (e.g. IL-6) that play crucial roles in controlling energy balance.
Collectively, these data highlighted the targeting of hypermetabolism and/or metabolic perturbations as a potential therapeutic strategy for ALS/MND.
The data from this study will evaluate the safety and tolerability of trimetazidine in patients with ALS/MND and the effect on oxidative stress proteins (IL-6, MDA and 8-OHdG. The change in metabolic index after using trimetazidine is an important argument to set up a phase 3 clinical trial.

Study objective

The objectives of this study are to determine:
• The safety and tolerability of trimetazidine in patients with ALS/MND
• The change from baseline in oxidative stress markers in patients with ALS/MND after the initiation of trimetazidine
• The change from baseline in energy expenditure in patients with ALS/MND after the initiation of trimetazidine
• The preliminary pharmcodynamic properties of trimetazidine on oxidative stress markers in patients with ALS/MND
• Exploratory associations of the effect of trimetazidine on oxidative stress markers relative to clinical features of hypermetabolism (increased energy expenditure) in patients with ALS/MND
• Exploratory associations of the effect of trimetazidine on oxidative stress

markers relative to clinical markers of disease progression (e.g. ALSFRS-R and SVC) in patients with ALS/MND

This study will provide evidence for the contribution of increased energy expenditure (i.e. hypermetabolism) in the pathophysiology of ALS/MND. It will also assess the preliminary effect of trimetazidine on clinical outcome measures of ALS/NMD. This information is necessary to further explore the effect of trimetazidine on disease progression in patients with ALS/MND in a potential phase 3 clinical trial.

Study design

The protocol describes a single-arm, Phase 2a open-label trial. Enrolment is planned for a total of 20 ALS/MND patients (participants) across 2 sites: Royal Brisbane & Women*s Hospital (Brisbane, Australia), and University Medical Centre Utrecht (Utrecht, Netherlands). Each site will enrol 18 participants.
All participants will receive trimetazidine, 35mg (slow release) oral tablet, twice-daily in an unblinded manner.
All participants will begin the study treatment sequentially, with time allowed before dosing the following participant. Study participation will continue until 28 days (4 weeks) after the last dose of the study drug. For each individual, study participation will be a total of 20 weeks (140 days), consisting of:
• 4-week (28 days) lead-in period to obtain a stable baseline measurement of ALS/MND-related oxidative stress markers (IL-6, MDA, and 8-OHdG), clinical markers of disease (ALSFRS-R and SVC), and to assess that measured energy expenditure is >=110% of predicted resting energy expenditure.
• 12-week (84 days) on-treatment phase, when patients will receive trimetazidine. Patients will visit the clinic at 6-week intervals, during which we will obtain a blood sample to measure the pharmacodynamic response. We will also collect information regarding the rate of disease progression (i.e. ALSFRS-R and SVC) and perform assessments to evaluate alterations in energy expenditure. At weeks 3 and 9, we will conduct a teleconference with patients to collect information on concomitant treatments, implement the ALSFRS-R, and inquire about AEs/SAEs.
• 4-week (28 days) wash-out with a close-out visit planned for 28 days after the last dose of the study drug.
AEs and SAEs will be collected and recorded throughout the entire trial duration (140 days ± 3 days). Here, study weeks are defined as consecutive calendar weeks, with Study Week 1 beginning from the start time of the first day of study drug administration.

Intervention

Trimetazidine is an anti-ischemic agent that is used in the treatment of coronary artery disease. Trimetazidine has not been shown to exert any effect

on coronary flow, contractility, blood pressure, or heart rate (HR). Moreover, it has no significant negative inotropic or vasodilatory properties, either at rest or during exercise.
Trimetazidine is available on the market as the 20 mg immediate-release (IR) tablets and the 35 mg modified release (MR) tablets. The 20 mg IR tablets are administered 3 times a day, while the 35 mg MR tablets are administered twice a day.
Trimetazidine MR tablets are orally bioavailable and the drug is rapidly absorbed from the intestinal tract. Trimetazidine has been shown to be safe and tolerable for long-term exposure in patients with chronic heart failure. Most importantly, trimetazidine significantly reduced energy expenditure in patients with chronic heart failure, and reduced the expression of oxidative (i.e. metabolic) stress markers that arise from the degradation of lipids (malondialdehyde (MDA) and 8-hydroxy-2*-deoxyguanosine (8-OHdG)) and pro-inflammatory cytokines/adipokines (IL-6). These are crucial oxidative stress markers known to be increased in ALS/MND patients and potentially associated with disease progression. Given the compelling evidence for the associations between oxidative stress, increased energy expenditure (hypermetabolism) and ALS/MND, trimetazidine may positively affect disease progression in patients with ALS/MND.

Study burden and risks

The energy metabolism and body composition are assessed using non-invasive methods such as respiratory calorimetry and air-displacement plethysmography (BodPod). Safety blood products will be determined by venous blood tests with a minimal risk of complications. Participants are required to visit the hospital 5 times in 20 weeks, each visit will take place in the morning after an overnight fasting.

All participants will receive trimetazidine 35mg (slow-release) twice a day (TID). Trimetazidine is a registered treatment for angina pectoris by the European Medicines Agency (EMA). Side-effects and pharmacological effect are known. So far we know, it is the first time trimetazidine will be studies in patients with ALS. We will study the effect of trimetazidine in patients with ALS. As the side effects will be monitored and are mainly mild, the hypothesis is that trimetazidine will be well tolerated. As ALS is a fatal, uncurable disease, the risk-benefit will be clinical equipoise.

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

• Age between 18 and 75 years
• Signed informed consent prior to the initiation of any study-specific procedures
• Familial or sporadic ALS/MND, defined as clinically possible, probable, probable laboratory supported or definite as per the El Escorial criteria
• Relative TRICALS risk score between -6.0 to -2.0 (75% of patients with ALS/MND)
• The use of riluzole will be permitted during the study. Individuals 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.
• Ability to swallow tablets
• Able to lie with torso elevated at a 35° angle for 30 minutes without respiratory support
• Able to give informed consent (as judged by the investigator) and able to comply with all study visits and all study procedures
• Females must not be able to become pregnant (e.g. post-menopausal, surgically sterile or using highley effective birth control methods) for the duration of the study.

• Females of child-bearing potential must have a negative serum pregnancy test at screening and baseline and be non-lactating

Exclusion criteria

• History of, or current diagnosis of diabetes or medical condition that impacts whole body energy expenditure (e.g. Hashimoto*s, heart disease)
• Parkinson*s disease or parkinsonism, tremor, restless-leg syndrome
• Safety Laboratory Criteria at screening related to significant kidney disease: Creatinine clearance < 50 mL / min (Cockroft-Gault) based on Cystatin C
• Tracheostomy or non-invasive ventilation (NIV) use > 22 hours per day
• Contraindication therapy:
Allergy for one of the product*s API*s or expedients.
Antihypertensive treatment [Trimetazidine may cause hypotension]
• Evidence of malignant disease
• Significant neuromuscular disease other than ALS/MND
• Ongoing disease that may cause neuropathy
• Pregnancy or breastfeeding
• Deprivation of freedom by administrative or court order

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-10-2021
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Trimetazidine
Generic name:	Vastarel

Ethics review

Approved WMO Date:	08-04-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	14-05-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	22-04-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-05-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-12-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-01-2023
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
Other	ACTRN12620000945921p
EudraCT	EUCTR2020-005018-17-NL
CCMO	NL75615.041.20