ISRCTN12895613 https://doi.org/10.1186/ISRCTN12895613

Can the drug acipimox relieve muscle symptoms in patients with mitochondrial myopathy?

Submission date
10/12/2018

Recruitment status
No longer recruiting

Registration date
03/01/2019

Overall study status
Completed

Last Edited
27/09/2022

Condition category
Nervous System Diseases

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

Plain English summary of protocol

Background and study aims
Mitochondria are tiny cell structures that play a critical role in the production of energy by the cell. When these tiny energy producing cell structures malfunction, it may result in chronic illnesses known as mitochondrial diseases. It is estimated that mitochondrial disease can affect up to 15,000 adults (and a similar numbers of children) in the UK. Mitochondrial diseases are rare, inherited conditions where muscle symptoms such as muscle weakness, tiredness and pain are extremely common and often draining. The study has been designed with the help of patients and carers who identified muscle symptoms to be the most important target for any new drug treatments. We plan to test a drug (acipimox) which has previously been used to treat high cholesterol and improve diabetic control. The drug has also been shown to boost production of cell energy by muscle cells and it is this role that we wish to test in patients with mitochondrial disease to see if we can to ease the unbearable muscle symptoms which are suffered.

Who can participate?
Patients with a confirmed genetic diagnosis of m.3243A> G-related mitochondrial disease, or single large-scale mtDNA deletion, with muscle involvement.

What does the study involve?
Participants will be asked to take a tablet 3 times a day, for 12 weeks. At the start and end of treatment, the participants will be asked to come to Newcastle upon Tyne in order to undergo a small muscle biopsy. They will also be asked to take part in a number of tests of normal everyday functions (muscle strength, walking, mental agility), and complete questionnaires asking about their mental health and well-being.

What are the possible benefits and risks of participating?
As this the first study in the world of acipimox in patients with mitochondrial disease, it is not known if the study will directly benefit participants. However, the information we gain may help other patients in the future, by helping us understand what drugs may be useful and can improve our testing techniques in mitochondrial clinics.

Participants will be asked to give up 3 days at the beginning of the trial before treatment, and 2 days at the end of treatment. Participants will also be closely observed during the trial and have follow up phone calls to check how they are doing. The trial drugs might cause side effects such as indigestion, headaches, reddening of the skin, hives and increased bleeding. During the trial patients will have samples of blood and muscle taken which may cause tiredness, however all tests are safe and routinely used in the mitochondrial clinics.

Where is the study run from?
This study is being run by the Newcastle University Clinical Trials Unit (UK) and takes place in The Newcastle Hospitals NHS Foundation Trust (UK).

When is the study starting and how long is it expected to run for?
Recruitment is estimated to start April 2019 and is expected to continue until January 2022.

Who is funding the study?
Medical Research Council

Who is the main contact?
Gillian Watson, gillian.watson@newcastle.ac.uk

Contact information

Type(s)
Scientific

Contact name
Miss Gillian Watson

Contact details
Newcastle Clinical Trials Unit
Newcastle University
1-4 Claremont Terrace
Newcastle upon Tyne
United Kingdom
NE2 4AE
+44 (0)1912088813
gillian.watson@newcastle.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2018-002721-29

Protocol serial number
40330

Study information

Scientific Title

Randomised, double-blinded, placebo-controlled, adaptive design trial of the efficacy of acipimox in patients with Mitochondrial Myopathy

Acronym
AIMM

Study objectives
The aim of this trial is to determine whether acipimox can be repurposed as a potent stimulator of mitochondrial biogenesis.

Ethics approval required
Old ethics approval format

Ethics approval(s)
North East – Newcastle and North Tyneside 1, 11/09/2018, ref: 18/NI/0199

Study design
Randomised; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Mitochondrial myopathy

Interventions
This is a randomised, double-blinded, placebo-controlled trial using an adaptive design model that will allow modification of the number of patients needed, as more information is collected. Randomisation will be stratified by baseline score on Fatigue Impact Scale; <40, ≥40

This single centre trial will take place over 16 weeks per participant. Participants will take a tablet of trial medication three times a day for a period of 12 weeks. Half of trial participants will receive the trial drug Acipimox (Olbetum 250mg capsules), daily dose = 750mg (250 mg x three times daily), with the other half receiving an identical ‘placebo’ treatment. As this is a double blinded trial, neither the doctor nor participant will know who receives active treatment.

Interested and potentially eligible patients, will provide full informed consent prior to screening assessments being conducted.

Screening assessments include:
1. Collection of demographic information
2. Review of medical history
3. Review of current medication
4. Urine pregnancy test (female participants only)
5. Screening blood samples (FBC - for platelets, creatinine clearance, AST, ALT, Gamma GT).
6. Contraceptive counselling
7. Final review and confirmation of eligibility

Screening blood samples and urine pregnancy test conducted during screening will be repeated if not all baseline assessments are complete, or the participant has not commenced trial medication, within 28 days of the screening visit.

Baseline and end of treatment (week 12) assessments:
Baseline and end of treatment visits will take place over 2 days (on average) per participant. The order in which non-functional assessments (i.e. NMDAS and QoL questionnaires) are completed and trial blood and urine sample are taken is variable and these can be scheduled as appropriate to the patient and visit timings. However, in order to avoid any effects on the performance of exercise and functional tasks, the skeletal muscle biopsy sample will take place after completion of all exercise and functional assessments.

The exercise test and skeletal muscle biopsy will be scheduled on separate days to allow sufficient recovery following exercise. The exercise test and functional assessments will usually be scheduled on separate days (although for some participants it may be possible to perform exercise testing and functional tests on the same day).

The order of assessments for the end of treatment visit (week 12) for each participant will be the same as at baseline.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Acipimox

Primary outcome(s)
ATP content in skeletal muscle will be measured from biopsy specimens using a luminescence assay at baseline and 12 weeks.

Key secondary outcome(s))
1. Health-related Quality of life:
1.1. Experiences of physical, mental, and social effects measured using the Quality of Life in Neurological Disorders (NeuroQol) at baseline and 12 weeks.
1.2. Mitochondrial disease-specific health related Quality of Life measured using the Newcastle Mitochondrial Quality of life questionnaires (NMQ) at baseline and 12 weeks.
1.3. Pain measure by the Visual Analog Scale (VAS) at baseline and 12 weeks.
2. Reported perceived fatigue:
2.1. Levels of fatigue measured using the Fatigue Impact Scale (FIS) at baseline and 12 weeks.
2.2. Impact and severity of fatigue measured using the Fatigue Severity Scale (FSS) at baseline and 12 weeks.
3. Symptom-limited cardiopulmonary fitness - This will include assessment of respiratory, cardiovascular and metabolic variables at rest, during and/or exhaustion (peak)
3.1. VO2, VCO2, Anaerobic Threshold (AT), Pulmonary Ventilation (VE), Respiratory Exchange Ratio (RER), and Breathing Frequency (f) via breath-by-breath indirect calorimetry measured by cycle ergometer at baseline and 12 weeks.
3.2. Work rate (Power, measured in watts) measured by cycle ergometer at baseline and 12 weeks.

3.3. Heart Rate (HR), Stroke Volume (SV), Cardiac Output (Q), and Arteriovenous Oxygen Difference (a-VO2 diff) via non-invasive bioreactance cardiac output measured by cycle ergometer at baseline and 12 weeks.
3.4. Rate of Perceived Exertion measured by cycle ergometer at baseline and 12 weeks.
3.5. Blood lactate measured by ear prick or blood test at baseline and 12 weeks.
4. Disease burden measured using the Newcastle Mitochondrial Disease Adult Scale (NMDAS) at baseline and 12 weeks.
5. Upper and lower limb function, balance and walking
5.1. Upper limb function measured by 9-Hole Peg Test (9-HPT) at baseline and 12 weeks.
5.2. Walking ability measured by the 6 Minute Walk Test (6MWT) and 10 Metre Timed Walk (10MTW) at baseline and 12 weeks.
5.3. Balance measured by Mini Balance Evaluation Systems Test (mini-BESTest) and 30-second Sit To Stand (STS) at baseline and 12 weeks.
5.4. Upper and lower limb function measured by the Scale for the Assessment and Rating of Ataxia (SARA) at baseline and 12 weeks.
6. Skeletal muscle analyses
6.1. ATP/ADP ratio measured by luminescence assay or metabolomics at baseline and 12 weeks.
6.2. NAD+/NADH ratio measured by metabolomics at baseline and 12 weeks.
6.3. mtDNA copy number as a marker of mitochondrial density measured by quantitative real-time PCR at baseline and 12 weeks.
6.4. Respiratory chain deficiency measured by sequential cytochrome c oxidase and succinate dehydrogenase (COX/SDH) histochemistry and quadruple immunofluorescence at baseline and 12 weeks.
6.5. mtDNA heteroplasmy measured using q-RT PCR (single deletion) or pyro sequencing (m. 3243A>G) at baseline and 12 weeks.

Completion date
19/01/2022

Eligibility

Key inclusion criteria
1. Must be able to provide full informed consent
2. Male or female patients ≥ 16 years of age
3. Patients must fulfil the following:
3.1. Genetically proven diagnosis of m.3243A>G mutation or single large-scale mtDNA deletion, and
3.2. Evidence of myopathy as confirmed by the investigator
4. Able and willing, in the opinion of the investigator, to comply with all trial requirements
5. Willing for their GP and Specialist (if applicable), to be informed of their participation in the trial
6. Be on a stable dose of any current regular medication for at least four weeks prior to trial entry.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group

Adult

Sex
All

Total final enrolment
21

Key exclusion criteria
1. Patients who are currently participating or have participated in a clinical trial of an investigational medicinal product within the 12-week period prior to the date of informed consent
2. Patients who have had an elective or emergency admission to hospital within the 4-week period prior to the date of informed consent
3. Patients with other known uncontrolled medical problems, which, in the opinion of the investigator, would preclude participation in the trial
4. Patients who are:
4.1. Pregnant
4.2. Breastfeeding
4.3. Of childbearing potential with a positive urine pregnancy test prior to starting trial IMP
4.4. Male or female of childbearing potential unwilling to use a double barrier method of contraception throughout the trial (postmenopausal women must be amenorrhoeic for at least 12 months to be considered of non-childbearing potential)
5. Patients with moderate to severe renal impairment (creatinine clearance < 60 ml/min)
6. Patients with a screening AST, ALT or Gamma GT result of more than 3 times the upper limit of normal
7. Patients with a platelet count of < 50 platelets/ ul of blood
8. Patients on treatment with methotrexate or other immunosuppressant medications
9. Patients with active known peptic ulcer or history of recurrent ulceration
10. Patients on treatment with warfarin, clopidogrel, regular high-dose (> = 300 mg OD) aspirin or other anticoagulant medications which in the opinion of the investigator precludes entry into the trial. Patients receiving high-dose aspirin who are able to come off aspirin for a period of 72 hours prior to any muscle biopsy sample will be eligible to participate
11. Patients with a medical history which in the opinion of the investigator contraindicates the use of low-dose aspirin
12. Patients who are already taking acipimox
13. Patients with an elective hospital admission scheduled during the trial period, which in the opinion of the investigator would preclude participation

Date of first enrolment
29/04/2019

Date of final enrolment
27/07/2021

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Newcastle upon Tyne Hospitals NHS Foundation Trust
The Royal Victoria Infirmary
Queen Victoria Rd
Newcastle upon Tyne
United Kingdom
NE1 4LP

Sponsor information

Organisation
The Newcastle Hospitals NHS Foundation Trust

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council; Grant Codes: MR/R006458/1

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		20/09/2022	27/09/2022	Yes	No
HRA research summary			26/07/2023	No	No