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The efficacy and mechanism of trientine in patients with hypertrophic cardiomyopathy

Submission date
28/07/2020

Recruitment status
No longer recruiting

Registration date
07/09/2020

Overall study status
Completed

Last Edited
15/01/2025

Condition category
Circulatory System

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

Plain English summary of protocol

Background and study aims
Hypertrophic cardiomyopathy (HCM) is the most common inherited heart condition. It leads to abnormal thickening and scarring of the walls of the heart. As a result, the heart can have trouble pumping blood as well as it should. This causes patients to develop breathing difficulties, chest pain, and fainting, which often get worse with exercise, and therefore can limit physical activity. Current treatments only aim to relieve the symptoms. There are no treatments that correct the underlying damage to the heart. Patients, caregivers, and researchers have identified a “critical need” for trials of medicines that target the HCM disease process.

Several studies in other diseases have shown that copper imbalance is associated with heart thickening similar to HCM, and that treatment with trientine, an oral medicine that increases copper removal in urine, can reverse this thickening.

This study will investigate whether trientine reduces heart muscle thickening, improves exercise capacity, improves heart function, and reduces abnormal heart rhythms in patients with HCM. The study will also assess how trientine works in HCM.

This research study aims to recruit 152 patients with HCM aged 18-75 years in the UK. Participants in the study will be prescribed either trientine or placebo for 1 year to compare the difference.

Who can participate?
Patients with hypertrophic cardiomyopathy aged 18-75 years can participate

What does the study involve?
If patients agree to take part, they will be asked to sign a consent form. Once the consent form is signed, the trial team will check and confirm that this study is suitable for the patient. If it is, they will be entered into the study. Participants will be randomly assigned to receive either trientine or a dummy pill.

Participants will be in the study for 1 year. During this time, they will be asked to attend the hospital for 6 visits. Study tests include blood tests, urine test, heart trace (ECG), heart magnetic

resonance imaging (MRI scan of the heart), 24-hour heart monitor, exercise test and pregnancy test if female and of childbearing age. A subgroup of participants will undergo an extra MRI scan.

What are the possible benefits and risks of participating?
Participants will receive closer follow-up than they would usually have and have more access to heart specialists than normal. They may have a more detailed assessment of their heart than they usually would.

Participants will help to determine whether trientine will be of benefit to other patients with HCM and will also contribute to a better understanding of HCM in general. This may lead to benefits for the participant and other people.

Trientine has been used in Wilson disease for more than 30 years. It is safe and well tolerated. Between 1-in-100 and 1-in-10 people experience nausea on starting trientine and between 1-in-1000 and 1-in-100 people develop a skin rash. Trientine can reduce blood iron levels. Between 1-in-1000 and 1-in-100 people develop anaemia (low blood iron level). Iron levels and blood counts will be monitored during the study. Iron supplementation in the form of tablets may be necessary in some cases. There have been isolated case reports of trientine being associated with inflammation of the bowel. All of the possible side effects resolve on reducing the dose or stopping it and are not associated with long-term effects.

Where is the study run from?
Manchester University NHS Foundation Trust (UK) and three other NHS foundation trusts in the UK

When is the study starting and how long is it expected to run for?
From July 2018 to April 2024

Who is funding the study?
The National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation (EME) Programme (UK)

Who is the main contact?
Mrs Carly Vaughan
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Study website
https://www.tempest-trial.org.uk

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number
2020-002242-17

IRAS number
283265

ClinicalTrials.gov number
NCT04706429

Secondary identifying numbers
CPMS 45988, IRAS 283265

Study information

Scientific Title
A randomised, double-blind, placebo-controlled, phase 2 evaluation of the efficacy and mechanism of trientine in patients with hypertrophic cardiomyopathy

Acronym
TEMPEST

Study objectives
Trientine will reduce LV mass, which will be associated with improved exercise capacity, reduced arrhythmia burden, and improved cardiac function. The reduction in LV mass will be mediated by a reduction in myocardial cellular mass and fibrosis and improved myocardial energetics, which will be determined by increased copper excretion.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 21/07/2020, Greater Manchester South Research Ethics Committee (3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)2071048127; gmsouth.rec@hra.nhs.uk), ref: 20/NW/0275

Study design
Multicentre interventional randomized controlled 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 (tempest@liverpool.ac.uk) to request a participant information sheet'

Health condition(s) or problem(s) studied
Hypertrophic cardiomyopathy

Interventions
The study will last for 1 year and involves 6 visits to the hospital.

The initial visit will have a number of assessments including a review of medical history, review of medications, pulse, blood pressure, height and weight, blood tests, ECG, 24 h heart monitor, and a pregnancy test, if applicable.

If the assessments performed at Visit 1 show that the patient is eligible for the study, Visit 2 will be arranged within 4 weeks for the patient to be randomised.

Participants will be randomised to receive either trientine (two 200 mg capsules, twice daily, 800 mg/day total) or placebo, in a 1:1 ratio. Block randomisation, stratified by site, will be implemented, with computer generated randomisation allocations and randomly varying block sizes. The randomisation code will be generated by an independent LCTC statistician who is not involved with this trial.

At Visit 2 a review of medications, blood test, urine test, exercise test, and a pregnancy test, if applicable, will take place. Participants will also have an MRI scan of the heart known as cardiovascular magnetic resonance (CMR) scan. A subgroup of participants will undergo an extra MRI scan called phosphorus magnetic resonance spectroscopy (31P MRS).

Study medication will be dispensed by the pharmacy at visits 2, 3, 4, and 5.

Visits 3, 4, and 5 will take place 13 weeks apart. At these visits all current medications are reviewed, measurements of pulse, blood pressure, height, and weight are taken. There will be a review of safety, compliance, and review of the patient's diary. An ECG, blood, and urine test are also performed, as well as a pregnancy test, if applicable.

Visit 6 will include the same tests as visits 3, 4, and 5, with the addition of height and weight, an MRI scan, 24 h heart monitor, and the exercise test. The subgroup will undergo 31P MRS.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Trientine (Triethylinetetramine dihydrochloride)

Primary outcome measure
Change in left ventricular mass index (LVMi, g/m2) is measured using a cardiovascular magnetic resonance (CMR) scan at baseline and week 52

Secondary outcome measures
1. Cumulative urine copper excretion is measured using urinary copper in urine samples given at baseline, 13, 26, 39 and 52 weeks
2. Change in exercise capacity is measured using cardiopulmonary exercise testing (CPET) at baseline and week 52
3. Change in number of non-sinus supraventricular heartbeats, presence and amount of atrial fibrillation, number of ventricular-origin beats, and presence and amount of non-sustained ventricular tachycardia, in 24 h is measured using ambulatory ECG heart monitoring at baseline, 13, 26, 39 and 52 weeks
4. Change in circulating high sensitivity troponin measured from blood samples given at baseline, 13, 26, 39 and 52 weeks
5. Change in LV global longitudinal strain, wall thickness, mass, volumes, and ejection fraction (EF) is measured using CMR at baseline and week 52 (Updated 07/11/2023 to remove strain rate)
6. Change in peak left ventricular outflow tract gradient is measured using CMR at baseline and week 52
7. Change in atrial volume and function is measured using CMR at baseline and week 52

Overall study start date
01/07/2018

Completion date
30/04/2024

Eligibility

Key inclusion criteria
1. Written informed consent given
2. Aged between 18 and 75 years inclusive (Updated 07/11/2023: previously between 18 and 70 years inclusive)
3. Hypertrophic cardiomyopathy (HCM), as defined by the European Society of Cardiology HCM guidelines as: “a wall thickness > = 15 mm in one or more LV myocardial segments that is not explained solely by loading conditions”. The same definition is applied to first-degree relatives of patients with HCM i.e. all participants are required to have a LV wall thickness > = 15 mm. Wall thickness is as measured on the most recent cardiovascular magnetic resonance (CMR) scan performed prior to the baseline visit. If CMR has not been performed previously, wall thickness measurement should be taken from the most recent echocardiogram performed prior to the baseline visit. (It is recognised that in the European Society of Cardiology guidelines a clinical diagnosis of HCM in first-degree relatives requires a wall thickness that is less than this value, however > = 15 mm is applied here in order to ensure that all participants have an unequivocal phenotype).

4. New York Heart Association class I, II or III at the most recent clinical assessment performed prior to the baseline visit

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
75 Years

Sex
Both

Target number of participants
Planned Sample Size: 152; UK Sample Size: 152

Total final enrolment
154

Key exclusion criteria
1. Previous or planned septal reduction therapy
2. Previously documented myocardial infarction or severe coronary artery disease
3. Uncontrolled hypertension, defined as a systolic blood pressure of >180 mmHg or diastolic blood pressure of >100 mmHg at visit 1
4. Known LV EF <50%, as measured on the most recent CMR scan performed prior to the baseline visit. If CMR has not been performed previously, the most recent echocardiogram performed prior to the baseline visit should be used.
5. Previously documented persistent atrial fibrillation
6. Anaemia, defined as haemoglobin being below the local site normal reference range, at visit 1
7. Iron deficiency, defined as serum iron being below the local site normal reference range, at visit 1
8. Copper deficiency, defined as serum copper being below the normal reference range, at visit 1
9. Pacemaker or implantable cardioverter-defibrillator
10. Known severe valvular heart disease, as demonstrated on the most recent heart imaging performed prior to the baseline visit
11. Previously documented other cardiomyopathic cause of myocardial hypertrophy (e.g. amyloidosis, Fabry disease, mitochondrial disease)
12. History of hypersensitivity to any of the components of the investigational medicinal product (IMP)
13. Known contraindication to MRI scanning
14. Pregnancy, lactation, or planning pregnancy. Women of childbearing capacity are required to have a negative serum pregnancy test before treatment, must agree to pregnancy tests at study visits as defined in the Section 8, and must agree to maintain highly effective contraception as defined in Section 8 during the study.

15. Any medical condition, which in the opinion of the Investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study

Date of first enrolment
29/03/2021

Date of final enrolment
30/04/2023

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Liverpool Heart And Chest Hospital NHS Foundation Trust
Thomas Drive
Liverpool
United Kingdom
L14 3PE

Study participating centre
Manchester University NHS Foundation Trust
Wythenshawe Hospital
Southmoor Road
Manchester
United Kingdom
M23 9LT

Study participating centre
Oxford University Hospitals NHSs Foundation Trust
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Study participating centre

Royal Brompton & Harefield NHS Foundation Trust
Royal Brompton Hospital
Sydney Street
London
United Kingdom
SW3 6NP

Study participating centre
University Hospitals of Leicester NHS Foundation Trust
Glenfield Hospital
Groby Road
Leicester
United Kingdom
LE3 9QP

Study participating centre
NHS Grampian
Aberdeen Royal Infirmary
Aberdeen
United Kingdom
AB25 2ZN

Study participating centre
Northumbria Healthcare NHS Foundation Trust
Wansbeck General Hospital
Ashington
Northumberland
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NE29 8NH

Sponsor information

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Manchester University NHS Foundation Trust

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lynne.webster@mft.nhs.uk

Sponsor type
Hospital/treatment centre

Website
https://mft.nhs.uk/

ROR
https://ror.org/00he80998

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: NIHR127575

Funder Name
National Institute for Health Research (NIHR) (UK)

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The results of the trial will be disseminated as early as possible in order to appropriately inform policy and practice. This will include academic journal publications and presentations at academic conferences, Lay summaries of the study findings will be posted to the trial website

and links to these summaries will be posted on patient group websites. Presentations will be made to patient groups and a symposium that brings together key stakeholders will be held.

Intention to publish date
01/09/2025

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?
Protocol file	version v2.0	09/07/2020	11/12/2020	No	No
Protocol article		03/05/2023	04/05/2023	Yes	No
HRA research summary			28/06/2023	No	No
Protocol file	version 5.0	25/08/2023	07/11/2023	No	No