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

Participant Information Sheet

Overview

- You have been invited to take part in a research study. Before you decide, it is important that you understand why the research is being done and what it will involve.
- TEMPEST is a research study that has been designed to test whether a drug called trientine dihydrochloride (also called Cufence) reduces heart muscle thickening, improves exercise capacity, improves heart function and reduces abnormal heart rhythms in patients with hypertrophic cardiomyopathy (HCM). The study is also assessing how trientine works in HCM.
- Participants in the study will be prescribed either trientine or placebo. A placebo is a medication with no active ingredients and is used to work out how effective trientine is.
- This research study aims to recruit 152 patients with HCM aged 18-75 years in the UK. Each patient will be involved for 1 year.
- Taking part is voluntary. If you don't want to take part then you don't need to give a reason.
- Please take time to read the following information carefully. **Part 1** tells you the purpose of the study and what will happen to you if you take part. **Part 2** gives you more detailed information about the conduct of the study.
- You can ask a member of your clinical team if there is anything that is not clear, or if you would like more information.
- If you wish you can discuss it with friends, relatives and/or get independent advice via your local Patient Advice and Liaison Service (PALS) or equivalent.

How to contact the study team

If you have any questions about the study, please talk to a member of your research team:

To insert details for Local PI/research team i.e.

Name

Telephone number

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PART 1: Purpose of the study and what will happen if you take part

Why are we doing the TEMPEST study?

Hypertrophic cardiomyopathy (HCM) is the most common inherited heart condition. Current treatments only aim to alleviate symptoms. There are no treatments that slow or reverse the underlying damage to the heart.

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

We want to find out if trientine reduces heart muscle thickening in patients with HCM. We would also like to see if it improves exercise capacity, improves heart function and reduces abnormal heart rhythms. The study will also assess how trientine works in HCM. The results from this study will be used to help us to understand the effects of trientine on the heart in patients with HCM.

Why have I been chosen?

You have been invited to take part in this study because you have hypertrophic cardiomyopathy.

Do I have to take part?

No, taking part is voluntary. It is up to you to decide whether or not you want to take part.

If you decide not to take part then you will still receive the usual treatment your hospital offers. Your clinical team can provide you with more information on this.

If you decide to take part you can also choose to stop at any time without giving a reason.

The decision you make on whether to take part or not will not affect the standard of care you receive now or in the future.

What will happen to me if I take part?

If you agree to take part, you will be asked to sign a consent form. You will be given a copy of the consent form and this information sheet to keep.

Once you have signed the consent form, we will check and confirm that this study is suitable for you. If it is, you will be entered into the study.

You will be in the study for 1 year. During this time, you will be asked to attend the hospital for 6 visits. Please see the study timeline on page 3, which sets out when the visits will occur.

At Visit 1, a member of the research team will review your medical history, record your pulse rate, blood pressure, height and weight. You will have a blood sample taken, have a heart trace (ECG), have a heart monitor fitted and be given a urine sample pot to return on the next visit. You will be given an envelope to post the heart monitor back. If you are female and able to have children you will have a pregnancy test at this visit and at visits 3-6. Details of the procedures are given below. The visit is expected to last 1-2 hours.

At Visit 2, the research team will confirm that you are eligible for the study. If you are, you will have a heart MRI scan and do an exercise test. Some patients will undergo two heart MRI scans. You will be assigned to treatment with either trientine or placebo. A placebo is a medication with no active ingredients and is used to work out how effective the trientine is. You will be given a diary that will include sections for recording study appointments, any side-effects you may experience and any missed medication doses. The research team will review the diary with you at each visit. The ECG may be done on this visit instead of visit 1. This visit is expected to last about half a day.

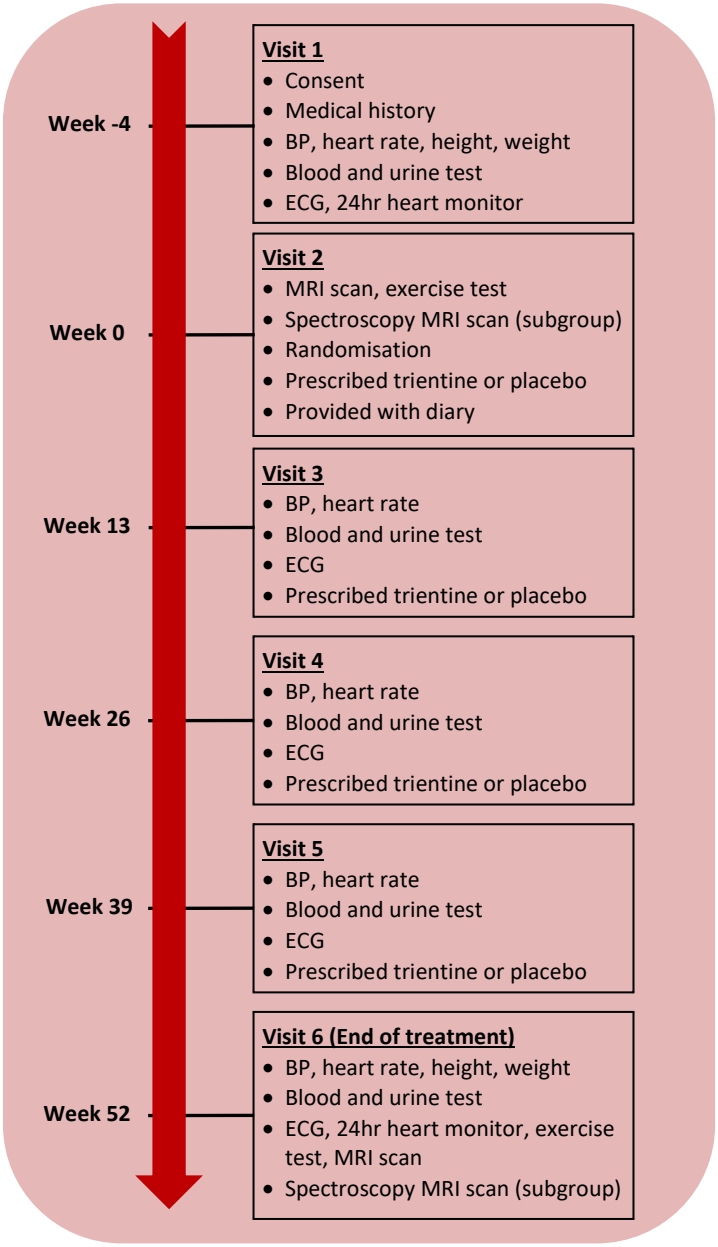
At Visits 3, 4 and 5 a member of the research team will review your medical history, record your pulse rate and blood pressure. You will have a blood sample taken, have a heart trace (ECG) and be prescribed more trientine or placebo, according to which

treatment you were originally assigned. These visits are expected to last about an hour.

At visit 6, the tests performed at Visits 1 and 2 will be repeated. The visit is expected to last about half a day. You will stop the study medication at Visit 6 and return to the standard treatment at your hospital.

Up to a £20 contribution to travel costs for each visit will be provided.

Study timeline



Study tests and procedures

Most of the tests are standard tests for patients with HCM and you will probably have experience of them.

Blood sampling: A blood sample will be taken in the usual manner. A sample of approximately 20-25ml or 4-5 teaspoons will be taken on each occasion.

ECG (heart trace): An ECG measures the electrical activity of the heart. It will be done in the usual way. Stickers will be put on your chest and limbs to which the leads will be attached.

24-hour heart monitor: This assesses heart rhythm. It will be done in the usual way. Stickers will be put on your body and attached via leads to a small box. You will wear it for approximately 24 hours.

Cardio-pulmonary exercise test (CPET): This assesses the amount of exercise that people can do. It will be done in the usual way. It involves walking quickly on a treadmill or cycling on a static bike in a controlled environment. You will breathe through a mask to measure your oxygen use and carbon dioxide production. Blood pressure and heart rhythm are monitored. You can stop at any time.

Heart MRI scan: Heart MRI scanning gives detailed information about the structure and function of the heart. The scanner is a 'doughnut-shaped' scanner. You will be asked to lie still on a comfortable bed and the bed will move into the scanner. During the scan you will receive some imaging contrast agent ('dye') called "gadolinium" through a cannula, or a small plastic tube, placed into a vein in your arm before the scan. The scan will last about 45 minutes.

Heart spectroscopy MRI scan: Some patients in the study recruited in Oxford and Manchester will have a second MRI scan that will measure how much energy the heart is making and using. The procedure is called magnetic resonance spectroscopy. Because only some patients are involved it is called a subgroup. This will take about 30 minutes and will not involve dye.

MRI scanning is considered to be very safe. It uses magnetic fields to make the pictures. It does not use potentially dangerous radiation. The NHS website describes MRI scanning as "painless and harmless", and "one of the safest medical procedures currently available". Some people who are claustrophobic do not like being in the scanner, although the bore of the scanner (the hole in the doughnut) is wide and you

will be able to talk with the radiographers at all times and the majority of people tolerate the scan well. Gadolinium contrast is used routinely in clinical heart MRI scanning. It is very well tolerated. Allergic reaction occurs very rarely (1 in 10,000 patients).

What is the drug being tested?

Trientine is also known as Cufence. Trientine is a medicine currently used in patients with a condition called Wilson's disease. In Wilson's disease there is an abnormal build-up of copper within the body that leads to heart muscle thickening similar to HCM. Trientine makes the body clear more copper in the urine and therefore reduces copper levels in the body. Studies have shown that patients with hypertrophic cardiomyopathy also have an excess of copper. In patients with diabetes, trientine reduces heart muscle thickness.

We therefore wish to study whether trientine can improve heart muscle thickening and quality of life in patients with HCM.

Trientine and the placebo are capsules which are taken by mouth. Two capsules are to be taken two times per day. You will remain on this dose for the duration of the study (1 year), unless this dose is reduced by the research team.

Each dose should be taken with water at least 1 hour before or 2 hours after food, and at the same time each day. If you miss a scheduled dose, that dose should be skipped. Capsules should be swallowed whole and should not be opened.

The pharmacy department at your hospital will dispense the trientine or placebo to you at Visits 2, 3, 4 and 5. It may also be dispensed at other visits, as needed.

The pharmacy department/research team at your hospital will advise on how to store the bottles of the study medication. Guidance on the appropriate storage conditions can also be found on the label of the study medication. You should use capsules from one bottle at a time rather than having multiple bottles opened at the same time. You should bring all opened and unopened bottles with you to each study visit.

If you are taking oral iron, you should take it at a different time to the study medication. It is also recommended that calcium or magnesium antacids (indigestion tablets) should be taken at a different time to the study medication. Zinc tablets should be avoided as they can reduce the effect of trientine. If you are taking a medicine called D-penicillamine, or start it during the study, please tell the study team.

Trientine capsules contain gelatin (bovine).

How will I know which treatment I'm going to have?

Whether you receive trientine or placebo will be decided at random by computer. This process is called 'randomisation' or 'random allocation'. You and the research team will not be able to choose which treatment you receive.

The trientine and the placebo capsules are identical and therefore you and the research team will not know which treatment you will take during the study. This is called a 'blinded trial'.

The pharmacy team in your hospital will know which treatment you are receiving so they can prepare the correct one. Treatment details can be made available if needed for your clinical care.

What are the benefits and risks of taking part?

You will receive closer follow-up than you would usually have, and have more access to heart specialists than normal. You may have a more detailed assessment of your heart than you usually would.

You will help to determine whether trientine will be of benefit to patients with HCM. You will also contribute to a better understanding of HCM in general. This may lead to benefits for you 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. 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. If you were to experience severe diarrhoea or abdominal pain, you should stop the study medication and tell the study team immediately.

All of the possible side effects resolve on reducing the dose or stopping it, and are not associated with long term effects.

What happens if I change my mind?

If at any point you decide to stop taking part in the study you will still receive treatment and the follow up usually offered by your hospital. If you do decide to stop taking part we will ask you if you would like to: 1. Continue to complete follow up visits for the study; or 2. Stop taking part with no more study visits.

Information on how we will handle your information in the event of you withdrawing is detailed in Part 2 of this Information Sheet.

What if new information becomes available?

Sometimes during the course of a research project, important new information becomes available about the medication that is being studied. If this happens, your doctor will tell you about it and discuss with you whether you want to or should continue in the study. If you decide to withdraw, your doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

On receiving new information your doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason you will be told why and your continuing care will be arranged.

What happens when the study finishes?

It is intended that the results of the study will be presented at conferences and published in medical journals so that we can explain to the medical community what the results of the study have shown. The results may also be used to apply to the regulatory authorities to make the drug widely available and/or for research related to the development of pharmaceutical products, diagnostics or medical aids. The results will be made available to participants via the TEMPEST website. Confidentiality will be ensured at all times and you will not be identified in any publication.

Any information derived directly or indirectly from this research, as well as any patents, diagnostic tests, drugs, or biological products developed directly or indirectly as a result of this research may be used for commercial purposes. You have no right to this property or to any share of the profits that may be earned directly or indirectly as a result of this research. However, in signing this form you do not give up any rights that you would otherwise have as a participant in research.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Detailed information is given in Part 2 of this information sheet.

Will my taking part in the study be kept confidential?

Yes. All the confidential information about your participation in this study will be kept confidential. Detailed information on this is given in Part 2.

PART 2: Detailed information about the conduct of the study

Who is running the study?

Manchester University NHS Foundation Trust is the Sponsor of this study and is responsible for managing it. They are based in the United Kingdom. They have asked that the day to day running of the study is carried out by the Liverpool Clinical Trials Centre ((LCTC), part of the University of Liverpool). The University of Oxford team are leading the magnetic resonance spectroscopy subgroup.

The study has been reviewed by the Medicines and Healthcare Products Regulatory Agency, the Health Research Authority and the National Research Ethics Service Committee to make sure that the study is scientifically and ethically acceptable.

The study (ref. 127575) is funded by the Efficacy and Mechanism Evaluation (EME) Programme, a Medical Research Council (MRC) and National Institute for Health Research (NIHR) partnership. The study medicine is being provided by Univar Solutions B.V. without charge. Your doctor will not receive any payment for including you in this study.

How will my information be collected and handled?

Manchester University NHS Foundation Trust is the Data Controller for this study and they, and the study team, will need to use information from you and sources such as your medical records and your GP. This information will include your initials, NHS number, name and contact details. This information will be used to do the research or to check your records to make sure that the research is being done properly.

Authorised individuals from Manchester University NHS Foundation Trust, the LCTC, the University of Oxford and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The only people in Manchester University NHS Foundation Trust, the LCTC and the University of Oxford who will have access to your name or contact details will be people who need to monitor or audit the consent and data collection processes. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

Data collected for this research study will be sent from your hospital to the LCTC. Data, such as the MRI scans, exercise tests and heart monitors, will be sent from your hospital to Manchester University NHS Foundation Trust and University of Manchester for central study analysis. If you are selected to undergo the spectroscopy, data will be sent from your hospital to the University of Oxford for central study analysis. After central analysis, results will be sent to the LCTC.

Information regarding safety, pregnancy and patients who are lactating will be provided confidentially and securely to Univar Solutions B.V., who are providing the study medication. Univar Solutions B.V. are based in the Netherlands and must follow our rules about keeping your information safe. The information provided to Univar Solutions B.V. will be coded and will not include your name or contact details

We will notify your GP that you will be taking part in the study for their information. We will keep all information about you safe and secure.

Once we have finished the study, we will keep the data for 25 years, so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

With your permission, data held by NHS Digital will be accessed using direct identifiers, including your NHS number and date of birth, as part of future research to follow-up your progress after you have finished this study. This future research will be conducted by the same research team at Manchester University NHS Foundation Trust as for the current study.

What are my choices about how my information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. If you choose to stop taking part in the study, we would like to continue collecting information about your health from central NHS records, your hospital and your GP. If you do not want this to happen, tell us and we will stop. In some cases, however, we may need to continue to collect limited information about any side-effects of the study treatment you may experience, or for example if you were to become pregnant. We will only do this where we are required to do so by law. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Information sharing for other research?

When you agree to take part in a research study, the information about your health and care may be beneficial to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research, or equivalent standards.

If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study.

Where can I find out more about how my information is used?

You can find out more about how we use your information at the following places:

- By asking a member of the research team
- At the TEMPEST website: www.tempest-trial.org.uk
- At www.hra.nhs.uk/information-about-patients
- In the Health Research Authority leaflet available from www.hra.nhs.uk/patientdataandresearch
- By contacting the Manchester University NHS Foundation Trust Data Protection Officer on DPO@mft.nhs.uk
- Further information can be found at https://research.cmft.nhs.uk/getting-involved/gdpr-and-research

What will happen to the blood and urine samples I give?

Some of your blood samples will be analysed at your hospital. Some of the urine and blood samples will be sent to laboratories outside of your hospital, and that of the sponsor, for central analysis, but will remain within the UK, and the results will be sent to LCTC. These samples will be coded and the team carrying out tests on the samples will not be given information they do not need to carry out the tests and analyse the results. Coded is not the same as anonymous. It will be possible to use the codes to identify that a result is from your sample. However, we do not plan to do this unless there is a good reason to do so. We will maintain this information so that we can properly manage the samples. For instance, sometimes we may need to update our record of your clinical details to help us interpret the results of the test. Samples taken for the purposes of the study will be destroyed at the end of the study, as per local procedures.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with one of your research team who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this by contacting local NHS Patient Advice and Liaison Service (PALS) or equivalent. Members of your local hospital team should be able to provide this information to you. Every care will be taken in the course of this clinical study. However, in the unlikely event that you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed and this is due to someone's negligence, then you may have grounds for a legal action for compensation against Manchester University NHS Foundation Trust but you may have to pay for your legal costs. The normal National Health Service complaints procedures should be available to you.

Thank you for taking the time to read and consider this information sheet. We hope it has been of interest to you.