University Hospitals Bristol NHS
NHS Foundation Trust

CARDIOMAN

Patient Information Leaflet

Treatment of Barth syndrome by CARDIOlipin MANipulation (CARDIOMAN): A randomised placebo controlled pilot trial conducted by the nationally commissioned Barth Syndrome Service

>>EVOLVE TAB: TRUST RESEARCH<<

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Contents

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Treatment of Barth syndrome by CARDIOlipin MANipulation

You are being invited to take part in a research study. Before you decide whether or not to take part, you need to understand why the research is being done, and what it would involve for you. Taking part in research is voluntary; it is up to you to decide whether or not to join the study. You are free to withdraw at any time, and if you choose not to take part in the research, you do not have to give any reason for your decision. Nobody will be upset, and the standard of care you receive will not be affected.

Please take time to read the following information carefully. **One of our team will go through the information leaflet with you, explain the study in more detail, and answer any questions you have**. Talk to others about the study if you wish, such as friends or relatives, and take time to decide. If you would like to take part, you will be asked to confirm by signing a consent form and you will be given a copy for your records.

What is the purpose of the study?
Barth syndrome is a life threatening genetic disease which affects young males. It is caused by abnormal fats (lipids) in the powerhouses of cells (mitochondria). Currently there is no treatment for Barth syndrome apart from supportive care for the symptoms experienced. However, scientific research has shown that several medicines may improve the fat abnormalities in human cells affected by Barth syndrome. One is a drug called bezafibrate, which is already used in children to lower blood fats and in adults with a muscle disease resulting from mitochondrial problems. Bezafibrate is the most tried and tested of these potential treatments. The purpose of this study is to see if bezafibrate is a safe and effective treatment for Barth syndrome.

Why have I been invited?
You have been invited to take part because you have been diagnosed with Barth syndrome. All males in the UK diagnosed with Barth syndrome who are eligible to take part in the study will also be invited.

What will happen to me if I take part?
If you decide to take part we will first ask you to sign a consent form. Following this, but before you are given any treatment, we will take some basic measurements (such as height and weight and blood pressure) and a cardiologist will perform an echocardiogram and an electrocardiogram (ECG) on your heart whilst you are at rest to see how your heart is functioning and then again whilst you do an exercise test on a specially designed exercise bike. During the exercise bike test we will also stick some stickers on different parts of your body, which

will be linked to a machine to detect how well your muscles are working.

We would also like to perform Magnetic Resonance Imaging (MRI) scans on your heart and leg muscles. The scans will involve you going into a MRI scanner and doing another short exercise test for part of the time in the scanner. You will be in the scanner for approximately one to one and a half hours. Our scanners are very modern, light and airy, with options such as music and films to help entertain you during the scan.

We would like to take about 4-6 teaspoons of blood from you to do some laboratory tests. This will require us to insert a needle into your arm. Some of the blood will be used to extract a certain type of cell (called lymphocytes) that can be made to multiply in the laboratory. We call these 'immortalised' cells. Some of you will have already provided a blood sample for immortalised cells for a piece of previous research done by Dr Bowron for the Barth Syndrome Service. If this is the case, we will ask for your permission to carry out the tests for our research on the cells that you have already provided. We will use these cells to test the effect of bezafibrate, and another drug called resveratrol, in laboratory conditions. This may help us to assess which patients might respond better in future if either or both medicines came into routine use for treatment.

Even if you have provided a sample previously, we still require a blood sample during your clinic visit to do the tests described below.

The blood collected during the clinic visit will be used to study mitochondrial cells. Other standard laboratory tests will also be performed to assess other aspects of your health.

All of the tests described above will be repeated twice more during the study: at the end of your first block of treatment and again at the end of your second block of treatment (this will be explained in greater detail later). You would not normally receive these tests as part of your routine care, except for an echocardiogram at rest. You will receive 4 months of bezafibrate or 4 months of a non-active drug called a 'placebo'. Then you will have a break of at least one month where you will not take any treatment. After this you will swap to the alternative treatment: so if you started on bezafibrate you will switch to 4 months of placebo and vice versa. The order in which you will receive the bezafibrate and the placebo will be determined by a process called 'randomisation'. This is similar to flipping a coin. Some participants will receive the bezafibrate first, followed by the placebo and some will receive the placebo first followed by the bezafibrate. You or your doctor will not be able to decide which treatment you will receive first.

Neither you nor your doctor will be able to tell which treatment you are receiving: both the bezafibrate and the placebo will look very similar. This is the best way for us to determine if bezafibrate really works.

We will ask you to visit your General Practitioner (GP) or your local hospital every month after you start treatment to have some blood tests. If you have had a heart transplant we would like to do an extra blood test two

weeks after you start treatment. These blood tests will help us assess if you are tolerating the drug and if it is safe. A research nurse will also regularly telephone you to ask about any symptoms or side-effects you may be having. This will happen after the first week of starting bezafibrate (or placebo) and then monthly thereafter.

We will continue to contact you for one month after you have finished both phases of treatment. The total time in the study will be 10 months.

What will I have to do?

To participate in the study you will have to take daily medication, in the form of tablets, for 4 months at a time as indicated by your doctor. Bezafibrate is currently used in other diseases/conditions but it has not yet been tested in people with Barth syndrome. If you are on any other medication, you should continue to take this unless your doctor tells you not to. If you have had a heart transplant we will ask you to stop taking your cholesterol lowering medicines (statins) since bezafibrate will have the same effect, but your doctor will talk to you about this if it is appropriate.

We will ask you to complete a questionnaire each time you come to the clinic for a study visit (3 times). This questionnaire asks questions about your health and well-being and will each take about 10 minutes to complete.

At the end of each four month period of treatment we would like to interview you to discuss your experience of the treatment and if you feel you have benefited in any way (such as increased energy or stamina). There will be two interviews in total. In the interview after the second

period of treatment we will also discuss your experience of participating in the trial as a whole, to help us improve the way we do future research in Barth syndrome. We expect that each interview will last approximately 20-40 minutes. A researcher will carry out the interview during your clinic visit in Bristol, or if it is more convenient for you by means of a Skype call. We would like to audio record the interviews as this will make sure that we accurately record everything that has been said. We will ask for your consent to do this. The interviews will be transcribed but we will not use your real name.

Some of the questions we ask during the interviews might cover sensitive issues such as the kind of physical or emotional problems you may have to face when you are living with Barth syndrome. This will help us to understand more about what it is like to live with Barth syndrome. Our researchers are very experienced and have worked on projects of this kind before. You can ask to stop the interview at any time if you wish.

The audio recordings will be held until the end of the study (in case of unforeseen problems with the transcription of your interview) and then destroyed. We may share your anonymised written information (not the audio recordings) with other scientists who are doing ethically approved research.
You will need to attend each study visit (3 in total): at the beginning of the study, at the end of your first 4 months of treatment and then again at the end of your second block of treatment. Each study visit will be 2 days in length, similar to when you normally come to Bristol.

Expenses

We will pay for your travel to and from the clinic, each time you need to come for a visit. Depending on where you live, we will also pay for your overnight accommodation costs up to a maximum of 2 nights per visit. Some refreshments will be provided during the clinic visits.

What alternatives are there to taking part in the study?

If you decide not to take part in the research study, then you will receive the normal care provided by the Barth Syndrome Service.

What are the possible disadvantages and risks of taking part?

Although bezafibrate is used by people with other diseases, it has not yet been tested in people with Barth syndrome, so we are not sure if the drug will work differently in people with Barth syndrome. This is why we are doing the study. Bezafibrate has a number of known side-effects and these are listed in the section below.

We require you to make two additional visits to Bristol as part of the study, which is more than normal. Some overnight stays may be required and may cause inconvenience.

We are asking you to undergo some tests which you may not have done before, such as questionnaires and exercise tests. The MRI scans will take approximately one to one and a half hours but there will be an opportunity to get out of the scanner part way through. If

you are uncomfortable in the scanner you can let us know at any time and we can stop the scan.
The blood samples will require us to insert a needle into your arm, which will be like your routine clinic blood tests.

After the first phase (4 months) of treatment, we are required to assess if the bezafibrate is working in those participants who are taking it. If the information we collect suggests that the bezafibrate is having no effect, we may have to finish the study after this first phase. It may mean that those participants who received the placebo first will not get the opportunity to take bezafibrate. However, we think that stopping the trial after the first phase is unlikely to happen.

If you have private health insurance you should seek advice from your insurer about your participation in the study as this may affect your insurance cover and your decision to participate.

What are the side effects of any treatment received when taking part?
Like all of the medicines that you already take, bezafibrate has potential side effects. The most common side effects experienced in people in whom bezafibrate has been tested are decreased appetite and gastrointestinal problems. This happens in between approximately 1 in 10 and 1 in 100 people.
Some less common side-effects (between 1 in 100 and 1 in 1000 people) are:

- allergic reactions
- dizziness and headaches
- abdominal pain, constipation, indigestion or heartburn, bloated tummy, diarrhoea, nausea

- problems with bile (from the liver).
- itching, raised itchy rash, sensitivity to light, hair loss
- muscle weakness, muscle pain, muscle cramp
- kidney failure
- reduced libido/erectile dysfunction (reversible on drug stoppage)

Some people have also experienced nerve damage, pins and needles, depression, insomnia and inflammation of the pancreas but this has been rare (i.e. 1 person in 1000-10,000).

The rarest side effects that have been seen in other people are in the following list but to give you an idea of how rare these are, less than 1 person in 10,000 has experienced them:

- low numbers of red and white blood cells, or platelets in the blood
- gallstones
- severe skin conditions such as erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis
- rhabdomyolysis - a condition in which damaged muscle tissue breaks down rapidly and enters the bloodstream, which can cause kidney failure
- lung disease

Because this drug has not yet been tested before in people with Barth syndrome, there may be other side-effects that we don't know about.

If you suffer from any side-effects when taking medication in the study you should tell your doctor, research nurse or specialist nurse. You can report it to us via the Patient Knows Best website, or you can telephone the research nurse (see contact details on the second page). The research nurse will contact you after the first week of starting treatment and then monthly thereafter to ask you if you have experienced any side-effects or other untoward event.

If you feel you are experiencing palpitations or muscle pain, or other side-effects that you feel are serious, you should contact the Barth Syndrome Service during working hours, on the usual number (**07795 507294**) or the study research nurse on **0117 342 8889**. If you would like to speak to someone out of office hours, the University Hospitals Bristol Paediatric Cardiology registrar is available via the BRI Switchboard (**0117 923 0000**) and will be able to contact someone from the Barth Syndrome Service urgently if necessary.

You are, of course, able to access your local medical services as normal (as if you weren't in the study) – either your GP or your local hospital.

Reproductive considerations

There are no known effects of bezafibrate on sperm or developing foetuses but if you are planning a family you should talk to your doctor. Whilst taking the study medication you should be careful to use contraception. If your partner becomes pregnant, please tell your doctor so they can give you appropriate advice.

What are the possible benefits of taking part?
There is no current specific treatment for Barth syndrome and you will receive treatment as part of this study, but we do not know if bezafibrate is effective. We cannot promise the study will help you but the information we get from this study will help improve the future treatment of people with Barth syndrome.

What happens when the research study stops?
If your doctor has reason to believe that bezafibrate has been beneficial for you, you will be able to carry on taking it after the study finishes. Your doctor will look at each case on an individual basis. If your doctor does not think that bezafibrate has helped you, your care will go back to the standard treatment offered before you started the trial.

After we have looked at the data obtained from the study and written the results we will contact all participants with a report of what we have found.

What if there is a problem?
If you have any concerns or questions about this study, please contact the research team, who will do their best to address your questions/concerns.

If you have concerns about the way you have been approached or treated during the course of the study, you may wish to contact the Patient Support and Complaints Team at:

A201
Welcome Centre
Bristol Royal Infirmary

Upper Maudlin Street Bristol
BS2 8HW

Tel: 0117 342 1050
Email: PSCT@uhbristol.nhs.uk

If you wish to make a formal complaint, please write to:

Chief Executive
University Hospitals Bristol NHS Foundation Trust Headquarters
Marlborough Street
Bristol, BS1 3NU

We have no reason to believe that you will be placed at greater risk by taking part in this research study. However, if something goes wrong and you are harmed during the research study there are no special compensation arrangements. The University Hospitals Bristol NHS Foundation Trust cannot offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.
If anything goes wrong as a consequence of taking part in the trial because negligence has occurred, University Hospitals Bristol NHS Trust, who is sponsoring the trial, will compensate you. Negligence would include, for example, a situation in which injury is caused by a deviation from the study protocol by the researcher. Your legal right to claim compensation for injury where you can prove negligence is not affected. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action against the University Hospitals Bristol NHS Trust, but you may have to pay your legal

costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my taking part in the study be kept confidential?
Your data will be stored and used in compliance with the relevant, current data protection laws; Data Protection Act 2018 and General Data Protection Regulation (GDPR) 2016.

University Hospitals Bristol NHS Foundation Trust is the sponsor for this study. It will be using information from you and your medical records in order to undertake this study and will act as the joint data controller for this study with CTEU Bristol who are responsible for the day to day running of this study. This means that they are responsible for looking after your information and using it properly.

All information collected about you during the course of the research will be kept strictly confidential. The information that will be collected includes personal information such as your name, address and NHS number, to allow us to keep in touch with you during your participation in the research, and information about your health. The information collected will be stored in a secure database held on the University Hospital Bristol NHS Trust IT network and will only be accessed by authorised members of staff involved in the research. This includes the hospital staff who are looking after you and the research team who are managing the study. The University Hospitals Bristol NHS Trust, along with the University of Bristol will collect, store and process your data. University of Bristol will be performing the laboratory tests on the samples and so will also collect, store and

process some data about you (such as results of the tests) but your name will not be used to identify your sample(s). We will keep identifiable information about you until the youngest person in the study turns 25 years old and a set of anonymised data will be held indefinitely.

Your medical notes will need to be seen by authorised members of the hospital research team, so they can collect information needed for this research study. With your consent, your GP will also be informed that you are taking part in the research study. Your GP may be asked to provide information from your records which is required for the research. Occasionally, other members of NHS staff or research staff may need to check your medical records. This will be done by NHS staff or by researchers who are bound by the same rules of confidentiality as all NHS staff. The confidentiality of your medical records will be respected at all times. Under no circumstances will you be identified in any way in any report arising from the study.

Individuals from University Hospitals Bristol NHS Foundation Trust and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The only people in University Hospitals Bristol NHS Foundation Trust and CTEU Bristol who will have access to information that identifies you will be people who need to contact you, collect and/or process your study data for subsequent analysis or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

In the future, we may receive requests from researchers at other organisations to share your data collected as part of this research study. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. However, we will only consider requests from organisations and researchers conducting research in accordance with the UK Policy Framework for Health and Social Care Research and we will ask for your permission before we share any of your information.

What if relevant new information becomes available?
Sometimes we get new information about the treatment being studied. If this happens, your research doctor will tell you and discuss whether you should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue.

What will happen if I don't want to carry on with the study?
You are free to withdraw from the study at any time, without giving a reason and it will not affect the future care you receive.

If you decide to withdraw from taking the study treatment, we will need to do a follow-up check with you one month after you withdraw so we can check your well-being and to ensure you are cared for in the appropriate way.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To

safeguard your rights, we will use the minimum personally-identifiable information possible. We will ask if we can continue to follow you up and collect data on you for the remainder of your time in the study (if you want to continue with the assessments and study visits but not take the medication). You are free to refuse this request if you wish. If you withdraw from the study entirely, we will not collect any further data on you after the time of your withdrawal. In addition, we will ask what you would like us to do with the samples we have collected from you. Any stored blood or tissue samples that can still be identified as yours will be destroyed if you wish but we will use the data obtained from the samples up until the time of your withdrawal.

You can find out more about how we use your information at: http://www.uhbristol.nhs.uk/about-us/privacy/

What will happen to any samples I give?

The blood will be collected during your clinic visit by a nurse or someone specially trained to take blood. The samples will be sent to various departments in University Hospitals Bristol and the University of Bristol where they will be tested. The samples sent to the University of Bristol will not have your name on them, so you can't be identified by the laboratory researchers. The samples sent to the pathology laboratories at University Hospitals Bristol will have your name on them so that the staff can test the samples using the normal hospital systems. However, none of the samples will be stored with your name on them. Samples will be stored in secure laboratories and will be accessed only by members of the research team.

After the study has finished, we would like to continue to store your samples and use them in potential future research. The samples will either be stored at the University of Bristol or sent to John Hopkins University in USA (who we work closely with in other areas of Barth syndrome). There will be a section on the consent form asking for your permission to do this. You will not be able to be identified from the samples stored.

Will any genetic tests be done?
No, we will not perform any genetic tests as part of this study.

What will happen to the results of the research study?
The results of the research will not be known for some time until after the end of the study (about 18 months to 2 years after the start of the study). The results will be published in the National Institute of Health Research Efficacy and Mechanisms Evaluation journal. This is a journal published by the funder of the study. The results may also be reported in other medical journals or presented at meetings. We will provide a summary of the results on the Patient Knows Best website and results will also be circulated through the Barth Syndrome Trust. During the course of the study we will ask you if you would like to receive a summary of the results by post after the research has finished. If you say yes, we will also send this to you.

Who is organising and funding the research?
The research is funded by the National Institute of Health Research; Efficacy and Mechanisms Evaluation Programme. University Hospitals Bristol NHS Foundation

Trust has overall responsibility for conduct of the study. The research is being organised and run on their behalf by the Clinical Trials and Evaluation Unit, University of Bristol.

Who has looked at the study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given a favourable opinion by South West – Central Bristol Research Ethics Committee.

The Medicines and Healthcare product Regulatory Authority (MHRA), which is in charge of ensuring the safety of medicines in the UK, has also looked at the study and given us permission to proceed.

Further information
You can obtain general advice on Barth syndrome and its treatment from the Barth Syndrome Trust

http://www.barthsyndrome.org.uk/
Tel: 01794 518 785

You can obtain **general information on clinical research** from the UK Clinical Research Collaboration (UKCRC), which produces a booklet called "Understanding Clinical Trials". This provides in-depth information on the design and conduct of clinical trials and aims to answer the questions of those considering taking part.

Electronic copies can be downloaded from the UKCRC website:

http://www.ukcrc.org/information-booklets-post/
Printed copies can be requested by emailing:

info@ukcrn.org.uk

Or contacting:

UK Clinical Research Collaboration
c/o Medical Research Council
One Kemble Street
London WC2B 4TS
Tel: 020 7395 2271

General information about research can also be found at www.uhbristol.nhs.uk/research-innovation

Thank you for taking the time to read this leaflet.

NHS
National Institute for Health Research

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