

# Investigating bezafibrate as a treatment for Barth syndrome

<b>Submission date</b> 17/12/2018	<b>Recruitment status</b> No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
<b>Registration date</b> 07/01/2019	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 10/03/2025	<b>Condition category</b> Nutritional, Metabolic, Endocrine	<input type="checkbox"/> Individual participant data

## Plain English summary of protocol

### Background and study aims

Barth Syndrome is a rare, life threatening, genetic disease which affects young males. It is caused by abnormal fats in the powerhouses of cells (mitochondria) and those who suffer with it often develop heart failure, heart rhythm abnormalities, bacterial infections, poor growth or feeding, weak muscles, developmental delay, severe exercise intolerance, lethargy and fatigue; all of which affect their daily life. In addition, about one third of males living with this disease in the UK have required a heart transplant. Research has shown that several treatments can improve the fat abnormalities in Barth Syndrome, one of which is a drug called bezafibrate. The aim of this study is to find out whether bezafibrate can be given safely and effectively to people with Barth Syndrome.

### Who can participate?

Males aged 6 and above with a Barth syndrome under the care of of the NHS Barth Syndrome Service

### What does the study involve?

Participants are randomly allocated to take either bezafibrate or an inactive (placebo) treatment for 4 months, followed by a one month break, and then 4 months of the other treatment (e.g. placebo if bezafibrate taken for the first 4 months and vice versa). Half of the participants take bezafibrate first; the other half take placebo first. Tests are performed after each 4-month treatment period, looking for benefit in blood cells, exercise capacity, heart function or quality of life. Laboratory work is also conducted to see the effect of bezafibrate on participants' cells and mitochondria.

### What are the possible benefits and risks of participating?

There is no current treatment for Barth Syndrome itself and symptoms are treated individually on a clinical basis. Therefore, the use of bezafibrate in this clinical trial is the first potential treatment available for the alleviation of the abnormal cardiolipin ratio demonstrated in these patients. Risks of taking part include the risks of the side effects of taking bezafibrate. In addition to this, participants are required to make additional visits to Bristol as part of the study, which will cause some inconvenience and participants will also be required to undergo additional tests that they would not usually be asked to do.

Where is the study run from?  
University Hospitals Bristol NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?  
April 2015 to January 2021

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

Who is the main contact?  
Lucy Dabner  
cardioman-trial@bristol.ac.uk

## Contact information

**Type(s)**  
Public

**Contact name**  
Ms Lucy Ellis

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## Additional identifiers

**EudraCT/CTIS number**  
2015-001382-10

**IRAS number**

**ClinicalTrials.gov number**  
Nil known

**Secondary identifying numbers**  
CPMS 40281

## Study information

**Scientific Title**  
Treatment of Barth Syndrome by CARDIOlipin MANipulation (CARDIOMAN): a randomised placebo-controlled pilot trial conducted by the nationally commissioned Barth Syndrome Service

**Acronym**

CARDIOMAN

**Study objectives**

Current study hypothesis as of 04/04/2019:

Bezafibrate (and/or resveratrol in-vitro) will increase mitochondrial biogenesis and potentially modify the cellular ratio of monolysocardiolipin to L4- cardiolipin, ameliorating disease phenotype in those living with the disease, providing that the drug is free of significant side-effects at clinically effective doses.

Previous study hypothesis:

1. Bezafibrate will modify the cellular ratio of monolysocardiolipin to L4- cardiolipin, ameliorating disease phenotype in those living with the disease, providing the drug is free of significant side-effects at clinically effective doses.
2. Bezafibrate (and/or resveratrol in-vitro) may have beneficial effects independent of any effect on cardiolipin ratio due to their abilities to influence a range of mitochondrial pathologies.

**Ethics approval required**

Old ethics approval format

**Ethics approval(s)**

NRES Committee South West - Central Bristol, 12/11/2015, ref: 15/SW/0228

**Study design**

Randomized; Interventional; Design type: Treatment, Drug

**Primary study design**

Interventional

**Secondary study design**

Randomised cross over trial

**Study setting(s)**

Hospital

**Study type(s)**

Treatment

**Participant information sheet**

Not available in web format, please use the contact details below to request a patient information sheet

**Health condition(s) or problem(s) studied**

Barth syndrome

**Interventions**

Current interventions as of 04/04/2019:

All participants will receive 4 months of the intervention (bezafibrate) and 4 months of the placebo. Participants are randomised in a 1:1 ratio to the allocated treatment arm they receive first. The sequence of random allocations will be generated by computer and will be concealed from all clinical and research personnel. Those first allocated to the intervention at

randomisation will be given bezafibrate followed by the placebo. Those first allocated to the placebo at randomisation will be given the placebo followed by bezafibrate. Both arms will have a minimum of 1 month washout period between the intervention and placebo administered, where no treatment is given.

**Intervention:** Bezafibrate taken orally in tablet formulation.

1. Children aged 6-9 years: Commence on 100mg once daily for the first month and if well tolerated increase to 100mg twice daily for the remaining 3 month treatment period
2. Children aged 10-17 years: commence on 200mg once daily for the first month and if well tolerated increase to 200mg twice daily for the remaining 3 month treatment period
3. Adults ( $\geq 18$  years): 200mg twice daily

**Placebo:** Tablet formulation with no active substance taken orally at the same time points. The placebo will look, taste and smell as similar as possible to the intervention.

Patients are followed up at the end of each treatment period (4 and 9 months) for information on exercise tolerance, drug action and tolerance, adverse events and quality of life.

**Previous interventions:**

All participants will receive 4 calendar months of the intervention (bezafibrate) and 4 calendar months of the placebo. Participants are randomised in a 1:1 ratio to the allocated treatment arm they receive first. The sequence of random allocations will be generated by computer and will be concealed from all clinical and research personnel. Those first allocated to the intervention at randomisation will be given bezafibrate followed by the placebo. Those first allocated to the placebo at randomisation will be given the placebo followed by bezafibrate. Both arms will have a 1 calendar month washout period between the intervention and placebo administered, where no treatment is given.

**Intervention:** Bezafibrate taken orally in tablet formulation.

1. Children aged 6-9 years: Commence on 100mg once daily for the first month and if well tolerated increase to 100mg twice daily for the remaining 3 month treatment period
2. Children aged 10-17 years: commence on 200mg once daily for the first month and if well tolerated increase to 200mg twice daily for the remaining 3 month treatment period
3. Adults ( $\geq 18$  years): 200mg twice daily

**Placebo:** Capsule formulation with no active substance taken orally at the same time points. The placebo will look, taste and smell as similar as possible to the intervention.

Patients are followed up at the end of each treatment period (4 and 9 months) for information on exercise tolerance, drug action and tolerance, adverse events and quality of life.

## **Intervention Type**

Drug

## **Phase**

Phase II

## **Drug/device/biological/vaccine name(s)**

Bezafibrate

## **Primary outcome measure**

Peak oxygen consumption on bicycle ergometry (i.e. peak VO<sub>2</sub>), assessed at baseline and in the final week of each treatment phase

### **Secondary outcome measures**

1. Monolysocardiolipin/tetralinoleoyl-cardiolipin MLCL/L4-CL ratio/cardiolipin profile in blood cells assessed via blood tests taken at baseline, 4 months and 9 months
2. PCr/ATP ratio in cardiac muscle assessed via <sup>31</sup>P Magnetic Resonance Spectroscopy at baseline, 4 months and 9 months
3. Skeletal muscle oxidative function assessed via <sup>31</sup>P Magnetic Resonance Spectroscopy at baseline, 4 months and 9 months
4. Quality of life (QoL) assessed using age-appropriate PedsQL questionnaires at baseline, 4 months and 9 months
5. Absolute neutrophil count assessed via blood test at baseline, 4 months and 9 months
6. Amino acid expression (plasma arginine and cysteine levels) assessed via blood test at baseline, 4 months and 9 months
7. Cardiac function (LVEF and shortening fraction) assessed via echocardiogram at baseline, 4 months and 9 months
8. Mitochondrial size in lymphocytes assessed via blood test at baseline, 4 months and 9 months
9. Numbers of mitochondria (per lymphocyte) assessed via blood test at baseline, 4 months and 9 months
10. Total area of mitochondria per lymphocyte assessed via blood test at baseline, 4 months and 9 months
11. Area of mitochondria as proportion of cytoplasm assessed via blood test at baseline, 4 months and 9 months
12. Mitochondria function and cristae organisation in lymphocytes assessed via blood test at baseline, 4 months and 9 months
13. Arrhythmia profile measured by 12-lead ECG at rest and during exercise (for potential rhythm abnormalities) at baseline, 4 months and 9 months

### **Overall study start date**

01/10/2014

### **Completion date**

21/01/2021

## **Eligibility**

### **Key inclusion criteria**

1. Male aged ≥6 years old
2. Clinical diagnosis of Barth syndrome with characteristic abnormality of the L4-cardiolipin /monolysocardiolipin ratio plus identified mutation in the tafazzin gene
3. Under the care of the NHS Barth Syndrome Service
4. Stable cardiac condition
5. Able to swallow bezafibrate tablets

### **Participant type(s)**

Patient

### **Age group**

Mixed

**Lower age limit**

6 Years

**Sex**

Male

**Target number of participants**

Planned Sample Size: 15; UK Sample Size: 15

**Total final enrolment**

11

**Key exclusion criteria**

1. Known hypersensitivity to bezafibrate, to any component of the product or to other fibrates
2. Known photoallergic or phototoxic reactions to fibrates.
3. Hepatic dysfunction and/or liver function tests greater than 2x normal
4. A shortening fraction of <25 (or a significant drop in shortening fraction in the previous year)
5. Documented atrial or ventricular arrhythmia (atrial/ventricular tachycardia or atrial/ventricular fibrillation) that has not been stabilised with treatment.
6. Renal impairment (creatinine clearance < 90 mL/min)
7. Pre-existing known gallbladder disease.
8. Recent unspecified significant deterioration in general health
9. Prisoners and adults lacking capacity to provide informed consent

**Date of first enrolment**

29/03/2019

**Date of final enrolment**

12/04/2019

**Locations****Countries of recruitment**

England

United Kingdom

**Study participating centre**

**University Hospitals Bristol NHS Foundation Trust**

Upper Maudlin Street

Bristol

United Kingdom

BS2 8HW

**Sponsor information**

**Organisation**

University Hospitals Bristol NHS Foundation Trust

**Sponsor details**

Research and Innovation  
Level 3  
Education Centre  
Upper Maudlin Street  
Bristol  
England  
United Kingdom  
BS2 8AE

**Sponsor type**

Hospital/treatment centre

**ROR**

<https://ror.org/04nm1cv11>

**Funder(s)****Funder type**

Government

**Funder Name**

NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: 12/205/56

**Results and Publications****Publication and dissemination plan**

The patient information leaflet and trial protocol will be available on request. Please contact [cardioman-trial@bristol.ac.uk](mailto:cardioman-trial@bristol.ac.uk).

When all of the data has been collected and analysed, the researchers will hold a social gathering to feed the information back to the patient/families directly and to thank them for their participation. They will send a lay summary to all people/families in the UK with Barth Syndrome.

Findings from the study will be submitted for publication in a peer-reviewed journal, selecting one with open access arrangements, under the NIHR Terms of Agreement, in order to allow rapid dissemination to the Barth syndrome community. The trialists will also present the findings at national/international paediatric, paediatric cardiology and metabolic disease conferences.

**Intention to publish date**

31/12/2021

Individual participant data (IPD) sharing plan

Anonymised individual patient data (baseline, intervention, outcome data and adverse events) will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the with the UK Policy Framework for Health and Social Care Research and MRC Policy on Data Preservation and Sharing regarding scientific quality, ethical requirements and value for money. Please contact Prof. Barney Reeves (cardioman-trial@bristol.ac.uk) to discuss any data requests. Data will be made available after the study has been closed and the primary publication is out. It will be made available indefinitely. Only data from patients who have consented for their data to be shared with other researchers will be provided.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Results article</a>		31/05/2021	01/06/2021	Yes	No
<a href="#">Basic results</a>	version 1.0	20/10/2021	20/10/2021	No	No
<a href="#">Protocol article</a>		31/05/2021	11/11/2022	Yes	No
<a href="#">Results article</a>	Qualitative interview substudy of self-regulation with ethical approval granted as part of this clinical trial within which it was conducted	29/09/2021	11/11/2022	Yes	No
<a href="#">HRA research summary</a>			28/06/2023	No	No
<a href="#">Results article</a>		01/08/2024	10/03/2025	Yes	No