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Investigating bezafibrate as a treatment for Barth syndrome

Submission date	Recruitment status
17/12/2018	No longer recruiting
Registration date	**Overall study status**
07/01/2019	Completed
Last Edited	**Condition category**
10/03/2025	Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] 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?
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Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2015-001382-10

Central Portfolio Management System (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

Study type(s)
Treatment

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 (≥ 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 (≥ 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(s)
Peak oxygen consumption on bicycle ergometry (i.e. peak VO2), assessed at baseline and in the final week of each treatment phase

Key secondary outcome(s))
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 31P Magnetic Resonance Spectroscopy at baseline, 4 months and 9 months
3. Skeletal muscle oxidative function assessed via 31P 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

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

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
6 years

Sex
Male

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
United Kingdom

England

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

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

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?
Results article		31/05/2021	01/06/2021	Yes	No
Results article	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
Results article		01/08/2024	10/03/2025	Yes	No
Protocol article		31/05/2021	11/11/2022	Yes	No
Basic results	version 1.0	20/10/2021	20/10/2021	No	No
HRA research summary			28/06/2023	No	No