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Bestrophin 1 treatment trial on the effectiveness of Ravicti

Submission date 17/10/2023	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [X] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 04/12/2023	**Overall study status** Completed	
Last Edited 16/09/2026	**Condition category** Eye Diseases	

Plain English summary of protocol

Background and study aims
This study will investigate whether the drug Ravicti is a therapeutic treatment for a group of inherited eye conditions called bestrophinopathies. Bestrophinopathies result from faults in bestrophin, a protein in the pigmented layer of cells at the back of the eye that facilitates the passage of chloride ions into the cells. The faulty bestrophin reduces the flow of chloride ions, preventing the normal function of the pigmented cells. This in turn disrupts the normal function of the adjacent light-detecting cells, causing sight loss. Bestrophin activity is easily measured in the clinic by the electrooculogram (EOG) which is characteristically abnormal in bestrophinopathy patients. In this study the EOG is a proxy measure of bestrophin function. Ravicti is an approved drug for an unrelated condition but is also known to improve the function of faulty proteins, including bestrophin. This study will test whether giving Ravicti to bestrophinopathy patients increases the function of their faulty bestrophin protein by measuring whether their EOG improves.

Who can participate?
Patients aged 18 - 65 years old with bestrophinopathy

What does the study involve?
The researchers will first measure the EOG in patients to establish a starting value before dosing them with Ravicti for 7 days. The researchers will then measure the EOG again to see if the EOG improves. Patients will then be Ravicti-free for 21 days before measuring the EOG again to see whether it returns to the starting value. Each patient will also undergo the same schedule using a placebo to determine whether any improvement in the EOG is due to Ravicti or is a coincidence resulting from just being part of the study.

What are the possible benefits and risks of participating?
This is a low-risk study using a repurposed drug usually used for the treatment of urea cycle disorders. Clinical interventions are low risk with the greatest risk being potential side effects to taking the test drugs. If any occur they are typically not serious. A liver function test is conducted on a blood sample and is necessary to ensure there are no abnormal liver markers that would indicate abnormal liver function, which would exclude the patient from the study. Blood will be taken by standard operating procedure (SOP) with existing risk assessment (RA).

There is a risk of bruising as a result of taking a blood sample. Pregnancy test will be by a urine dipstick and is necessary to ensure female participants are not pregnant, which will exclude them from the study. There is the risk of emotional upset if a patient discovers they are unexpectedly pregnant.
The tests carried out are all standard care procedures that will be performed in accordance with existing SOP and RA. All are considered low-risk. EOG and ERG are variables that may change in response to drug treatment and are necessary to measure the primary outcome of the study. The remaining tests are not expected to change but are required to establish eye health.
Dosing with the study drug and placebo may be associated with side effects which are typically mild. These are listed in the protocol and the Patient Information Sheet (PIS) and will be discussed with potential participants during the taking of informed consent. A contact number for the study clinician, or their deputy, is provided on the patient's drug diary. Participants can contact a study doctor, or their deputy, 24 h/day if they need any advice about taking the drug or are unwell after taking it. The clinician can un-blind the participant for appropriate treatment if required.

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

When is the study starting and how long is it expected to run for?
October 2023 to July 2025

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
genetics.research@mft.nhs.uk

Contact information

Type(s)
Principal investigator

Contact name
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Additional identifiers

Integrated Research Application System (IRAS)
1006836

Protocol serial number
B01914

Study information

Scientific Title
Ravicti as therapy for bestrophinopathies: a double-blind crossover randomized controlled trial

Acronym
BETTER

Study objectives
The main research objective of the trial is to compare the effect of glycerol phenylbutyrate on the electrooculogram (EOG) light peak to dark trough (LP:DT) ratio in patients with bestrophinopathy.

The study hypothesis is that treatment with glycerol phenylbutyrate will increase mutant bestrophin 1 activity in patients with bestrophinopathy. Thus, the primary objective is that this treatment will result in a significantly increased EOG LP:DT ratio, compared to treatment with a placebo, after 7 days of dosing.

The null hypothesis is that treatment with glycerol phenylbutyrate has no significant effect on the EOG compared to a placebo.

In lay terms, the aim is to show whether treatment with this drug produces a measurable effect in a specific eye test that is part of standard of care for these patients.

The secondary objective is that if there is a change in the EOG LP:DT ratio after dosing with glycerol phenylbutyrate, does it return to baseline 21 days after cessation of treatment?

In lay terms, does any measurable effect in the eye test result return back to its previous value once you stop taking the drug?

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 27/11/2023, North East - Tyne & Wear South Research Ethics Committee (NHSBT Newcastle Blood Donor Centre Holland Drive, Newcastle upon Tyne, NE2 4NQ, United Kingdom; None available; tyneandwearsouth.rec@hra.nhs.uk), ref: 23/NE/0202

Primary study design
Interventional

Study design
Randomized cross-over double-blind placebo-controlled trial

Study type(s)
Efficacy

Health condition(s) or problem(s) studied
Autosomal dominant best vitelliform macular dystrophy (BVMD) or autosomal recessive bestrophinopathy (ARB)

Interventions
In this study the researchers are testing whether glycerol phenylbutyrate (Ravicti) will help make the bestrophin 1 protein work properly for patients where this does not, and are performing eye tests to see if they can measure that. The BETTER trial is a double-blind crossover trial, which means participants will receive both the placebo and the trial medication glycerol phenylbutyrate (Ravicti) during the trial. However, participants will not know which medication they are taking at either time point. Neither will the study doctor or assessors. Only the pharmacist dispensing the medication will know what treatment arm they have been assigned to. This is so the researchers can analyse all results and data gathered during the trial and see if there is an immediate effect of the glycerol phenylbutyrate (Ravicti).

Dose:
Colourless to pale yellow liquid. 1.1 gfmL of glycerol phenylbutyrate. 11.2 ml/m²/day (12.4 g/m² /day) body surface area given orally in three equally divided dosages rounded up to the nearest 0.5 ml for 7 days.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Ravicti (glycerol phenylbutyrate)

Primary outcome(s)

EOG LP:DT ratio measured using electrooculogram on Days 8 and 36. These measurements will determine if the primary objective has been achieved (measurable effect of dosing at the end of the dosing period).

Key secondary outcome(s)
EOG LP:DT ratio measured using electrooculogram on Days 1 and 29 (baseline periods 1 and 2) and on Day 57. These measurements will determine whether the secondary objective has been achieved (return to baseline value following cessation of dosing)

Completion date
29/07/2025

Eligibility

Key inclusion criteria
1. Participants capable of giving informed consent
2. Age 18-65 years old
3. Best corrected visual acuity recorded as better than hand movements at recruitment
4. Clinical and molecular diagnosis of ARB or BVMD
5. Able to speak and understand English

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
65 Years

Sex
All

Total final enrolment
10

Key exclusion criteria
1. Participation in other CTIMP in the last 12 weeks
2. Pregnant or breastfeeding
3. Liver morbidity
4. Treatment for acute hyperammonaemia
5. Unable to speak and understand English
6. Urea cycle disorder
7. Known hypersensitivity to phenylbutyrate

8. Reduced phenylbutyrate absorption due to pancreatic insufficiency or intestinal malabsorption
9. Contraindicated concomitant medications:
9.1. Treatment with probenecid (which may inhibit the renal excretion of metabolites of 4PBA including phenylacetylglutamine and phenylacetate)
9.2. Treatment with drugs with a narrow therapeutic index that are substrates of CYP3A4 (4PBA weakly induces CYP3A4 in humans and so may decrease the systemic exposure to drugs that are its substrates of CYP3A4 e.g., alfentanil, quinidine, cyclosporine)
9.3. Treatment with midazolam (4PBA can decrease the systemic exposure of midazolam)

Date of first enrolment
01/03/2024

Date of final enrolment
18/06/2025

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
St Mary's Hospital
Oxford Road
Manchester
England
M13 9WL

Sponsor information

Organisation
Manchester University NHS Foundation Trust

ROR
https://ror.org/00he80998

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Data will be suitable for sharing. These data are gathered as part of a proof-of-concept trial, potentially to be used to inform a larger-scale trial in future if study endpoints are achieved. The researchers will make anonymised data available to other research opportunities should patients consent to future research opportunities in a timely manner; however, they do reserve the right to not publish data until they have published/gained the required impact. However, the researchers will withhold sharing of data until the results have been validated, presented at conferences, and published in peer-reviewed journals.
Data will not be made available to other researchers within MFT/University of Manchester or to those in external teams within an existing data sharing agreement until primary outputs are published/impact reached. The study team will endeavour to produce primary outputs without delay.
Strategies to limit sharing restrictions will include data being anonymised. Participant information sheets and consent forms will include information on plans for data sharing and enable participants to give explicit and informed consent to such data sharing. Sensitive genotypic data will be kept confidential.

Added 16/12/2025:
The datasets generated during and/or analysed during the current study will be available upon request from Dr Eva Lenassi (eva.lenassi@mft.nhs.uk) in a spreadsheet format (i.e., Excel file).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		16/09/2026	16/09/2026	No	No
Participant information sheet	version 1.0	15/09/2023	24/10/2023	No	Yes
Participant information sheet	version 2.0	26/07/2024	18/05/2026	No	Yes

Plain English results			16/09/2026	No	Yes
Protocol file	version 1.1	17/11/2023	24/04/2024	No	No
Protocol file	version 1.6	02/05/2025	18/05/2026	No	No
Statistical Analysis Plan	version 1.0		16/09/2026	No	No