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BETTER Trial

Patient Information Sheet

Bestrophin 1 treatment trial on the effectiveness of Ravicti/BETTER Trial.
(B01914)
Principle Investigator: Dr Eva Lenassi

You are invited to take part in a study that will determine whether a medication called glycerol phenylbutyrate (Ravicti®) is an effective treatment for bestrophinopathies which are a group of untreatable inherited retinal disorders leading to sight loss.

If you choose to take part, you will need to meet the inclusion criteria mentioned below and be between 18 and 65 years old and have a clinical diagnosis of Autosomal Recessive Bestrophinopathy (ARB) or Best vitelliform macular dystrophy (BVMD). You will need to be able to provide informed consent and agree to participate in the study timeline.

What is the purpose of this research?

Bestrophinopathies, a group of untreatable inherited retinal disorders can lead to irreversible sight loss and there is presently no proven treatment for this group of conditions. People consider sight to be their most important sense, and its loss has a significant detrimental impact on an individual's quality of life.

The researchers are working to 'ensure no one gets left behind just because they have a rare disease' (UK Strategy for Rare Diseases, 2013).

In this study we are testing whether the medication in the form of glycerol phenylbutyrate (Ravicti), will help make the bestrophin 1 protein work properly for patients where this does not, and we are performing eye tests to see if we can measure that.

Why have I been asked to take part?

You have been invited to take part in the BETTER trial as you meet the following inclusion criteria:

- Participants capable of giving informed consent
- Age 18 - 65 years old
- Best corrected visual acuity recorded as better than hand movements at recruitment
- Clinical and molecular diagnosis of Autosomal Recessive Bestrophinopathy (ARB) or Best vitelliform macular dystrophy (BVMD).

What would taking part involve?

The BETTER trial is a double-blind crossover trial, which means you will receive both the placebo and trial medication: glycerol phenylbutyrate (Ravicti) during the trial. However, you will not know which medication you are taking at either time point. Neither will your study doctor or assessors. Only the pharmacist dispensing the medication will know what treatment arm you have been assigned to. This is so we can analyse all results and data gathered during the trial and see if there is an immediate effect of the glycerol phenylbutyrate (Ravicti). The study will take just over 8 weeks.

<u>Part 1</u>

If you decide to take part, we will first determine if you are eligible for the study and meet the above eligibility criteria. To do this, you will attend a screening visit in the Genomic centre, 6th Floor, St Mary's hospital where you will complete relevant eligibility tests (liver function test- blood test/sample, pregnancy test – urine sample) and the clinical team will assess your vision, medical history, and any current medications you are taking.

Once all tests are completed and the results demonstrate you are eligible for this trial, you will then attend a second visit for a repeat review of your current medication and for further eye testing as part of the study. These eye tests include:

- **electroretinogram (ERG)** which looks at how well the retina at the back of your eye is working.
- **electroocoulogram (EOG)** which will measure the corneo-retinal standing potential that exists between the front and the back of the human eye.
- **Fundus Autofluorescence Photography (FAF)** is a non-invasive diagnostic test that involves taking digital photographs of the back of the eye without a contrast dye.
- **optical coherence tomography (OCT**) which helps us to view the health of your eyes in greater detail, by allowing us to see what's going on beneath the surface of the eye.

You will then be selected randomly to either the trial medication; glycerol phenylbutyrate (Ravicti) or the placebo. You will not be aware of which medication you have been randomised to. Both Ravicti and the placebo are an oral liquid medicine, that needs to be kept at room temperature. Participants will be trained on how to dispense the medication.

You will then attend a third visit a week after your second visit to repeat a liver function test (blood test/sample), a review of any serious adverse events and eye testing (ERG, EOG, FAF, OCT). We plan to see immediate results from these eye tests in comparison to those taken prior to you starting the medication. The EOG test at the end of dosing must be immediate (as scheduled 7 days later) to avoid missing any effect the drug treatment has on the EOG. Therefore, your visit dates will be confirmed with you prior to dosing so there is high confidence that you can attend according to your assigned schedule.

We will then provide a three week break of no treatment which is called a 'washout' period. This will prevent us from mis-interpreting observations about the previous treatment you were on with the next treatment in Part 2 and ensure there is no crossover.

Part 2

After three weeks of no further treatment, you will then attend visit 4 where the clinical team will check for the other medication, including a repeat of liver function blood tests, serious adverse events (SAE) checks, and further eye testing (ERG, EOG, FAF, OCT). You will then take the other medication (either glycerol phenylbutyrate (Ravicti) or placebo) for a further 7 days and then attend visit 5 to review the immediate effects of this medication.

Your final visit will be three weeks after the last dose of the second medication, and we will do the final relevant tests (SAE check, liver function blood test, pregnancy urine test, Eye testing and a review of concomitant medications). This will be the final visit and the end of your participation in the trial. There is no further follow up beyond this point.

Trial Design

Eligibility *Participant identified by the study team and sent an invite and patient information sheet. If the patient is happy to take part, study coordinator will arrange visit 1.*		
VISIT 1	Informed consent. Screening tests of liver function (blood test), pregnancy (urine), assessment of medical history and visual acuity test.	Screening visit
VISIT 2	Received results of visit 1 tests to ensure eligibility. Randomise to medication or placebo and complete eye tests prior to treatment.	Day 1 on trial
Take placebo/medication for 7 days		
VISIT 3	Complete eye tests to review any change after taking the medication/placebo. We will also do a blood test to check your liver, assess medical history and check for any serious adverse events.	Day 8 on trial
Three weeks break of no treatment		
VISIT 4	You will be given the other treatment you did not receive at Visit 2 (either placebo and or medication) and complete eye tests prior to the next treatment. We will also do a blood test to check your liver, assess medical history and check for any serious adverse events.	Day 29 on trial
Take placebo/medication for 7 days		
VISIT 5	Complete eye tests to review any change after taking the medication/placebo. We will also do a blood test to check your liver, assess medical history and check for any serious adverse events.	Day 36 on Trial
Three weeks break of no treatment		
VISIT 6	For the final visit, you will complete eye tests prior to the next treatment. We will also do a final blood test to check your liver, assess medical history and check for any serious adverse events.	Day 57 on trial
End of trial		

What are the possible benefits of taking part?

Bestrophinopathies can lead to irreversible sight loss and there is presently no proven treatment for this group of conditions. Your participation will be beneficial to this field of research as we plan to develop possible future treatments for this condition. Whilst you may have no personal benefit in taking part in this trial, this research will look to bring benefits to society / others with a similar condition in the future. You will be compensated for your travel when participating in this study as we will cover all reasonable travel expenses with receipts for trial visits.

What are the possible disadvantages and risks of taking part?

Ravicti® (glycerol phenylbutyrate medication which will be used in this trial) is a more acceptable formulation to patients because it is an odourless, tasteless liquid. Ravicti is approved for use in patients from the age of 2 months and other types of the same drug (4PBA (Buphenyl®) have been approved for clinical use since 1996 for other treatments.

Patients have used Ravicti® for other treatments at MFT prior to this study, and although patients have not reported any major side effects, it may be that you experience minor issues when taking the medication but this is likely to be temporary. The most common side effects of taking Ravicti in adults include diarrhoea, flatulence, headache, abdominal pain, vomiting, tiredness, decreased appetite and indigestion or heartburn. See full list of side effects Glycerol phenylbutyrate | Drugs | BNF | NICE (https://bnf.nice.org.uk/drugs/glycerol-phenylbutyrate/)

If you do experience any side effects listed above that you are worried about, you can contact the study team who will be able to discuss your concerns with you.

Do I have to take part?

No, you do not have to take part if you do not wish to, your decision will not affect any standard of care you receive at Manchester University NHS Foundation Trust.

What happens if I change my mind?

Taking part in this study is completely voluntary and if you decide at any point you no longer want to take part you can withdraw from the study and you will continue to receive standard of care within the NHS. If you decide to withdraw whilst taking the medication, we would require you to attend an end of study visit where we might ask you for a blood test to check liver function, pregnancy and PK sample which would check whether the drug is out of your system.

What happens if something goes wrong?

If you have a concern about any aspect of this study, you should ask to speak with the lead researchers who will do their best to answer your questions (**Eva Lenassi, Principal Investigator)**. If you remain unhappy and wish to complain formally, you can do this by contacting local NHS Patient and Liaison Service (PALS) by telephone on 0161 291 5600, which does have a message facility or by email at 'pals@mft.nhs.uk'.

The hospital is insured to carry out clinical research through the NHS Indemnity scheme, however the normal National Health Service complaints procedures should be available to you. In the event that something does go wrong and you are harmed during the research 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 your legal costs.

Who has reviewed this study?

This study is being sponsored by Manchester University NHS Foundation Trust (MFT) and funded by the Medical Research Council (MRC).

All research in the NHS is approved by the Health Research Authority (HRA) and reviewed by an independent group of people called a Research Ethics Committee (REC). The Research Ethics Committee is made up of experts, non-experts, and members of the general public. Together they review research applications to ensure your safety, rights, wellbeing, and dignity are protected at all times.

This study has been reviewed and given favourable opinion by **XXXX**.

What will happen with the results of the study?

Once we have results from the study and have finalised analysis, we plan to present our findings to study participants either in person (should participants wish) or via a patient leaflet. We plan to publish our findings in the form of paper publications. We can direct you to these publications once they are made available to the public. We will not publish or shared any personal data in this publication and only data analysis/anonymised results will be used to support these publications.

Please note that after completing the trial, the drug will not be available to be prescribed and that study doctor will discuss choices for future medical care at the final visit

How will we use information about you?

We will need to use information from you and from your medical records for this research project.

This information will include the following:

- Initials

- NHS number
- Name
- Contact details
- Medical History including test results

Only people in the study team will be able to access and use this information to do the research or to check your records to make sure that the research is being done properly. 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. We will keep all information about you safe and secure.

We will inform your GP that you are taking part in this study. Once we have finished the study, we will keep some of the data so we can check the results during analysis, and no one outside of the MFT research team will be able to access any personalised data about your participation in this study. We will write our reports in a way that no-one can work out that you took part in the study. The information collected about you may be used to support other research in the future and may be shared anonymously with other researchers. This is so any benefit we find in this study can be utilised in other areas of research and potentially lead to future treatments.

What are your choices about how your 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.
- 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.
- 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 you find out more about how your information is used?

You can find out more about how we use your information

- at https://research.cmft.nhs.uk/getting-involved/gdpr-and-research
- by asking one of the research team
- by sending an email to GeneticEyeResearch@mft.nhs.uk
- by ringing us on (0161 701 9138)