Manchester Genomics Research Team
Manchester Centre for Genomic Medicine
St Mary's Hospital
Oxford Road
Manchester
M13 9WL
Email: genetics.research@mft.nhs.uk
Telephone: 0161 276 4542

BETTER Trial

Participant Information Sheet

Bestrophin 1 treatment trial on the effectiveness of Ravicti/BETTER Trial.
(B01914)
Principal 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, a group of inherited retinal disorders leading to sight loss.

Before you decide whether to take part, it is important that you understand why the research is being conducted and what it will involve. Please take time to read the following information carefully before deciding whether to take part. Please ask if there is anything that is not clear or you would like more information. Thank you for taking the time to read this.

What is the purpose of this research?

Bestrophinopathies are a group of inherited retinal disorders that are associated with alterations in the bestrophin 1 protein. They can lead to irreversible sight loss and there is presently no proven treatment for these conditions.

In this study we are testing whether the medication Ravicti® (an odourless, tasteless liquid taken by mouth), can help improve the function of the bestrophin 1 protein in individuals with the two most common types of bestrophinopathy, Autosomal Recessive Bestrophinopathy (ARB) or Best vitelliform macular dystrophy (BVMD).

Why have I been asked to take part?

You have been invited to take part in the BETTER trial because you have a clinical and molecular diagnosis of Autosomal Recessive Bestrophinopathy (ARB) or Best vitelliform macular dystrophy (BVMD).

Am I suitable to take part?

You are suitable to take part if you
(i) are between 18 and 65 years old;
(ii) have a clinical diagnosis of Autosomal Recessive Bestrophinopathy (ARB) or Best vitelliform macular dystrophy (BVMD)
(iii) have vision that is recorded to be better than HM (hand movements) at the time of recruitment
(iii) have no liver disease, you are not pregnant or breastfeeding
(iv) are able to provide informed consent
(v) agree to participate in the study timeline.

Patients attending Manchester University NHS Foundation Trust or The Leeds Teaching Hospitals NHS Trust are eligible to be considered for the trial, taking place at Manchester Centre for Genomic Medicine.

What would taking part involve?

The BETTER trial involves taking orally (by mouth) the trial medication Ravicti® for 7 days. A placebo (i.e. a treatment that has no active properties) will also be taken for another 7 days, either before or after receiving Ravicti®. As part of the trial, you may be contacted by the research team by phone, email or post. A set of tests will be performed to assess if the trial medication has had an effect on the function of the retina at the back of your eye. The study will take around 6-12 weeks and can be thought as having the following two parts.

Part 1

If you decide to participate, we will first determine if you meet the eligibility criteria for the study. To ensure this, you will be invited to attend a screening visit at the Manchester

Centre for Genomic Medicine, 6th Floor, St Mary's Hospital. At this visit, the clinical team will ask about your medical history and assess your vision. A set of blood tests (including a liver function and a pregnancy test) will be conducted.

Once all tests are completed and the results confirm that the eligibility criteria for the trial are met, you will be invited to attend a second visit within 7 days. The main focus of this second appointment would be to conduct a set of eye tests. These will include:

- **an electroretinogram (ERG)**. This is a test that looks at how well the retina is working. It involves recording from sensors (electrodes) placed close to the eye and analysing the electrical signals produced by the retina in response to flashing lights. Part of this test is carried out in the light, and part of it follows a period of 20 minutes adaptation to darkness. The test involves attaching two self-adhesive electrodes to the temples, and a third to the forehead; a fine nylon thread (about the thickness of a hair) is then laid across the lower eyelid so that it rests against the white of the eye. The test takes about 40 minutes and is not painful (although it can sometimes produce a sensation similar to that of an eyelash in the eye).
- **an electroocoulogram (EOG).** This is a test that is used to assess the integrity of the retinal pigment epithelium (RPE), the layer of the retina that nourishes the light-sensitive cells. In addition to the electrodes left in place from the first test, a further two small self-adhesive electrodes are placed on the bridge of the nose. You will then be asked to perform a series of guided eye-movements (in light and dark) over a period of 34 minutes. This test also takes about 40 minutes and is not painful.
- **fundus autofluorescence imaging (FAF)** is a diagnostic test that involves taking digital photographs of the back of the eye.
- **optical coherence tomography (OCT**) is another imaging test that helps us to view the the retina in greater detail.

You will then be selected randomly to either take the trial medication (Ravicti®) or the placebo. You will not know which medication you are going to be taking at different timepoints of the trial. Your study doctor or assessors will not know either. Only the pharmacist dispensing the medication will know in which group you have been assigned to. Both Ravicti and the placebo are an oral liquid medicine that needs to be kept at room temperature. You will be trained on how to dispense the medication.

You will then attend a third visit 7 days after taking your medication. This visit will involve performing another blood test (to recheck liver function) and repeating the eye tests. Subsequently, there will be a three week break of no treatment, called a 'washout' period. There is some flexibility with the washout period from 2 – 5 weeks.

Part 2

After the breakof no treatment, you will attend a fourth visit to repeat the liver function blood tests and the eye tests. Subsequently, you will take the other medication (either

Ravicti® or placebo) for a further 7 days and then attend a fifth visit to review the immediate effects of this medication.

Your final visit will be 2-5 weeks after the last dose of the second medication and will involve performing a liver function blood test, a pregnancy test, and a set of eye tests. This will be the final visit and the end of your participation in the trial. There is no further follow up beyond this point.

Eligibility *Participant identified by the study team and sent an invite and patient information sheet. If the patient is happy to take part, the study coordinator will arrange visit 1 and contact the patient by phone, email or post.*		
VISIT 1	Informed consent. Screening tests including assessment of medical history, liver function blood test, pregnancy test and visual acuity test.	Screening visit
VISIT 2	Review results of visit 1 tests to confirm eligibility. Random assignment to medication or placebo group. Completion of full set of eye tests prior to treatment.	Day 1 on trial
Take placebo/medication for 7 days		
VISIT 3	Repeat the eye tests to evaluate if there is any change after taking the medication/placebo. Perform liver function blood tests, assess medical history and check for any adverse events.	Day 8 on trial
'Washout' Period- Break of no treatment		
VISIT 4	Start taking the treatment that was not received at Visit 2 (either placebo or medication). Repeat the eye tests prior to the next treatment. Perform liver function blood tests, assess medical history and check for any adverse events.	14-35 days after Visit 3
Take placebo/medication for 7 days		
VISIT 5	Repeat the eye tests evaluate if there is any change after taking the medication/placebo. Perform liver function blood tests, assess medical history and check for any adverse events.	7 days after Visit 4

'Washout' Period- Break of no treatment		
VISIT 6	Final visit. Repeat eye tests. Perform liver function blood tests, assess medical history and check for any adverse events.	14-35 days after Visit 5
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 would like 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® is considered an acceptable type of medicine and is an odourless, tasteless liquid. It has been approved for use in patients from the age of 2 months. Notably, a different type of the same drug (4PBA (Buphenyl®) has been approved for clinical use since 1996 for other treatments.

Patients have used Ravicti® for other treatments in our Hospital prior to this study. Although no major side effects have been reported, minor issues may be experienced when taking the medication but these are 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. The full list of side effects can be found here 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 liver function blood test, a pregnancy test and a blood sample which will be used to 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 the North East – Tyne & Wear South Research Ethics Committee.

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 share 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 our Hospital's 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 genetics.research@mft.nhs.uk
- by ringing us on 0161 276 4542