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PARTICIPANT INFORMATION SHEET

IMPase in treatment-resistant depression

We would like to invite you to take part in our research study. Before you decide, it is important that you understand why the research is being done and what it would involve for you. Please take time to read this information and discuss it with others if you wish. If there is anything that is not clear, or if you would like more information, please ask us.

- We are studying a medicine called ebselen in people who have depression, but haven't been helped sufficiently by their current antidepressant medication
- We want to understand if ebselen can alter the way that people react to emotional material delivered by a range of computer tasks
- If you participate we will ask you to take either ebselen or placebo capsules for 7 days. The study will involve coming to the Neurosciences building at the Department of Psychiatry on three occasions-

(i) The first visit will be to assess if you are eligible to take part in the study and will involve taking your medical history and completing some questionnaires. This will take about two hours.

(ii) The second visit (baseline visit) will involve completing the computerised tasks, filling in some questionnaires and having an MRI brain scan. At the end of this visit we will also give you either ebselen or placebo capsules to take at home for seven days. There is a 50% chance of getting one or the other.

(iii) For the third and final visit (post-treatment visit), we will repeat the computerised tasks, questionnaires and the MRI brain scan. We will also ask you for a blood sample, although this is optional.

- You can stop taking part in the study at anytime
- You will get £100 if you complete the study
- Please read the rest of the sheet for more information and do not hesitate to ask if something is not clear.

What is the purpose of the study?

While most patients with depression do well with first line treatment such as psychotherapy or medication, some patients are not helped sufficiently by antidepressant medication (so-called 'treatment resistant depression'). One effective treatment is this situation is to add a drug called lithium to the antidepressant medication. However, lithium has a number of problematic side effects. To replace lithium with other safer drugs we need to have a better understanding of how lithium works biochemically to relieve depression.

One way in which lithium might be working, is by inhibiting an enzyme in the brain called IMPase. IMPase controls the amount of a brain chemical messenger called inositol. Our team at Oxford, have recently been working on an anti-oxidant drug called ebselen, which we have found, like lithium, inhibits IMPase. In animal models and healthy volunteer studies, we have shown that ebselen has some effects similar to lithium but has a better safety profile. The purpose of the present study is therefore to find out whether ebselen has potential antidepressant effects in people not being helped by the antidepressant medication.

To study whether ebselen has potential antidepressant effects we will examine its effects on the way that people respond to emotional material. Our research has shown that drugs that work in depression, affect how people process emotional information. These effects can be found very early on in treatment and predict subsequent antidepressant effect. Therefore, if ebselen shows similar effects to antidepressants in these computerised tasks, it would suggest that ebselen should be pursued as an antidepressant treatment in treatment-resistant depression.

Why have I been invited?

You have been invited to take part because you are aged 18-70 and have symptoms of depression despite having tried at least one antidepressant medication for at least 4 weeks. We believe you have either expressed an interest in hearing more about this study, or have previously expressed an interest in participating in our studies (please do let us know if this is no longer the case), or you have agreed for your treating clinician to pass on your contact details to the study team. In total, we will be recruiting 50 participants with depression.

Do I have to take part?

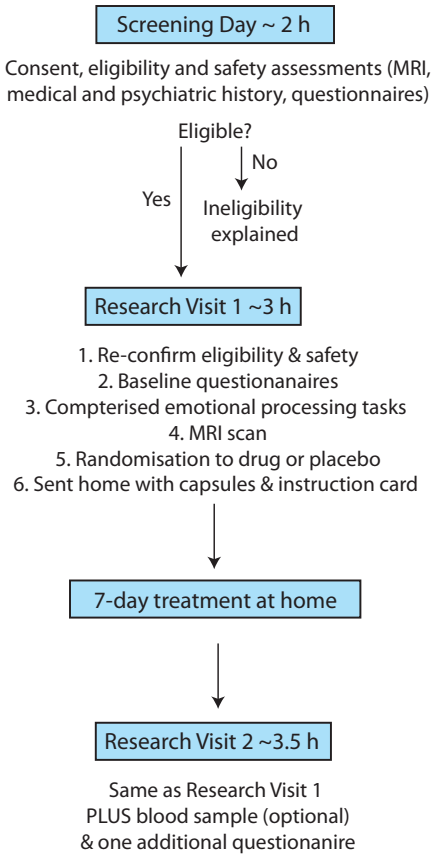
No, taking part in the study is completely voluntary. If you do decide to take part in this study, we will ask you to sign a consent form, but you can still withdraw at any time without giving a reason and with no impact on your normal medical care. You will be able to ask any questions or express any concerns at any point during the study.

What will happen to me if I decide to take part?

If you decide to take part, there will also be an initial telephone conversation to determine your suitability for participation in the study. If suitable, we will invite you to the Warneford Hospital for three visits in total.

1. Screening visit
2. Research visit 1
3. Research visit 2

Please see flow chart below.



Please see details of what each visit involves below.

Screening visit

You will be invited for a Screening Visit at the Neurosciences Building, Warneford Hospital, following on from the initial telephone conversation. The screening process will take about two hours and during this time we will check whether you meet the criteria for participation in our study. This visit is designed to make sure that taking part in the study is safe and appropriate for you, and to ensure that you have a clear understanding of the study procedures.

Once we have explained the study information, we will take your consent and carry on with the study procedures. We will ask you some detailed questions about your mental health, your previous history of treatment for depression, and ask you to fill in some questionnaires about your mood. We will also ask you to fill in an MRI safety screening questionnaire. For female participants we will also perform a pregnancy test; a positive result will mean you will not be able to take part in the study. We will inform you of the results and keep all results confidential. If you are suistable for the study and willing to participate, we will write to your GP informing them of your participation.

Research visit 1

If you meet the study criteria and want to continue, you will be asked to return again to the Neurosciences Building, Warneford Hospital for the first research visit.

This visit will last around three hours in total. At the beginning of the session, we will briefly re-check that you are still suitable to take part (including another urine pregnancy test for female participants and an MRI safety questionnaire), and we will also ask you about any medications you may be currently taking. You will be asked to fill in some questionnaires about your mental health and to complete simple computer-based tasks involving responding to positive and negative pictures of facial expressions, or positive and negative words. Following this we will accompany you to the Oxford Centre for Human Brain Activity (OHBA), which is also based at the Warneford Hospital, to undertake a short brain scan (see below for more details, under 'What is MRI Scanning?'). The scan we will carry out (magnetic resonance spectroscopy or MRS) is a specialised form of MRI and will be used to measure inositol levels in the brain. This will enable us to measure the effect of ebselen/ treatment on the IMPase enzyme.

You will have to lie as still as possible in the scanner for ~ 30-40 minutes. Once scanning is complete, you will be accompanied back to the Neurosciences building, where you will be randomly assigned to take either ebselen (the active drug) or placebo (a dummy capsule), twice a day for 7 days.

You will have a 50% chance of taking ebselen and a 50% chance of taking placebo and neither you, nor the researchers involved will know which group you have been assigned until the end of the studyf. This is in order to prevent any effects that might be caused by treatment expectations. Information about your allocation will be stored securely during the study and 'unblinding' (finding out which group you were in) will only occur if it is thought necessary for medical reasons.

At the end of the visit, you will be given the study capsules with an instruction card of how to take them, and with contact information for one of the researchers, whom you can contact at any time if you have any concerns or if you are experiencing any side-effects.

Treatment Week

During this week you will be required to take the capsules, as per the instructions provided, at home. You will be asked to note down what time each day you took the medicine, and if you felt any side-effects. You can always call us if you have any concerns or queries during the week. If there is any change in your health status or medication use during the week, please inform a member of the study team.

In case there are any scheduling problems with dates, we may extend the treatment period by a maximum of an additional 3 days (so total treatment period of 10 days). But this will be done with your prior knowledge and consent.

Research visit 2

At the end of the 7-day treatment, you will be asked to come back to the Neurosciences building.

This visit will last ~around three and half hours in total. All the study procedures as per Research visit 1 will be repeated (except the urine pregnancy test for female participants), including the questionnaires, computerised and other tasks, and the MRI scan. In addition, we will also request a small blood sample (~2 teaspoons) which we will use to determine drug levels at a later date. Any unused sample will be destroyed. The blood sample is optional, and you do not have to provide one, should you not wish to. We will also ask you to guess, using a percentage scale, if you thought you were on placebo or ebselen.

At the end of the research visit 2, we will take back any unused medication, if any.

Information about the drug used in the study

Ebselen is a selenium containing antioxidant medicine which has been studied in several trials in Japan as a neuroprotective treatment to help people recover from acute stroke. You cannot currently buy it as it is an experimental drug, but it has been used in several clinical trials as well as other experimental medicine studies, which means that it has been through all the safety checks that are required for new medicines.

Results on about 250 patients who took ebselen have been published. The dose used in these studies was 150 mg twice daily for two weeks and no specific unfavourable effects of ebselen were seen compared to placebo. Ebselen was also studied by Sound Pharmaceuticals (Seattle) in single doses up to 1600 mg in 32 healthy volunteers. Ebselen was well tolerated and again, no side effects different to placebo were observed. The reported side effects were dizziness, nausea and headache, which occurred equally in people taking placebo and in those taking ebselen.

A different study used doses of up to 1200 mg daily ebselen for four days for the prevention of hearing loss in 82 healthy participants and no adverse effects were identified.

In Oxford, a clinical trial of ebselen for the treatment of bipolar disorder sponsored by the University of Oxford (CI Prof Philip Cowen) has recently been completed in collaboration with the Oxford Health NHS Foundation Trust. In this study 60 patients experiencing mania or hypomania were given either placebo or ebselen (1200 mg daily for three weeks) in addition to their regular medication. The blind for the study has not currently been broken; however, no serious or unexpected adverse reactions were noted.

In this study we will require you to take 1200 mg of ebselen per day for one week (maximum up to ten days). We will obtain ebselen from Aptuit, Oxfordshire, UK which is a pharmaceutical services company and has manufactured the drug according to standards set by the UK regulations.

Computerised emotional testing

The computerised emotional processing tasks involve testing your responses to positive versus negative faces and words. We will ask you to complete a number of simple, psychological, computerised tasks and some verbal tasks, which will enable us to study the ways in which ebselen affects emotional reactions. These will involve pushing keys in response to words and pictures presented on the screen. The tasks will take about 1.5 hours, but you will be able to rest between the different tasks, if you would like to.

What is MRI scanning?

MRI scanning works by using powerful magnetic fields to examine the tissues of the body. It is used widely in medicine to provide images inside many different parts of the body to help doctors detect diseases or to guide treatments. MRI is a routine procedure that is safe, painless, and involves no ionising radiation (i.e. 'X-rays').

Having an MRI scan involves simply lying still inside the scanner. During this time, you will be made comfortable and you will be able to contact researchers at all times. You will not feel anything, although you will hear some quite loud noises. As some of the scans are noisy, we would give you earplugs to make this quieter for you. It is important that these are fitted correctly as they are designed to protect your hearing.

As well as MRI scans to obtain an image of your brain for research purposes only, we will use a special method called magnetic resonance spectroscopy (MRS), which is designed to measure the levels of brain chemicals in a particular region. Both MRI and MRS are safe, and thousands of people have such scans every year. However, because of the magnetic fields involved, some people are not suitable for MRI scanning (See *Are there any possible disadvantages or risks from taking part?* below).

The scanning will take around 45 minutes altogether. In the scanner, you will be asked to lie on your back and be as still as possible. More information about the MRI scanner is given in the next

section. Whilst in the scanner you will have easy access to a call button should you wish to stop the scan or speak with the radiographer or operator at all times.

What should I consider?

You will not be able to participate in the study if you,

a) have, or have had previously, a diagnosis of bipolar disorder, schizophrenia, or emotionally unstable personality disorder
b) have taken drugs such as antipsychotics or lithium for the treatment of the current episode of depression, or recently had electroconvulsive therapy
c) are currently experiencing suicidal thoughts
d) are currently dependent on drugs or alcohol
e) are currently pregnant, breastfeeding or planning a pregnancy
f) have a Body Mass Index (BMI – kg/m^2) below 18 and above 36
g) are claustrophobic
h) have metallic implants or other devices in your body that make you unsafe to go into the scanner
i) have previously participated in a study using the same, or similar, emotional processing tasks in the last three months
j) have participated in a research study involving the use of medication in the last three months
k) have any planned medical treatment during the duration of the study that might interfere with study procedures

Birth control requirements

The effects of the study drug on an unborn baby or when given to a pregnant woman have not been fully investigated. Therefore, pregnant women or women planning a pregnancy during the study must not take part. During the study, both men and women must use a highly effective method of contraception if engaging in sex with risk of pregnancy, starting from Visit 1 (Screening Visit) until 30 days after receiving the study treatment. Female participants must not breastfeed, and male participants must not donate sperm. The researchers will confirm acceptable forms of contraception with you.

Advice for the week of study treatment

For the duration that you are on the study drug, we advise you not to drink alcohol. As this is an investigational drug, we do not know if the drug can be affected by alcohol and therefore, as a precaution, we would advise against it.

Future research participation

We will ask you if you would like to be contacted about research participation in the future; this is completely optional and does not affect your involvement in the current research project. Agreeing to be contacted does not oblige you to take part in any future studies.

Are there any possible disadvantages or risks from taking part?

Questionnaires: Sometimes clinical interviews and psychological questionnaires can ask for information that might be potentially upsetting (for example, information about your mood). All clinical assessments will be performed by a trained researcher who can provide adequate information and treat any sensitive issues with care. You are under no obligation to answer the questions if they make you uncomfortable. We will also do our best to make you feel as comfortable as possible throughout the whole study.

Emotional processing tasks: The computerised tasks involving emotional processing have been extensively used in many previous studies with no adverse effects. It is unlikely that you will find any task distressing; you can however cease testing at any time if you do find it unpleasant or too tiring.

MRI: The MRI brain scan is a safe procedure that does not involve exposing you to any radiations. However, because they use a large powerful magnet to work, MRI scanners are not suitable for everybody. Because of this, you will be asked pre-screening safety questions to help determine if you are able to take part. Normally, MRI scanning for research purposes would not be performed without further investigation if you have a heart pacemaker, mechanical heart valve, mechanical implant such as an aneurysm clip, hip replacement, or if you carry other pieces of metal that have accidentally entered your body. Also, if you suffer from claustrophobia, you may find being scanned difficult. If you think you might be claustrophobic, please discuss this in advance with the researcher, or let the radiographer or operator know before your scan.

In preparation for your scan and for your comfort and safety we will ask you to change into pocket-less and metal free 'pyjama-style' top and trousers. You may keep your underwear and socks on, but we would ask women to remove underwired bras; if you have a suitable non-wired bra you may wear this instead. Please avoid any fabrics that contain metallic threads or have been silver impregnated (often marketed as sport, anti-microbial/bacterial, or anti-odour). Metal jewellery including body piercing must also be removed. Eye shadow and mascara must also be avoided, since some types contain materials that can interact with the magnetic field. If you wish to wear eye makeup to your scan we can provide makeup removal wipes but you are advised to bring your own makeup to reapply. Lockers are provided to secure your personal belongings and clothing. You will be introduced carefully to the scanner and allowed to leave at any stage.

While there is no evidence to suggest that MRI is harmful to unborn babies, as a precaution, the Department of Health advises against scanning pregnant women unless there is a clinical benefit; a pregnancy test will be done during your Screening Visit and then again on Research Visit 1. As some of the scans are noisy, we will give you earplugs to make this quieter for you. It is important that these are fitted correctly as they are designed to protect your hearing.

It is important to note that we do not carry out scans for diagnostic purposes, and therefore these scans are not a substitute for a doctor's appointment. Our scans are not routinely looked at by a doctor; rather our scans are intended for research purposes only. Occasionally a possible abnormality may be detected. In this case, we would have the scan checked by a doctor. If the doctor felt that the abnormality was medically important, you would be contacted directly and recommended to have a hospital (NHS) diagnostic scan arranged. All information about you is kept strictly confidential.

Blood sample: Although taking blood is a very safe procedure, it can sometimes be uncomfortable and may result in localised bruising. Only trained staff members will take blood, and pressure will be applied afterwards to minimise any bruising.

Drug: Potential side-effects from the drug will be monitored throughout the treatment. Previous studies have reported side effects such as dizziness, nausea and headache, which occurred at a similar frequency in people taking placebo and in those taking ebselen. The purpose of the screening visit is to make sure that it is safe for you to take the study medication. If you experience any side-effects during the course of the study, you should contact the research team or your GP immediately.

What are the possible benefits of taking part?

The study will not be of direct benefit to you, but we hope that the information we obtain will help improve the treatment of depression.

Will my General Practitioner/family doctor (GP) be informed of my participation?

After the screening session we will contact your GP to inform them that you are taking part in the study and to provide them with contact details and this information sheet in case they know of any reason why you should not complete the study; this is to help ensure your safety and well-being. Additionally, any relevant medical information identified during the study procedures that requires follow-up will be passed on to your GP, only after discussion with you and if you give permission.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence.

Your data will be collected by clinical researchers and de-identifiable, which means that it will be

coded and only the study investigators will have access to the code. All the investigators have a duty of confidentiality towards you, exactly as in usual medical practice. Responsible members of the University of Oxford, Host Institution or appropriate regulatory authorities may be given access to data for monitoring and/or audit of the study to ensure we are complying with regulations. All will have a duty of confidentiality to you as a research participant. In addition, we would like to contact your Clinical Care Team/GP to inform them of your participation in the study. All study data will be stored for a minimum of ten years and then disposed of securely.

Your personal contact details will be stored in paper format, separately from your de-identifiable data and retained until the research is published. We will also be storing samples in a de-identifiable form to certified laboratories or companies for drug level analysis in this project. The overall results of the study may be published in scientific journals. However, all personal data will remain confidential, and no data relating to individual participants will be published.

Further information about your rights with respect to your personal data is available at http://www.admin.ox.ac.uk/councilsec/compliance/gdpr/individualrights/]. You can find out more about how we use your information by contacting our study team (email: Nisha.singh@psych.ox.ac.uk or telephone: 01865 6182224) or Professor Philip Cowen (Email: phil.cowen@psych.ox.ac.uk or telephone: 01865 618311).

Will I be reimbursed for taking part?

Upon completion of all your visits you will receive £100 for your participation in the research. In case you are screened but do not fulfil the study criteria, you will still be reimbursed £25 for your time. Also, if you complete the Screening visit and Research Visit 1, but not Research Visit 2, you will be reimbursed £50 for your time. Reasonable travel expenses will also be reimbursed on production of receipts, or a mileage allowance will be provided as appropriate.

What will happen to the samples I give?

Anonymised blood samples will be processed in the Neurosciences building on the same day as they are collected to separate the plasma from the blood cells. The plasma will then be frozen and shipped to another laboratory or a commercial company at a later date for the analysis of drug levels. Any excess sample will be disposed of.

What will happen to my data?

University of Oxford is the sponsor for this study based in the United Kingdom. We will be using information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Oxford will keep identifiable information about you for 10 years after the study has finished

Data protection regulation requires that we state the legal basis for processing information about you. In the case of research, this is 'a task in the public interest.' The University of Oxford is the data controller and is responsible for looking after your information and using it properly.

We will keep identifiable information about you for 6-12 months after the study has finished. This excludes any research documents with personal information, such as consent forms, which will be held securely at the University of Oxford for 10 years after the end of the study. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. Oxford Health NHS Foundation Trust and the Department of Psychiatry, University of Oxford will collect information from you and/or your medical records for this research study in accordance with our instructions.

Oxford Health NHS Foundation Trust will use your name, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from the University of Oxford and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The Department of Psychiatry, University of Oxford will pass these details to the University of Oxford along with the information collected from you and/or your medical records. The only people in the University of Oxford who will have access to information that identifies you will be people who need to contact you to for safety reasons or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details. De-identified research data may be shared with academic or industrial collaborators in and outside the EU.

What will happen if I don't want to carry on with the study?

You can withdraw from this study at any time, without explanation. If you do withdraw from the study, we will remove and securely destroy your data. If you withdraw from the study after completing the

7 days of treatment we may request to keep and analyse your data. Withdrawing from the study will not have any impact on your standard medical care.

What will happen to the results of this study?

We hope to publish the results of the study in the scientific literature. You will not be identified in the publication. The results of the study may also be posted on the Departmental and University websites and presented at conferences (again in such a way that no individual could be identified.) We will be happy to send you a summary of the results of the study via email, or post if you wish.

What if there is a problem?

The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study. If you wish to complain about any aspect of the way in which you have been approached or treated, or how your information is handled during the course of this study, you should contact Professor Philip Cowen (email: phil.cowen@psych.ox.ac.uk or telephone: 01865 618311) or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 616480, or the head of CTRG, email ctrg@admin.ox.ac.uk. The Patient Advisory Liaison Service (PALS) is a confidential NHS service that can provide you with support for any complaints or queries you may have regarding the care you receive as an NHS patient. PALS is unable to provide information about this research study. If you wish to contact the PALS team please contact : 0800 328 7971, via email: PALS@oxfordhealth.nhs.uk.

How have patients and the public been involved in this study?

In designing this study, we have taken into account previous patient opinions on the frequency of participant visits and the tests that we will carry out.

Who is organising and funding the study?

The study is sponsored by the University of Oxford and is funded by grants from the Medical Research Council. The researchers are not being paid specifically for including you in this study. Please note that because this is a University research study, you will not be under NHS care during the study; your participation is for research purposes only.

Professor Cowen (with scientists from the Department of Pharmacology) is named as an inventor on a University patent for the use of ebselen in treatment resistant depression which is currently pending approval. While Professor Cowen therefore has a potential conflict of interest, the integrity of this trial is maintained by the statistical team and the data analysts who are not listed on the patent and have no potential conflicts of interest.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect participants' interests. This study has been reviewed and given favourable opinion by _____Research Ethics Committee.

Participation in future research:

If you have agreed to be contacted about future research participation, we will hold your personal contact details separately from this study on an encrypted hard drive. This will be stored securely in a locked filing cabinet in a room that is locked when unoccupied and will be accessible by named researchers only. These data will be destroyed 10 years after the end of the study. All potential contact will come from the research team in the first instance. Agreeing to be contacted does not oblige you to take part in future research, and you can be removed from this register at any time if you wish.

Further information and contact details:

Thank you for reading this information sheet. If you have any questions please get in touch with Nisha Singh: 01865-618224 or nisha.singh@psych.ox.ac.uk

Professor Philip Cowen, Professor of Psychopharmacology
Professor Catherine Harmer, Professor of Cognitive Neuroscience
Dr Nisha Singh, Senior Postdoctoral Researcher in Psychopharmacology
Dr Beata Godlewska, Research Psychiatrist

Thank you for considering taking part.