INFORMATION SHEET FOR PARTICIPANTS

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YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET TO KEEP

STUDY TITLE: 'TRANSLATIONAL VALIDATION OF $5HT_7$ ANTAGONISTS AS A TREATMENT FOR COGNITIVE IMPAIRMENT IN BIPOLAR DISORDER: A PROOF OF PRINCIPLE NEUROIMAGING STUDY'

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Invitation to take part

We would like to invite you to participate in this research study. Please only participate if you want to; choosing not to take part will not disadvantage you in any way. It is important that you understand why the research is being done, and what your participation will involve before deciding whether to take part. Please take time to read the following information carefully and discuss it with others including your GP, if you wish. Ask us if there is anything that is not clear or if you would like more information.

Thank you for reading this information.

What is the purpose of the study?

Bipolar disorder is a serious mental health problem in which people experience repeated episodes of depression and elevated mood. Around 60% of people with bipolar disorder experience problems with their attention and memory, known as cognitive impairment, which greatly affects the ability to work and hold relationships. Currently there are no effective drug treatments for cognitive impairment experienced by people with bipolar disorder.

Medications which block a type of brain chemical receptor, called the $5HT_7$ receptor, may be a promising new treatment for cognitive impairment experienced by people with bipolar disorder. The purpose of this study is to understand how blocking the $5HT_7$ receptor using an investigational drug called JNJ-18038683 can change brain function in people with bipolar disorder and

also in healthy people. JNJ-18038683 is not currently licensed for use in patients. In this study, we will investigate how blocking the $5HT_7$ receptor changes brain function by asking participants to take two 10 mg JNJ-18038683 tablets or two placebo tablets every morning at around 9am for one week. A placebo is a tablet that has no active drug effect. After one week of each type of treatment (JNJ-18038683 or placebo), we will invite people taking part in this study to have a brain scan called a Magnetic Resonance Imaging (MRI) scan (see page 3). We will obtain images of both the structure and function of the brain. Structural images provide detailed information about the brain anatomy, whilst functional images show us which areas of the brain might be involved when performing specific thinking tasks.

We will ask people taking part in the study to perform thinking and mood tasks whilst being scanned in the MRI scanner. We will then compare differences in brain function shown on the scan whilst taking JNJ-18038683 or placebo. This will allow us to examine how blocking $5HT_7$ receptors in the brain changes brain activity and cognitive function. We hope this study will help us to understand how blocking $5HT_7$ receptors changes brain activations in people with bipolar disorder and healthy people. This may allow us to better understand whether $5HT_7$ blockers may be a potential treatment for cognitive impairment in people with bipolar disorder.

What will taking part involve?

Taking part in the study involves attending 4 study visits:

- Visit 1: A screening visit (to assess whether you are suitable for the study).
- Visit 2: A baseline visit where we will assess your attention, memory, concentration and mood before starting the study medications.
- Visit's 3 & 4: Two imaging visits where you will have an MRI scan to assess the effects of study medications on brain function, and also where we will assess your attention, memory function, concentration and mood.

You will take two 10mg JNJ-18038683 tablets every morning for one week and two placebo tablets every morning for one week, with a two-week period between each treatment to allow the study medications to leave your system. Neither you nor the study team will know which treatment is JNJ-18038683 and which is placebo until all the participants have finished the study.

The study visits are described in more detail below:

Visit 1: Screening Visit

You will be asked to attend a screening session lasting approximately 2 hours to ensure that you are suitable to take part in the study. You will be asked to sign a consent form and we will ask you some questions about your past and current medical and mental health history. A doctor will perform a physical examination to ensure that you are fit and healthy. Measurements taken will include blood pressure, heart rate, ECG (tracing of your heart), analysis of urine and taking a blood sample. We will also ask you to complete questionnaires about your mood, memory performance and personality. If you are not eligible to enter the study after the screening assessment we will destroy your information.

Visit 2: Baseline Visit

This visit will last for approximately 2½ hours. During this visit, we will repeat the physical examination, including blood pressure, heart rate, ECG (tracing of your heart), and analysis of urine and blood samples, to ensure that your health hasn't changed since the screening visit and that you are still suitable to participate in the study. Women of childbearing potential will also have a urine pregnancy test. We will then ask you to complete some questionnaires which assess your mood, other aspects of your mental/emotional functioning, and your sleep. You will also complete some detailed tests of your memory, attention and concentration with a researcher.

At the end of the visit, you will then be provided with the first week of the study medication and a study diary. We will ask you to use the study diary to record that you have taken the medication each day and whether you experienced any side effects. We will ask you to start the study medication at 9am the morning after the baseline visit. A researcher will also call you within 24 hours of starting the medication to ask you whether you have experienced any problems after taking the first day of medication.

Visit's 3 & 4: Imaging visits

Each of these visits will take place on your seventh day of taking the study medications (JNJ-18038683 or placebo) and will last around 4½ hours. At the start of each visit we will do a brief physical examination, including blood pressure, heart rate, ECG and analysis of urine and blood samples, to check your health. We will then ask you complete mood, sleep and overall mental/emotional functioning questionnaires and repeat the tests of your memory, attention and concentration. You will then be asked to have an MRI scan which will last about 1¼ hours. The scanner is made up of a large magnet with a central tunnel which you lie inside during the scan. The scanner uses changes in magnetic fields to obtain a precise picture of your brain. For further details of what having an MRI is like, please click on: https://www.youtube.com/watch?v=6vtKS-MA5n4

Whilst lying inside the MRI scanner you will be asked to complete computer tasks which will appear on a small screen. Using a hand-held response pad, you will be asked to respond to visual information presented to you on the screen. The exact nature of the tasks will be explained to you before the scan, and if necessary you can practice performing the task outside of the scanner. These tasks are designed to test your memory and emotional processing.

When the scanner is on it makes a loud knocking noise, so you will be provided with headphones to wear during the session. The scan can be stopped at any point if you feel uncomfortable. We will also give you an alarm buzzer to press if at any time you feel that you need to come out of the scanner.

Following the scan, a doctor will carry out a brief physical examination and you will then go home as long as the study clinician has decided that it is safe for you to leave. Three weeks later, on day 7 of your second course of study medications, you will be invited to attend the centre again where we will ask you to complete the same procedures as visit 3. 14 days after the final study visit, you will receive a phone call from one of the study investigators to check your health.

Why have I been invited to take part?

We are inviting people with bipolar disorder and healthy people with no history of mental health problems to be involved in this study.

Do I have to take part?

Participation is completely voluntary. You do not have to take part. You should read this information sheet and if you have any questions you should ask the research team. You should not agree to take part in this research until you have had all your questions answered satisfactorily.

What restrictions do I need to follow during the study?

You'll be asked to not drink alcohol for 24 hours before each study visit. Before to coming to the unit for your study visit you may have a light breakfast. We will provide you with a light lunch on during each imaging visit. You will also have to abstain from caffeine during each study visit until you have completed all tests.

Are there any reasons why I can't take part in the study?

The following reasons are likely to mean you can't take part in the study:

- If you have, or have had, any serious medical or neurological conditions
- If you have a history of major psychiatric disorder, such as major depressive disorder, autism, or attention deficit-hyperactivity disorder (with the exception of bipolar disorder for participants with bipolar disorder).
- If you are currently taking any of the following medications listed below: alprenolol, amitriptyline, amphetamine, aripiprazole, atomoxetine, bufuralol, carisoprodol, carvedilol, chloramphenicol, chlorpheniramine, chlorpromazine, citalopram, clomipramine, clonidine, clopidogrel, codeine, cyclophosphamide, debrisoquine, desipramine, dexflenfluramine, dextromethorphan, diazepam, donepezil, duloxetine, encainide, esomprazole, flecainide, fluoxetine, fluvoxamine, haloperidol, hexobarbital, imipramine, indomethacin, isocarboxazid, labetalol, lansoprazole, lidocaine, lurasidone, methoxyamphetamine, metoclopramide, mexilletine, minaprine, moclobemide, nebivolol, nelfinavir, nilutamide, norphenytoin, nortriptyline, omeprazole, ondansetron, oxycodone, pantoprazole, paroxetine, perhexiline, perphenazine, phenacetin, phenelzine, phenformin, phenobarbitone, phenytoin, primidone, progesterone, proguanil, promethazine, propafenone, propafenone, propranolol, propranolol, R-mephobarbital, rabeprazole, risperidone, S-mephenytoin, S-metoprolol, sparteine, tamoxifen, teniposide, thioridazine, timolol, tramadol, tranylcypromine, venlafaxine, voriconazole, vortioxetine, warfarin, zuclopenthixol.

If you are planning to use these medications after participating in the study you must be willing to commit to not starting them until two weeks after completing the study. If you are unsure, you should discuss this with your GP or psychiatrist prior to beginning the study.

- If you are allergic to JNJ-18038683 or other medications with $5HT_7$ antagonist properties such as lurasidone (Latuda) or vortioxetine (Trintellix).

- If you have taken part in a research study involving administration of an experimental drug within the last 3 months or plan to do so up to two weeks after completing the study.
- If you are currently regularly using recreational drugs such as cannabis or cocaine.
- For women: if you are currently not using an effective contraceptive method, plan to get pregnant in the next three months, or if you are currently pregnant or breast feeding.
- If you have any metallic or electronic objects in your body, e.g. pacemaker, cochlear ear implants, fixed dental braces.
- If you have a history of history of claustrophobia or are unable to lie still in a MRI scanner for a period of around 1¼ hours.
- If you weight more than 126kg (19 stone 12 pounds)
- For people with bipolar disorder: if there is likely to be a change in dose or type of your regularly prescribed mental health medications the month before the screening visit or a likely change during your participation in the study.
- For healthy people: if you have a family history of severe mental illness such as psychosis, bipolar disorder or schizophrenia.

For your own safety, it is vital that you tell us about any illnesses you have, or have had, any medications that you are taking, and whether any of the above applies to you.

Are there any side effects associated with JNJ-18038683?

JNJ-18038683 is an investigational drug and there may be unknown side effects associated with its use. Initial studies which examined safety and side effects (known as phase 1 studies) in healthy people found that side effects occur in those who took JNJ-18038683 and also occur in those who took a placebo. In general, side effects reported for JNJ-18038683 were mild to moderate in severity. These studies investigated drug effects in groups of 7-14 participants. The following side effects, which occurred more frequently in one or more people taking JNJ-18038683 at a dose of 20mg or less compared to people taking placebo, were reported: tiredness, dizziness, headache, drop in blood pressure when standing up, increased heart rate when standing up, abdominal pain, nausea, constipation, feeling physically weak, chest pain, symptoms of a cold/nasal congestion, fatigue, feeling cold, insomnia, muscle pain, joint pain, back pain and increased rates of skin reaction to ECG stickers.

A larger study, which examined the effects of JNJ-18038683 in people with depression, found that JNJ-18038683 had acceptable tolerability at the dose we plan to use. None of the 73 participants treated with 10mg JNJ-18038683 for one week and then 20mg for 6 weeks, experienced serious side effects.

Side effects that were reported more commonly in people treated with JNJ-18038683 than with placebo include indigestion, constipation, upper respiratory tract infections (for example colds and flu) and palpitations (heartbeats that suddenly become more noticeable). These side effects were usually mild to moderate in severity. This study also found a slightly increased heart rate and a slightly decreased blood pressure in people treated JNJ-18038683.

In case you experience side effects, we will provide you with a contact card when you receive the medication that will include an out of hour's phone number so that you can contact a study clinician for advice, in case of emergency or if you begin to feel unwell.

If you experience an emergency, please call 999 or 112 immediately for assistance.

Pregnancy

It is important that women who take part in the study do not become pregnant during the study, and that partners of men who take part in the study also do not become pregnant during the study. This is because there have been no studies into the effect of the JNJ-18038683 in pregnancy or on male sperm function. Adequate contraception must be used during the study and continue for 3 months after the study is over.

What are the side effects from the scanner?

The scan itself is not believed to have any side effects. However, the scanner is enclosed and people who suffer from claustrophobia may find it uncomfortable or unacceptable.

What are the possible disadvantages and risks of taking part?

You may experience side effects when taking JNJ-18038683 as described above. It can be slightly uncomfortable when you have your blood taken – but it is the same procedure that would be used in an NHS clinic or at your doctor's surgery. The MRI scanner is operated within Medicines and Healthcare Products Regulatory Agency (MHRA) guidelines. This technique uses a large magnet and radio-waves. It is not believed to have any risk associated with it, although it is necessary to keep metallic objects away from the magnet.

You should be aware that there is a possibility that your participation in the study and the study tests may reveal an unexpected result that may have relevance for your physical or mental health. In the unlikely event of this happening, we will discuss this with you and, if necessary, contact your GP to

arrange follow-up or in an emergency ensure that you are assessed by an Accident and Emergency department.

What are the possible benefits from taking part?

There is no specific direct benefit to you from taking part in the study; however, the main advantage of this research is that participants will be taking part in an important research study that could provide important new information on cognitive impairment in bipolar disorder. You will also be financially compensated for your time.

Will I be compensated for my travel expenses and time?

You will be paid £200 to compensate you for your time if you complete the study. We will also reimburse reasonable travel expenses and provide you with a light lunch during imaging sessions. If you do not complete all the study visits, we will pay you pro rata for your time.

What if new information becomes available?

If unexpected information of potential clinical importance is found during the study we will discuss the matter with you and, if you give your permission, refer the matter to your GP or any other appropriate health care worker.

Will my taking part be kept confidential?

What you tell us about yourself during the study is regarded as strictly confidential and any information you provide will be held securely. Your participation is entirely voluntary. If you change your mind during the time you are participating in the study, you are free to stop your participation and to have your data withdrawn from the study, and destroyed, without giving any reason, until the completion of all data analysis. All data for analysis will be anonymised or in coded form, with any decoders kept separately in locked cabinets within a locked room or in encrypted Microsoft excel files on password protected computers. Imaging data will be stored on the Department of Neuroimaging, King’s College London image processing network in coded form, which also requires login details for access. Participant codes may include initials.

When we report the results of the study, we will not reveal the names of any participants or any other personal details. We may share coded anonymised data from this study with our study collaborators, Janssen Research and Development LLC, and external partners. When coded data are shared, the key to the code will remain at King's College London and the key to the code will not be provided to Janssen Research and Development, LLC, its affiliates or any other research partners. At all times, there will be no possibility of you

as individuals being personally linked with study data to those outside the study team.

The General Data Protection Regulation (GDPR) and the 2018 UK Data Protection Act will apply to all information provided by participants during the study and will be held on password-locked computer files and locked cabinets in locked offices within King's College London. No study data will be able to be linked back to any individual taking part in the study.

King's College London is the sponsor for this study based in the United Kingdom. We will be using information from you 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. King's College London will keep identifiable information about you for seven years after the study has finished.

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.

You can find out more about how we use your information at https://www.hra.nhs.uk/information-about-patients/.

King's College London will use your name 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 King's College London and regulatory organisations may look at your medical and research records to check the accuracy of the research study. South London and Maudsley NHS foundation trust will pass these details to King's College London along with the information collected from you. The only people in King's College London who will have access to information that identifies you will be people who need to contact you for study purposes 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, contact details, or other information.

What will happen to any samples I give?

Blood samples will be stored at the Centre for Neuroimaging Sciences at King's College London where they will be processed and stored securely until the end of the study. After the blood samples have been analysed for specific research purposes, they will be disposed in accordance with the Human Tissue

Authority's Code of Practice. Only the research team will have access to your samples (which will be only identifiable by a unique identification number). Blood samples may be used to measure JNJ-18038683 blood levels on each imaging visit day. Blood samples may also be used to analyse DNA to determine bipolar disorder polygenic risk scores. Urine samples will be destroyed on each study day after urine drug tests and urinalysis safety assessments have been completed.

How is the project being funded?

The project is being funded by the Medical Research Council, UK. Janssen Research and Development LLC are providing the study medications (JNJ-18038683 and placebo).

What will happen to the results of the study?

We will produce a final report summarising the main findings at the end of the study, which will be sent to you at your request. We also plan to communicate the study findings through publication in scientific journals and presentations at conferences.

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 your interests. This study has been reviewed and given favourable opinion by the London - Camberwell St Giles Research Ethics Committee.

Other Compensation Arrangements

The Sponsor, King's College London, will at all times maintain adequate insurance in relation to the study through its own professional indemnity, and has made arrangements to cover no-fault compensation for harm as a result of the study that could not be anticipated. This does not affect your legal rights to seek compensation, if you are harmed due to someone's negligence.

Complaints

If this study has harmed you in any way or if you wish to make a complaint about the conduct of the study, complaints to the IoPPN should be addressed to Dr Gill Dale. Director of Research Quality; Head, Joint R&D Office of South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology & Neuroscience (IoPPN), P005, Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King's College London, De Crespigny Park, London SE5 8AF.

For complaints to the NHS, the NHS complaints mechanism should be used. The Patient Advice and Liaison Service (PALS) provides advice and information about the NHS services. Complaints should be addressed to PALS, 0800 731 2864 or pals@slam.nhs.uk

What if I have further questions?

If you have any questions or require more information about this study, please contact:

Dr Natalie Gottlieb,
Centre for Affective Disorders,
Institute of Psychiatry, Psychology and Neuroscience Email:
5HT7study@kcl.ac.uk
Telephone: 07725 179208

Thank you for reading this information sheet and for considering taking part in this research