TO BE PRINTED ON HEADED PAPER

PARTICIPANT INFORMATION SHEET & INFORMED CONSENT FORM

Trial Title: A randomised, placebo-controlled, double-blind trial of the antidepressant efficacy of a novel CNS-penetrant P2X7 receptor antagonist, JNJ-54175446, in people with major depressive disorder, an incomplete response to monoaminergic antidepressant drugs, and a biomarker profile predictive of active P2X7 signalling

(Short Title: ATP - **A**ntidepressant **T**rial with **P**2X7 Antagonist

JNJ-54175446)

You are being invited to take part in a research trial. Before deciding whether to take part, you need to understand why this research is being done and what it involves. Please take time to read the following information carefully and talk to others about the trial if you wish. Please ask us if anything is not clear or if you would like more information. Please take time to decide whether or not you wish to take part.

Section 1 tells you the purpose of this trial and what will happen to you if you take part.

Section 2 gives you more detailed information about the conduct of the trial.

Section 1: Purpose of the trial and what will happen

1. What is the purpose of the trial?

Depression affects over 300 million people globally and is one of the main causes of severe disability. Symptoms of depression often persist despite adequate antidepressant drug therapy, possibly because currently available antidepressant drugs have a similar mechanism of action. It is therefore important to identify new treatments that work in a different way.

There is evidence to suggest that some patients with depression have increased levels of inflammation in the body. Animal studies support the link between increased inflammation and the development of a range of depressive symptoms. Hence, it is suggested that anti-inflammatory mechanisms may offer a new approach to treating depression.

This trial (**ATP)** aims to test whether a new anti-inflammatory drug has the potential to treat patients suffering from depression who have not responded to their current medications. This will be carried out using a series of questionnaires and clinical assessments. We also wish to find out how the drug affects the body by measuring the levels of biomarkers in your blood and saliva. A biomarker is a biological molecule in the body tissues, blood or other bodily fluids that can be measured and can be used to indicate whether a process is as expected or not. We will also take images of your brain to assess the effects of the drug on the brain structure and function.

2 What is the drug being tested?

The drug being tested in this trial is JNJ-54175546, developed by Janssen Pharmaceuticals, which blocks the activity of the P2X7 receptor. The P2X7 receptor is produced by immune cells in the brain. Laboratory experiments have shown that the P2X7 receptor can trigger inflammation and drugs that block the P2X7 receptor can

reduce inflammatory activation of immune cells. We believe that inflammation of the brain can cause depression in some people and that JNJ-54175446 may have anti-depressant effects by blocking the inflammatory response of immune cells in the brain. However, we don't yet know that JNJ-54175446 will reduce inflammation in humans.

JNJ-54175446 is an unlicensed drug and is not available as a treatment outside of clinical trials. It has been tested in 6 studies with healthy men and women, and in 1 trial with patients with depression. Approximately 300 people have received the drug so far.

3 Why have I been invited?

If you have been invited to participate in this trial, it is because you have previously been diagnosed with depression, which continues despite standard drug treatment.

We plan to include about 142 participants from 5 centres across the UK.

4 Do I have to take part?

Participating in this trial is completely voluntary. If you decide to participate you will be asked to sign an Informed Consent Form, however you are still free to change your mind and leave the trial at any time without giving a reason. If you choose not to participate or to leave the trial, your future medical treatment and normal standard of care will not be affected in any way.

5. What will happen to me if I take part?

If you are interested in taking part, you will be asked to answer pre-screening questions which will allow the research team to assess your eligibility. The research team will call you to discuss your participation, potential eligibility (through a series of general health and drug usage questions) and answer any queries you may have.

If you agree to participate in the trial, you will attend a screening clinic visit. At this visit you will be asked to sign the Informed Consent Form at the end of this document and will be given a copy to take away and refer to later. After you have signed the Informed Consent Form, you will undergo various screening assessments to check that you are eligible to take part in this trial. See Trial Schedule section below for more details.

If you are eligible to take part, you will be allocated to one of the two groups in the trial. One group will receive 50mg/day of JNJ-54175446 and the other group will receive a placebo. A placebo is a dummy drug that looks like the trial drug and is given the same way but will contain no active ingredients and will have no effect on you. You will be asked to take 1 capsule (50mg) a day for 8 weeks.

You will be allocated to only one of the treatment groups throughout the trial. This allocation will be done in a random way (by chance), much like flipping a coin. You will have a 50% chance of receiving JNJ-54175446.

The trial is double-blinded, which means that neither you nor your research team will know which treatment you are receiving. However, if for medical reasons your research team needs to find out which treatment you are receiving, they will be able to do so.

From this point onwards, both JNJ-54175446 and placebo will be referred to as ‘trial drug’.

During the treatment period, you will attend 3 clinic visits. After the treatment period, you will attend a follow-up visit around 7 to 14 days after your last dose. As JNJ-

54175446 is currently unlicensed, once you have completed the trial you will no longer have access to the trial drug.

Trial schedule

For further details about individual tests and what they involve, please see the Trial Procedures section below.

In the light of the Covid-19 pandemic, your trial team will contact you by phone/email prior to every visit to check that you are well enough to attend and do not require quarantine due to Covid-19. You and your trial team will also take the necessary safety precautions according to national and local guidelines, such as social distancing.

Screening clinic visit

The screening visit will last about 4 hours.

The trial team will discuss the trial with you and answer any questions you have. If you are still keen to take part, you will sign the Informed Consent form and proceed with the assessments listed below.

The screening visit will include:

- An assessment of your depression, mental health and stress levels
- A physical examination will be carried out to assess your health status.
- Measurement of your height and weight for calculation of body mass index (BMI).
- Alcohol breath test
- Blood sample collection for:
  - Clinical safety tests
  - Genetic analysis (to look at the P2X7 receptor) and an inflammation biomarker test (to look at C-reactive protein or CRP)
  - Pregnancy test (if applicable)
- Urine collection for:
  - Safety tests
  - Recreational drugs screening
- Review of your medical history (the research team will ask you about your medical and psychiatric history, including any family history of depression.)
- Demographic data collection (month and year of your birth), age, gender and ethnicity.), occupation and marital status
- 12-lead electrocardiogram (ECG) measurements (x 3)
- Measurement of vital signs including blood pressure, pulse/heart rate, and body temperature.
- Review of medications and other therapies: You and your trial doctor will review the medication(s) you are currently taking and which antidepressant medications you have already taken in the past, and any other therapies you are undergoing.
- Training on the use of activity monitoring device
- Instructions for the collection of saliva samples

During the screening visit we might find you are ineligible to take part. In that case, we will conclude the screening process as soon as we establish that you are not eligible.

In any case, at the end of the visit we will provide you with an expenses claim form for the completion of the screening visit.

Post screening telephone call

Once we are able to confirm your eligibility including receiving your laboratory results, a member of the research team will call to inform you whether or not you are eligible to take part in the trial. This will be available around 5 to 20 days after your screening clinic visit.

Please note that there is a 50% chance that you will not be eligible to take part due to low CRP levels. In that case, we will not carry out genetic analysis of your P2X7 receptor.

At this point, **if you are eligible**, we will post you a saliva collection pack, an activity monitoring device, a guide to using the activity monitor. Please wear the activity monitor once you have received it. You will also have to collect your saliva samples on any day within 3 days before your next clinic visit and bring the samples to your next clinic visit.

If you are not eligible to take part, you will return to your standard care.

Treatment Phase

During the treatment phase, you will attend 3 clinic visits. Visits are planned for Day 1 (Visit 1), around Day 28 (Visit 2) and Day 56 (Visit 3). These visits will last between 3.5 hours and 5 hours. You should let your research team know if you require a break during any of the cognitive assessments.

If you are tested positive with Covid-19, or require self-isolation, please let your research team know as soon as possible. Your clinic visits may be delayed in such cases.

For **visits 1 and 3** only, please fast (do not eat or drink anything other than water) for 10 hours before these visits.

For **visit 2 and 3**, please do not take your trial drug before these visits.

These visits will include:

- Review of eligibility (*Visit 1 only*)
- Alcohol breath test (*Visit 1 only*)
- Blood sample collection for:
    - Clinical safety tests
    - Research biomarker analysis *(Visits 1 and 3 only)*
    - Analysis of trial drug concentrations
- Urine sample collection for:
    - Safety tests
    - Recreational drugs screening
    - Pregnancy test (if applicable)
- 12-lead ECG measurement
- Measurement of vital signs
- Assessment of side effects
- Review of medications and therapies started since last visit

- Assessment of your depression, mental health and stress
- Completion of self-reported questionnaires
- Completion of a series of computerised cognitive tasks
- Magnetic Resonance Imaging (*Visits 1 and 3 only*)
- Review of completed medication diary
- Counting the number of capsules remaining *(Visit 3 only)*.

You will receive trial medication on Visits 1 and 2, and will start your trial drug at the end of Visit 1.

If visit 2 is delayed due to Covid-19 reasons, you may be prescribed and sent the 2nd bottle of trial drug.

Your research team will also contact you by phone after visit 1 (Phone check #1) and after visit 2 (Phone check #2) to ask if you have any side effects, if you have been able to take the trial drug daily and if you have had any changes to you antidepressant therapies or other medications. This is usually around 10 days after your visits.

After phone check #2, the trial team will also send you a second saliva collection pack. You will have to collect your saliva samples within 3 days before your next visit (visit 3) and bring the samples to your next clinic visit.

Follow-up clinic visit

You will attend a follow up clinic visit between 7 to 14 days after your last dose of the trial drug. The follow up visit will last about 1.5 hours and will include:

- Brief physical examination and medical review
- Assessment of your mental health
- 12-lead ECG measurement
- Measurement of vital signs
- Body weight measurement
- Blood sample collection for:
    - Clinical safety tests
- Urine sample collection for:
    - Safety Urinalysis
    - Pregnancy test (if applicable)
- Assessment of side effects
- Completion of self-reported depression questionnaire
- Completion of Participant feedback form
- Review of medications and therapies started since last visit

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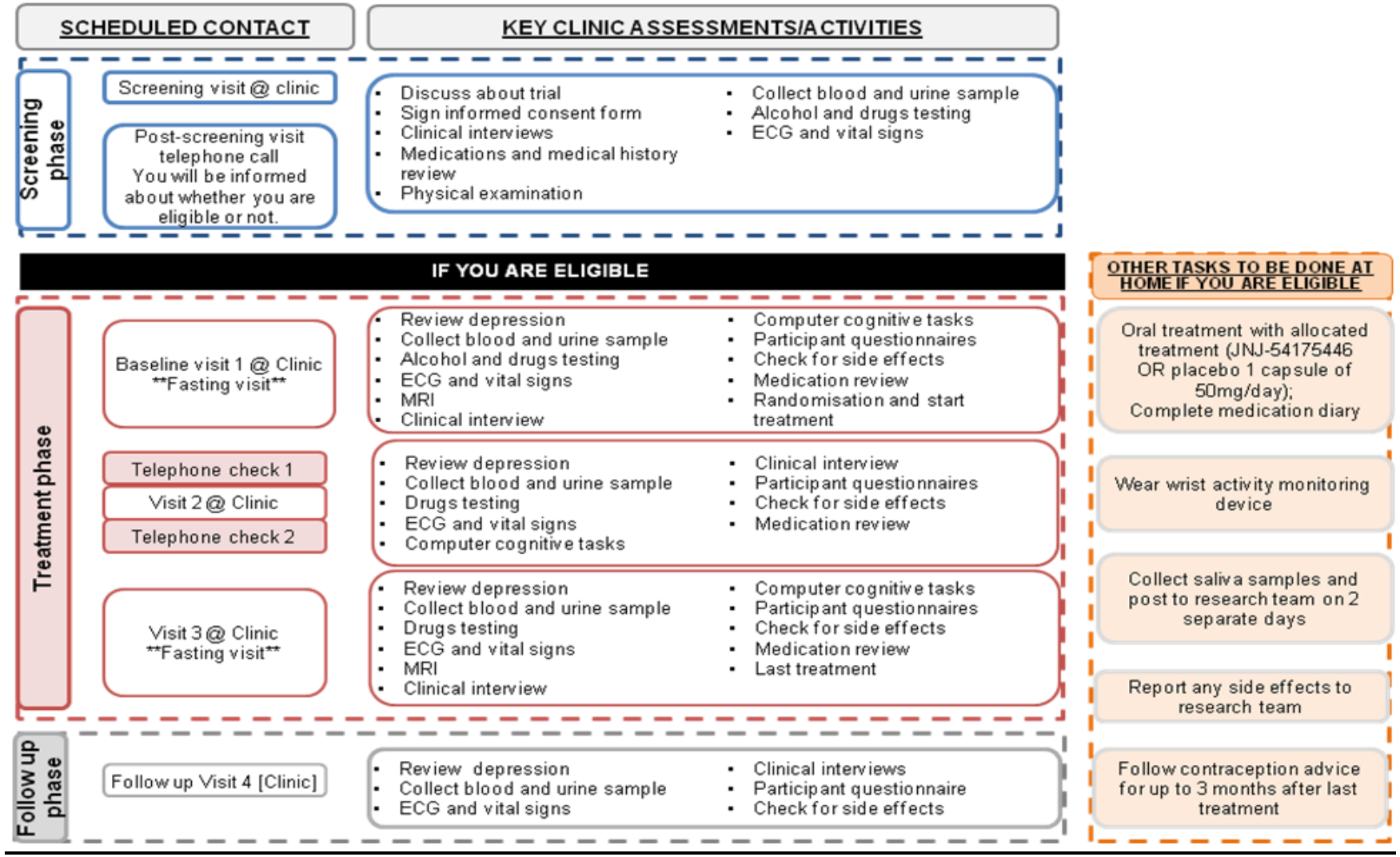
SUMMARY OF PARTICIPANT'S TRIAL JOURNEY



Trial procedures

Assessment of depression, mental health and stress:

At screening and throughout the trial, you will be asked questions about your depression, sleeping and eating patterns, moods, feelings and any thoughts of harming yourself.

At Visit 1 only, you will also be asked questions about any unpleasant experiences or abuse you might have experienced during your childhood.

Vital signs:

You will be asked to rest lying down for at least 5 minutes prior to measurement of your blood pressure, pulse/heart rate and body temperature.

12-lead Electrocardiogram (ECG):

An ECG is a non-invasive and painless procedure for checking your heart function and only takes a few minutes to complete. During the test, 10 sticky patches are placed on your chest, legs and arms. For men it may require a very small area to be shaved in order for the pads to be attached directly to your skin. These patches are connected to a machine which shows the electrical activity of your heart. You will be asked to rest lying down for at least 5 minutes in a quiet setting prior to the ECG.

Computerised cognitive tasks:

You will complete various cognitive tests on a computer during your treatment visits. These tests will measure various aspects of cognition including attention, response to stimulus, learning, memory and recall capability. These tests will take around 45-60 minutes to complete.

Magnetic resonance imaging (MRI):

MRI is a non-invasive procedure involving a radio-frequency and magnetic fields to produce images of your brain and body, and would take up to a maximum of 90 minutes to complete. You will be asked to lie still and relax on a bed which then moves into a short ‘tunnel’. This ‘tunnel’ is quite narrow so if you are claustrophobic (have a fear of small spaces) you might find this uncomfortable. The radiographer conducting your scan will monitor you throughout, and will stop the scan if necessary.

At certain times, the MRI scanner produces loud noises. You will be given earplugs or headphones to wear to minimise this.

During the scan, you will be asked to carry out a cognitive task which consists of a series of stimuli that will allow you to win or lose small amounts of virtual money, and you would do so by clicking a button in the MRI scanner.

Blood sample collection:

At every visit you will be asked to provide blood samples for clinical safety assessments to ensure that you do not have any conditions or infections that may affect whether you are able to receive the trial drug. These samples will be sent to a central laboratory in the UK to be analysed.

You will also be asked to provide blood samples for research analysis. These samples will be used to help scientists understand how the trial drug works, or why it may cause side effects. These samples may also help scientists to understand depression, how people may respond differently to the trial drug, and help develop further tests related to the trial drug or depression.

Over the duration of the trial, a total of about 280 ml (~16 tablespoons) of blood will be taken. No more than 120 ml (~7 tablespoons) will be taken during a single clinic visit. Where possible, the blood samples for research will be taken at the same time as the safety blood samples.

Urine samples:

You will be asked to provide urine samples at every clinic visit to check for any conditions or infections that may affect whether you are able to receive the trial drug. A urine recreational drug screen will also be carried out. Note that you will not be able to take part or continue in the trial if you test positive for recreational drugs including opiates, cocaine, (meth)amphetamines, MDMA or ecstasy, cannabinoids, and benzodiazepines.

6. What will I have to do?

By taking part in this trial, you will be required to attend up to 5 clinic visits, each lasting between 1.5 hours and 5 hours. For **visits 1 and 3**, you will have to fast overnight (at least 10 hours) prior to your visit (do not eat or drink anything except water). Breakfast will be provided upon completion of the blood and urine collections. After breakfast, additional assessments will be performed.

For all visits, please also avoid strenuous exercise within 24 hours of your clinic visit as this may affect some laboratory results and assessments.

At the visits you must give correct and accurate information about your medical history, current medical conditions, medications you are taking and any non-drug therapies you are undergoing. You should also tell your research team about any health problems you have during the trial.

You must not take part in other interventional or drug studies during this trial.

You must not donate sperm or eggs from the start of taking the trial drug until at least 3 months after the last dose.

During the trial, you will also be required to out carry out trial activities at your home and these are described below.

Trial drug and completion of medication diary

It is important that you take your trial drug regularly.

Please follow these instructions when taking your drug:

- The trial drug is in the form of capsules. You will have to take 1 capsule a day only in the morning with a glass of water, within 30 minutes of having your breakfast.

- Please swallow your capsules whole; do not crush, chew or dissolve your capsule.

- Except for day 1, you should take your trial drug at around the same time each day until visit 3.

- If you miss a dose at the normal dosing time, please refer to your medication diary for specific instructions. Please do not take extra doses to compensate for any missed doses.

- On the day of your clinic visits (Visits 2 and 3), please do **NOT** take your trial drug. You will do that during your visit after blood collection.

- You will be given a medication diary at Visit 1. In this diary, you will have to record the date and time that you take the drug. You can also record any side effects in the diary.

The trial drug should be stored at room temperature. Please keep the drug out of reach of children or persons with a limited capacity to understand. The trial drug must be taken only by you.

The trial drug should be kept in its original bottle, please do **not** place your trial drugs in separate containers such as a pill container/dosette box.

Please remember to bring your medication diary and trial drug and bottle(s) to every clinic visit. Your research team will take a copy of your diary at Visit 2 and return the original diary to you to complete.

Do **not** throw away any unused drug. All unused trial drug and the original bottles must be returned to the research team.

Restrictions on medication, therapies and diet:

Medications and other therapies

At the start of the trial, your research team will ask you about any medications you are taking, including current antidepressant medication, and any non-medication therapies you are undergoing Non-medication therapies include psychotherapy, acupuncture, electrical or magnetic stimulation. Please do not make any changes to these medications and therapies between your screening and follow up visit.

During this trial, you should not take any new drugs or remedies unless your research team has approved them. This includes all prescription and over-the-counter drugs, vitamins, herbal medication, and vaccines. Please also do not start any new non-medication therapies.

Paracetamol and ibuprofen are allowed on an ‘as needed’ basis, but please inform your research team at your next visit and note any health issues in your medication diary.

Please avoid grapefruit and Seville oranges, and products which contain them as they may interact with the trial drug.

Vaccinations

You may receive any of the licensed COVID-19 vaccines prior to or during the trial as the study drug and vaccines do not interact with each other or affect the effects of each other. We are required to record information of your vaccinations including name of vaccine and dates / planned dates of the vaccinations.

Live vaccines are not allowed within 4 weeks of starting the study drug or during the trial.

Alcohol

Limited amounts of alcohol, up to 2 units daily (for example, a small glass of wine (175ml) or one pint (500ml) of 4% beer) is allowed. However please avoid alcohol before your screening and baseline clinic visits as this might influence your alcohol breath testing. You will not be able to take part or continue with the trial drug if the results are positive.

Activity monitoring:

If you are eligible, you will be sent an activity monitoring device (Figure 1) which looks like a watch that you will wear on your wrist. Prior to taking the first dose of the trial drug you will be asked to wear the activity monitoring device for at least 7 days. You will then have to wear the device every day, throughout the day and when you sleep, until your last treatment visit. The activity monitoring device is water-resistant and can be worn during bathing/showering or swimming. However, if you experience any discomfort, please stop wearing it and inform the research team.

You will not be able to keep the device at the end of your participation in the trial.

Figure 1: Wearable activity monitoring device

Saliva collection:

If you are eligible to take part, your research team will send to you a saliva collection pack, containing 6 saliva collection tubes after the eligibility phone call. You will have to collect 6 samples on any day within 3 days before your baseline visit.

You will be sent a second pack after phone call check #2 and you will have to collect 6 samples on any day within 3 days before visit 3.

You should bring these samples to your next clinic visit.

A separate saliva collection instructions leaflet is included with the packs.

Reporting of any side effects:

You should tell the research team if you feel unwell or different in any way. If you have any major concerns or are feeling very unwell please contact your research team immediately using the contact numbers at the end of this information sheet.

Contraception:

Please share this information with any sexual partners if appropriate.

Trial medicines could harm an unborn baby or nursing infant. You will not be able to take part in this trial if you are pregnant or breastfeeding. You should not participate in this trial if you are planning to become pregnant or father a child during the trial or within 3 months after the trial. The effect of the study drug on your eggs or sperm is unknown, that is why you must agree not to donate eggs or sperm during the trial and

for at least 3 month after your last dose of study drug. If you are sexually active with a woman who is pregnant, you must use a condom to avoid exposing the unborn baby.

To minimise the risk of pregnancy during the trial, both you and your partner must use one of the following options of contraception:

Women are required to use one of the following		**one of the following barrier methods**
• Oral contraceptive (either combined or progestogen alone) • Contraceptive implant, injections or patches • Intrauterine device (coil or intrauterine system) • Vaginal ring	**and**	• Male or female condom • Cap • Diaphragm

NOTE: Do not use two barrier methods at the same time as this may damage the condom or cap.

You do not need to use contraception if:

- you have only one partner, and the man has had an operation to cut the tubes that carry sperm (vasectomy)
- you are a man and have had a vasectomy
- you (or your partner) are a woman who cannot become pregnant
- you practice true abstinence as part of your usual and preferred lifestyle (no sexual activity from point of consent until 3 months after the last dose of trial medication). If you become sexually active, you must use one of the methods listed above.

If you or your partner becomes pregnant during the trial or within 3 months of stopping treatment, you should inform the research team immediately. They will discuss this with you. The research team will ask for your permission or that of your pregnant partner to stay in contact throughout the pregnancy and obtain information regarding the outcome of the pregnancy.

You should also inform your midwife or doctor that you have received an experimental drug.

Inform your insurers:

You should discuss your participation in this trial with any insurance provider you have (e.g. travel insurance, protection insurance, life insurance, income protection, critical illness cover and private medical insurance) and seek advice if necessary, as failure to notify them may affect or invalidate your cover.

7. What are the side effects of the drug being tested?

At every visit, you will be asked about any side effects. You can also record them in the medication diary as a prompt for your next visit.

The possible discomforts, side effects, and risks related to JNJ-54175446 treatment are not all known as only 311 men and women have received either the placebo or the active drug in clinical trials. All medications have side effects. Most side effects are mild to moderate, but some may be serious and /or require treatment or additional testing. Up to now, the side effects reported during treatment with JNJ-54175446 in healthy volunteers were mild (95%) and moderate (5%) in severity. The most frequently observed side effects related to JNJ-54175446 include:

- Headache (very common, approximately 10%)
- Fatigue (common, between 1 to 10%)
- Dizziness (common, 1 to 10%)
- Nausea (common, 1 to 10%) and
- Somnolence (sleepiness or drowsiness) (uncommon, less than 1%)

All these side effects disappeared when the medication was stopped.

In a trial of patients with major depressive disorder, 2 patients were withdrawn because of severe side effects assessed by the Principal Investigator as related to JNJ-54175446. One patient was withdrawn due to headache, and the other due to gastrointestinal symptoms including flatulence, feeling of pressure in the abdomen, recurrent abdominal pain, dyspepsia (indigestion) and nausea (feeling or actually being sick).

In a 6-week long study in rats, JNJ-54175446 was found to cause toxicity to the testis. Changes observed in the study indicated a change in semen quality. The significance of this finding in the male rats to humans is not known. The dose you will be taking is lower than the dose that can damage the testis in rats. However there might still be a small risk that the compound may cause decrease in fertility in man which might or might not be recovered when the medication is stopped.

There may be side effects with the use of JNJ-54175446 that are not yet known. Sometimes during a trial, new information about the trial drug might be noted. It is possible that any new information might make you change your mind about being in the trial. Therefore, you will be informed if any significant new information becomes available.

Your safety will be supervised by the research team throughout your participation in the trial.

8. What are the possible disadvantages and risks of taking part?

There is a risk that we may discover some anomalies during the trial. We will inform your GP or other health care professionals as appropriate.

Clinic visits:

You will have to attend 5 clinic visits as part of the trial, each lasting between 1.5 and 5 hours. For visits 1 and 3 you will have to fast (at least 10 hours) and must avoid strenuous exercise 24 hours before the visit. There is a risk that you might feel faint due to the fasting. You will be asked to complete various tasks at these visits and there is a risk that you will feel fatigued at the end of the visit.

Blood samples:

You may experience mild pain and bruising in your arm from the sample collection. Potential side effects caused by blood samples being taken include fainting (please tell the research team straight away if you feel faint), redness, pain, bleeding, bruising and rarely, infection and blood clots (which may cause inflammation, swelling and pain). If you do experience side effects from having blood samples taken they are most likely to be minor and will pass quickly.

MRI:

MRI scanning is generally very safe, however there are certain circumstances where it must be avoided, for example if you have metal objects attached to or inside your body (e.g. stents, shrapnel, plated fractures) or electronic devices (e.g. heart pacemaker). The radiographer will go through these with you before your scan.

There is a small risk that we may discover some previously unknown anomalies on your MRI scan. In the event that this happens, it will be discussed with you.

Questionnaires:

You will be asked questions about your depression, mental health and stress levels. At Visit 1, you will also be asked about any childhood abuse or unpleasant experiences. Some of these questions may cause embarrassment or make you uncomfortable. If you wish to stop at any point during the questionnaires, please let the research team know.

9. What are the possible benefits of taking part?

There is no guarantee that you will benefit from taking part in this trial. You may experience an improvement in your symptoms. However, information collected as part of your participation in this trial may benefit patients with depression in the future.

10. What are the alternatives for treatment?

If you choose not to take part, you will continue with the treatment you have been receiving as normal.

11. What happens when the trial stops?

When the trial stops, the trial drug will not be available to you and you will also have to return the activity monitoring device to your trial team. You will return to your normal treatment for your depression and will continue to be seen by your normal doctor as usual.

12. Expenses & Payment?

If you take part in this trial, we would cover all necessary reasonable travel expenses and, if it would help, we can arrange transport by taxi for your clinic visits. In addition, we will reimburse you for your time and inconvenience. The reimbursements you will receive will depend on the number of clinic visits completed:

- Completion of screening visit: £25

- Completion of treatment visits 1 to 3: £125 per visit

- Completion of follow up visit: £100

If you currently receive state benefits, you should check with the Department of Work and Pensions whether the reimbursement for your participation in the trial might affect the benefits you receive.

Section 2: Trial Conduct

13. What if new information becomes available?

Sometimes during the course of a trial, new information becomes available which might affect your decision to continue participating in this trial. The research team will contact you to discuss the new information and whether you wish to continue participating in the trial. If you still wish to continue on the trial, you will be asked to sign a new Informed Consent Form.

The trial sponsor, the regulatory authority or the research team may decide to stop the trial at any time. If that happens, we will tell you why the trial has been stopped and arrange for appropriate care for you.

14. What if I decide I no longer wish to participate in the trial?

You are free to leave this trial at any time without giving a reason and without affecting your future care or medical treatment. If you decide not to participate any further, you will no longer receive the trial drug. No further tests will be performed on you and no further research samples will be collected. Any data already collected or results from tests already performed on you or your samples will continue to be used in the trial analysis.

The research team may also choose to withdraw you from the trial if they feel it is in your best interests or if you have been unable to comply with the requirements of the trial. Reasons for trial withdrawal could include:

- You have experienced a serious side effect
- You are unable to complete the visits, trial drug or trial documentation as required
- You become pregnant or plan to become pregnant

If you have experienced any serious side effects which require you to withdraw from the trial, the research team will follow-up with you regarding your progress until the side effect has stabilised or resolved.

15. What if there is a problem?

Any complaint about the way you have been dealt with during the trial or any possible harm you might suffer will be addressed. If you have any concerns about any aspect of this trial you should speak to your research team who will do their best to answer your questions.

In the event that something does go wrong and you are harmed by taking part in the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Cambridgeshire and Peterborough Foundation Trust or the University of Cambridge. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).The University has obtained insurance which provides no-fault compensation i.e. for non-negligent harm, you may be entitled to make a claim for this.

If you wish to complain or have any concerns about any aspect of the way you have been approached or treated during this trial, you can do this through the NHS complaints procedure. In the first instance it may be helpful to contact the *(to be*

completed locally as appropriate – in England this will refer to the Patient Advice and Liaison Service (PALS)) at your hospital.

16. Will my taking part in this trial be kept confidential?

Cambridgeshire and Peterborough NHS Foundation Trust (CPFT) and University of Cambridge are the joint sponsor for this clinical trial based in the United Kingdom. We will be using information from you and your medical records in order to undertake this trial and will act as the data controller for this trial. This means that we are responsible for looking after your information and using it properly. The Sponsor organisations will keep your personal identifiable information and unique trial ID, 5 years after the trial has finished ensuring your safety and allowing the trial to be reviewed by the authorities after it is finished. The personal identifiable information collected in this trial includes your month and year of birth, age, gender, marital status, education and occupation.

Your rights to access, change or move your information are limited, as the Sponsor organisations need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from this clinical trial, 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 the Sponsor uses your information below:

For Cambridgeshire and Peterborough NHS Foundation Trust, please visit http://www.cpft.nhs.uk/about-us/privacy.htm

For University of Cambridge, please visit:

https://www.medschl.cam.ac.uk/research/information-governance/, or email

the Information Governance team at: researchgovernance@medschl.cam.ac.uk

[When making your PIS site specific, please select the relevant section below depending on where participants have been recruited.]

FOR PARTICIPANTS RECRUITED FROM CPFT ONLY

CPFT and CUH (Cambridge University Hospitals)will collect your name, month and year of birth, contact number and address, and NHS number. This information will be stored in a secure online management system that is managed by the University of Cambridge. Your local research team at CPFT and a small number of research staff from the central research office and Sponsor organisation will have access to your identifiable information. This information is required so that your research team can contact you about the trial and make sure that relevant information about the trial is recorded for your care, and so that the central trial team may monitor the progress of the trial. If you do not consent to participate, your information will be deleted. Authorised individuals from the Sponsor(s) and regulatory organisations may look at your medical and research records to check the accuracy of this trial. CPFT will pass these details to the Sponsor along with the information collected from you and your medical records. The only people in the Sponsor organisation(s) who will have access to information that identifies you will be people who need to contact you in relation to this trial and to audit the data collection process. CPFT will keep identifiable information about you from this trial for ## years after the trial has finished.

FOR PARTICIPANTS RECRUITED AT OTHER SITES (NOT CAMBRIDGE):

[add local site name] will collect your name, month and year of birth, contact number and address, and NHS number. This information will be stored in a secure online management system that is managed by the University of Cambridge. This information is required so that your research team can contact you about the trial and make sure that relevant information about the trial is recorded for your care. We will pass this information about you to a small number of research staff from the central research office so that they can monitor the progress of the trial. If you do not consent to participate, your information will be deleted. Authorised individuals from the Sponsor(s) and regulatory organisations may look at your medical and research records to check the accuracy of this trial.

Your local research team will keep identifiable information about you from this trial for [5 or enter local policy] years after the trial has finished.

[for all sites]

Once you have agreed to participate in this trial you will be allocated a Participant ID Number. This is a unique trial number that will be used on all of your trial documentation along with your month and year of birth. Your date of birth is considered personal information. We collect this personal information on trial documentation to help ensure that the data we receive as part of your trial participation is correctly allocated to you. By cross checking these two unique references we can ensure the integrity of the data.

Your personal information will form part of the trial data held by the research team and will be used for monitoring, quality checking and analysis purposes. If the trial drug is to be sent to you by courier, your name, contact number and delivery address will be shared with the courier for this purpose only. Your personal information will not be shared with any other 3rd parties and will not be published in any way. 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. Only anonymous trial data, without any personal information will be published at the end of the trial. All information collected about you as a result of your participation in the trial will be kept strictly confidential. Your personal and medical information will be kept in a secured file and be treated in the strictest confidence.

We will need to inform your GP of your participation in this trial so that any medical decisions made by your GP account for any treatment you are receiving as part of this trial.)

When you complete the computerised cognitive tasks, some of the data will be stored on a secure system ('Cloud storage system') hosted in the USA. These data will not contain any personal information and you cannot be identified from the data. These data will be sent to the Sponsor at the end of the trial.

17. What will happen to my samples?

All research samples collected from you will be labelled with only your unique trial ID, month and year of birth.

Clinical blood and urine safety assessments:

At every visit, clinical blood safety assessments will be carried out at a central analysis laboratory in the UK. Results will be sent back to your research team for review. Urine samples will be analysed at your local hospital and will also be reviewed by your research team.

C-reactive protein (CRP) measurement:

We will also check the level of C-reactive protein (CRP) in your blood. CRP is a protein produced naturally by your body and it is increased if there is inflammation in the body. The blood level of CRP naturally varies with time and between people. It is quite normal for CRP levels to be low but, if it is very low, we do not think that you will benefit from taking an anti-inflammatory drug to treat your depression. For this reason, we will check your CRP level at screening and you will not be eligible to take part if your CRP test result shows a low level in your blood. We will also continue to measure CRP at the other visits to look at how CRP level varies with time.

There is a 50% chance that your CRP level will be too low to be eligible to take part.

Genetic testing:

Genetic material such as DNA will be extracted from the blood samples you provide. DNA carries the information that determines our traits. For example, our DNA determines the colour of our hair and eyes. DNA may also explain why some people respond to some medications and others do not. It may also explain why some people get some diseases and others do not.

The results of tests done in these samples are only for research. They will not be used for your medical care nor will they be used to make a diagnosis about your health.

At screening, if you fulfil all other eligibility criteria, we will send your DNA to an external lab in the UK/EU for genetic analysis of P2X7 receptor to check whether or not you have a loss of function P2X7 receptor gene. If you have this, you are unlikely to respond to the trial drug and will not be eligible to take part and we will inform you of this result. We may also send anonymised DNA to an external laboratory in the UK for genetic analysis of other genes in addition to the P2X7 gene. These results will not be given to you, the trial team members or your general practitioner. All lab(s) carrying out these genetic analyses will not be able to identify you from the sample.

Other research tests:

At every treatment visit, some of the blood taken from a vein in your arm will be used to analyse levels of the drug in your blood (pharmacokinetic analysis) as well as other biomarkers.

Samples may be analysed locally by your research team or stored temporarily at a central facility at the University of Cambridge (Department of Medicine) before being sent for analysis by partners of the NIMA Consortium in the UK. Anonymised samples may be analysed with the help of an external party to achieve the aims of this trial. Pharmacokinetic analysis will take place in a central laboratory located in The Netherlands.

Saliva samples will be analysed by a central laboratory at King's College London for levels of cortisol, a biomarker of stress.

If you consent, any blood and saliva samples remaining at the end of the trial will be stored in an approved central facility to be used in future approved research studies.

18. What will happen to the results of the trial?

The results of the trial will be anonymous and you will not be able to be identified from any of the data produced. When the results of this trial are available, they may be published in peer reviewed medical journals and used for medical presentations and conferences. They will also be published on the EU Clinical Trial Register website, a central registry for all clinical studies conducted in the EU.

At the end of the trial, a copy of the anonymised data will be sent to Janssen Pharmaceuticals who will carry out the analysis in collaboration with the Sponsor. Your identifiers will not be sent and the people who analyse the information will not be able to identify you. Anonymous datasets from the trial will become 'open data' and will be stored in an online database so that it is publicly available. This is important to the research process as it allows other researchers to verify results and avoid duplicating research. Data are made available free of charge to anyone interested in the research and we would have no control over how these data are used.

If you would like to obtain a copy of the published results please contact your research team directly who will be able to arrange this for you. Updates on the trial and summary of results will also be made available on the NIMA consortium website (https://www.neuroimmunology.org.uk/).

19. Who is organising (sponsoring) and funding the trial?

This trial is sponsored by Cambridgeshire and Peterborough NHS Foundation Trust and the University of Cambridge, and is conducted as part of the work of the Wellcome Trust Neuroimmunology and Alzheimer's Disease (NIMA) Consortium.

The trial is primarily funded by the Wellcome Trust. Janssen Pharmaceuticals is partially funding the trial and will also be providing the trial drug free of charge. Other funding will be provided by GlaxoSmithKline (GSK) and Lundbeck as part of their contribution to the NIMA Consortium.

20. Who has reviewed this trial?

All research within the NHS is reviewed by an independent group of people called a Research Ethics Committee to protect your interests. This trial has been reviewed and given favourable opinion by East of England - Cambridge Central REC committee. The Medicines and Healthcare Products Regulatory Agency (MHRA) who are responsible for regulating medicines in the UK have also reviewed this trial.

21. Further information and contact details

For further information about the trial, please contact during normal working hours:

Principal Investigator:
Name: [enter site PI name]
Tel number: [site PI contact]

Research team:
Name: [enter name]
Tel number: [site contact]
Email: [enter local site email]

In the event of an emergency, please call the emergency services number 999.

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INFORMED CONSENT FORM

Trial Title: A randomised, placebo-controlled, double-blind trial of the antidepressant efficacy of a novel CNS-penetrant P2X7 receptor antagonist, JNJ-54175446, in people with major depressive disorder, an incomplete response to monoaminergic antidepressant drugs, and a biomarker profile predictive of active P2X7 signalling

Short Title: ATP - **A**ntidepressant **T**rial with **P**2X7 Antagonist JNJ-54175446

Principal Investigator: _____ **Participant Number:** _____

If you agree to these statements, please initial on the lines.

1	I have read and understood the Participant Information Sheet version 5.0, dated 9th March 2021 for the above trial and I confirm that the trial procedures and information have been explained to me. I have had the opportunity to ask questions and I am satisfied with the answers and explanations provided.	_____
2	I understand that my participation in this trial is voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected.	_____
3	I understand that my month and year of birth (personal information) will be collected on the trial documentation and stored in the trial database, but that this information will be kept in the strictest confidence and none of my personal data will be published.	_____
4	I understand that members of the central trial team will have access to my personal information as detailed in section 16 in order to monitor the progress of the trial.	_____
5	I understand that sections of my medical notes or information related directly to my participation in this trial may be looked at by responsible individuals working on behalf of the sponsor, regulatory authorities and research personnel where it is relevant to my taking part in research and that they will keep my personal information confidential. I give permission for these individuals to have access to my records.	_____
6	I understand that my GP will be informed of my participation in the ATP trial, sent trial details and also be provided with any clinically relevant results identified from my trial assessments.	_____

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7	I have read and understood the compensation arrangements for this trial as specified in the Participant Information Sheet.	
8	I understand that the doctors in charge of this trial may close the trial, or stop my participation in it at any time without my consent.	
9	I have read and understood my responsibilities for the trial including using appropriate contraception as listed in section 6.	
10	I agree to give saliva, blood and urine samples for this trial. I understand how these samples will be collected and that the saliva and blood samples will be sent to central laboratories and collaborators of this trial for analysis. I understand that these laboratories may be outside of the UK and I will not be identified by the researchers carrying out these analyses.	
11	I understand that samples I donate will undergo analysis that will include genetic analysis. Only results that are directly linked to my eligibility for the trial will be shared with me.	
	OPTIONAL:	
12	I agree to be contacted for future approved studies for which I may be eligible.	
13	I agree that any of my blood or saliva samples provided as part of this trial and which remain after the trial has been completed, may be stored and used in other approved studies.	

I agree to participate in the ATP trial:

Name of participant	Signature	Date

Name of person taking consent	Signature	Date

Time of Consent (24hr clock) _____:_____

1 copy for the participant, 1 copy for the trial team, 1 copy to be retained in the hospital notes.