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Antidepressant trial of a novel P2X7 receptor blocker JNJ-54175446

Submission date	Recruitment status	[X] Prospectively registered
25/02/2019	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
26/03/2019	Stopped	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
21/08/2023	Mental and Behavioural Disorders	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims

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. The aim of this study is 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. The researchers also wish to find out how the drug affects the body by measuring the levels of biomarkers in the 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. The researchers will also take images of the brain to assess the effects of the drug on the brain structure and function.

Who can participate?

Patients aged between 18 and 60 who are currently experiencing symptoms of depression and are being treated with an antidepressant medication

What does the study involve?

Participants are randomly allocated to take either the new drug or a placebo (dummy) drug (one capsule a day) for about 8 weeks alongside their current antidepressant medication. Participants make 6 clinic visits to the research centre over about 14 weeks, and are also contacted by phone four times including a pre-screening phone call. Participants have to fast overnight before two of the visits. Over the duration of the trial, participants provide blood and urine samples for various tests, and undergo ECG and MRI scans (2 MRI scans). Participants also have to complete some activities at home including continuous wear of an wrist activity monitor, complete a daily sleep diary and provide saliva samples.

What are the possible benefits and risks of participating?
Participants may experience some improvements in their symptoms of depression. They will be compensated for reasonable travel expenses. They will receive up to £500 for their time and effort in the trial. The exact amount will depend on the number of visits completed. The drug has been tested on more than 300 people already and has been shown to be very safe. Mild side-effects that were seen include headache, fatigue and nausea. Participants will not receive any more trial drug after the trial, even if their symptoms improved during the trial.

Where is the study run from?
Cambridge Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for?
June 2018 to June 2022

Who is funding the study?
Janssen Pharmaceuticals and the Wellcome Trust (UK)

Who is the main contact?
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Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2018-001884-21

Protocol serial number
39882

Study information

Scientific 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

Acronym
ATP

Study objectives

The primary hypothesis of this study is that adjunctive treatment with JNJ-54175446 50mg qd, compared to placebo, will cause a significant reduction in depressive symptom severity measured (MADRS total score) after 8 weeks of treatment.

The secondary hypotheses are:
1. Adjunctive antidepressant treatment response to JNJ-54175446, ie. Improved symptoms, fatigue and cognitive scores, will be greatest in MDD patients with peripheral biomarker evidence for P2X7-mediated inflammation.
2. Adjunctive antidepressant treatment response to JNJ-54175446 will be associated with changes in structure and function of brain reward circuit components, e.g., ventral striatum and medial prefrontal cortex, which have previously been implicated in mood disorders and the brain' s response to peripheral inflammation.
3. Anti-inflammatory effects on depressive symptom scores could be measurable within 2 weeks after start of treatment, based on clinical data suggestive of a rapid mood-lifting effect of anti-TNF antibodies in the treatment of patients with rheumatoid arthritis and "comorbid" depressive symptoms.
4. That JNJ-54175446 50mg qd will be safe and well-tolerated based on the following considerations: (i) the prior clinical safety database on JNJ-54175446, has demonstrated good safety and tolerability for similar dosing regimens in healthy volunteers and MDD patients; and (ii) the low affinity of the P2X7 receptor for ATP means that it is only activated by abnormally high levels of ATP, under stress conditions, and has no known functional role at lower, more physiological, levels of ATP.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 04/06/2019, East of England – Cambridge Central REC (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS; +44 (0)207 104 8108; nrescommittee.eastofengland-cambridgecentral@nhs.net), ref: 19/EE/0035

Study design
Randomised; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Major depressive disorder

Interventions
Participants will be randomised 1:1 to either active drug or placebo. This will be carried out using a web-based randomisation system. Eligible participants will be randomly allocated to receive either 50 mg/day JNJ-54175446 or placebo for 8 weeks. Participants will be assessed at weeks 2, 5 and 8 using a standard clinical depression scale and the scores compared between those treated with placebo and those treated with JNJ-54175446. To understand more about the effects of JNJ-54175446 on the immune system and the brain, patients will also complete additional blood tests, questionnaires and MRI brain scans at different visits throughout the trial.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
JNJ-54175446

Primary outcome(s)
Depression symptoms measured using the Montgomery-Åsberg Depression Rating Scale (MADRS) at baseline and week 8 (Visit 4)

Key secondary outcome(s))
1. Depressive symptom severity measured using:
1.1. Clinician-reported scales MINI and HDRS17 at screening and baseline and MADRS at weeks 2 and 5
1.2. Participant-reported questionnaires SHAPS, QIDS-SR16, GAD-7, Chalder Fatigue Questionnaire, Perceived Stress Scale, Beck's Depression Inventory and Childhood Trauma Questionnaire at baseline and over time at every visit until week 8
2. Suicidality assessed using the Columbia Suicidal Severity Rating Scale assessed at every clinic visit (screening, baseline visit 1, visit 2, visit 3, visit 4 and follow up visit 5)
3. Cognitive function assessed using computerised cognitive tasks designed to test for emotion-independent functions, emotion-dependent functions and sustained attention at baseline and over time at every visit until week 8
4. Stress assessed by cortisol levels in the saliva before baseline and before the last dose
5. Fatigue and activity measured using an activity monitor at baseline and over time until week 8
6. Functions of the autonomic nervous system measured by variability in heart rate at baseline and week 8
7. Brain structure and function assessed by functional MRI scan at baseline and week 8
8. Peripheral immunophenotypes measured by various biomarker assays looking at proportions of immune cells, level of cytokine release, CRP protein (marker of inflammation) levels, and gene expression at baseline and week 8

Completion date
01/06/2022

Reason abandoned (if study stopped)
IMP supplier withdrew support

Eligibility

Key inclusion criteria
For a detailed description of inclusion criteria please refer to protocol section 10.1
1. Provided written informed consent
2. Between the age of 18 to 60 years inclusive
3. Meets the DSM-5 diagnostic criteria for MDD (International Classification of Diseases (ICD)-code F32.x and F33.x), without psychotic features, as confirmed by the M.I.N.I 7.0 (Mini International Neuropsychiatric Interview 7.0)
4. Has Hamilton Depression Rating Scale (HDRS) score of > = 17

5. BMI between 18 and 36 kg/m2 inclusive
6. Currently being treated with one antidepressant monoaminergic drug (e.g. SSRI, SNRI, TCA) at an adequate dose, and for at least 6 weeks and for a maximum of 24 months
7. Must be medically stable based on clinical laboratory tests, medical history, vital signs, and 12-lead ECG performed
8. Agree to practice highly effective method of birth control as stated in the protocol
9. A woman of childbearing potential must have a negative serum pregnancy test at screening
10. Agree not to donate eggs or sperm from start of dosing and for at least 3 months after receiving the last dose of study drug

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
15

Key exclusion criteria
For a detailed description of exclusion criteria please refer to protocol section 10.2
1. Has a primary DSM-5 diagnosis of posttraumatic stress disorder
2. Has failed more than 3 treatments despite an adequate dose and duration, in the last 24 months
3. Loss of function allele at one or both of two SNPs on the P2RX7 gene: rs3751143 (1487 A> C) and rs1653624 (1703 T> A)
4. Has a current or recent history of clinically significant suicidality
5. Has a history of moderate or severe substance or alcohol use disorder according to DSM-5 criteria, except nicotine or caffeine, within 12 months before screening
6. Has positive test result(s) for alcohol or drugs of abuse (including methadone, opiates, cocaine, cannabinoids, amphetamine/methamphetamine and ecstasy)
7. Has a current diagnosis of a psychotic disorder (e.g. schizophrenia, bipolar disorder), an eating disorder (e.g. anorexia, bulimia), or learning disability or a personality disorder that is considered by the investigator to interfere with the ability of the subject to adhere to the protocol (e.g. narcissistic personality, borderline personality disorder)
8. Has used:
8.1. Monoamine oxidase inhibitors (MAOIs) within 12 weeks before screening
8.2. Within 6 weeks prior to enrolment use of other antidepressant drugs not belonging to the allowed classes of SSRI, SNRI, or TCA.
9. Is currently treated with antipsychotic drugs (D2-antagonists; except for low-dose quetiapine), lithium, other mood stabilizers or opiates
10. Unable to complete MRI scans

11. Has current signs/symptoms of liver or renal insufficiency, diabetes mellitus (type I and II), hypothyroidism or hyperthyroidism without stable treatment, or other significant and uncontrolled medical conditions
12. Is a woman who is pregnant or breastfeeding
13. Is a man who plans to conceive a child while enrolled in this study or within 3 months after the last dose of IMP
14. Has a history of malignancy within 5 years before screening
15. Has received an investigational drug/vaccines, used an invasive investigational medical device within 60 days before the planned first dose of IMP, or has participated in 2 or more interventional clinical studies in the previous 1 year, or is currently enrolled in any drug or non-drug interventional study
16. Venous blood concentration of C-reactive protein, measured by high sensitivity assay (hs-CRP) less than 1 mg/L

Date of first enrolment
09/09/2019

Date of final enrolment
10/06/2022

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
Fulbourn Hospital
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Study participating centre
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Sponsor information

Organisation
Cambridgeshire and Peterborough NHS Foundation Trust

ROR
https://ror.org/040ch0e11

Organisation
University of Cambridge

Funder(s)

Funder type
Industry

Funder Name
Janssen-Cilag Ltd; Grant Codes: RNAG/374

Funder Name
Wellcome Trust; Grant Codes: RNAG/375

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a publically available repository.
Name of repository: APOLLO (https://www.repository.cam.ac.uk/)
Type of data shared: All of the individual participant data collected during the trial, after deidentification.
Data will become available indefinitely after the final trial report has been submitted and

following key publications. Data will be available to anyone who wishes to access the data for any purpose.
Participants will be informed that de-identified trial data will become open data after the trial, and will be asked to provide their written consent.
Data will be available via the Apollo website, the specific weblink is not yet known.

IPD sharing plan summary

Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No