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A trial to understand how immune function affects symptoms of psychosis

Submission date
28/06/2022

Recruitment status
No longer recruiting

Registration date
13/07/2022

Overall study status
Completed

Last Edited
04/07/2025

Condition category
Mental and Behavioural Disorders

[X] Prospectively registered
[X] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Psychotic disorders like schizophrenia cause suffering to millions of people and a considerable proportion of people who are treated with antipsychotic drugs do not get better. Research suggests that low-grade inflammation (over-activity of one aspect of the immune system, which can be measured by a blood test) may play a role in the development and persistence of psychotic symptoms. Inflammation may also make it difficult for patients to get better despite taking antipsychotic medication.

The aim of this study is to test whether reducing inflammation with an anti-inflammatory drug called tocilizumab improves psychotic symptoms and memory function in people with psychosis. For this study, we will be recruiting approximately 60 people with first episode psychosis who are within three years of diagnosis. Eligible participants will be treated with either a single intravenous infusion of tocilizumab or normal saline (dummy drug). Tocilizumab is an anti-inflammatory drug used in the NHS for treatment of rheumatoid arthritis. These participants will be selected based on a number of inclusion/exclusion criteria including age (18-40 years), and evidence of inflammation (confirmed by a blood test). Assessments of psychiatric symptoms and blood samples will be carried out before infusion, and after infusion on day 7, 14 and 28. In addition, memory tests and a brain scan (optional) will be performed before infusion and after infusion on day 14. In addition, we will recruit, 30 participants with first episode psychosis who do not have evidence of inflammation, and a further 30 participants who do not have any history of mental illness. This would allow us to compare similarities and differences among three groups: psychosis with evidence of inflammation; psychosis without evidence of inflammation; people without psychosis.

Who can participate?
Eligible participants will be aged 18 - 40 years, meet ICD-10 criteria for schizophrenia and related psychotic disorders (F20, F22, F25, F28, F29) within three years of first contact with psychiatric services (defined by acceptance to Early Intervention in Psychosis Services), who have evidence of low-grade inflammation and inflammation-related symptoms (i.e., anhedonia and amotivation).

What does the study involve?
Participants will be randomised into two groups to receive single intravenous infusion of normal saline (placebo) or tocilizumab (a humanised monoclonal antibody that inhibits IL-6 signalling and is licensed in the UK for treatment of rheumatoid arthritis). Data on the primary outcome (i. e., anhedonia), other psychiatric measures, and blood samples will be collected at baseline and after infusion around day 7, 14, and 28. Cognitive and neuroimaging data will be collected at baseline and 14 days post-infusion. We will also recruit approximately 30 patients with psychosis without evidence of inflammation and 30 people with no history of mental illness. This allows for comparison of the baseline characteristics of inflammation-related psychosis.

What are the possible benefits and risks of participating?
This study will help us to understand whether inflammation plays a role in causing psychosis, and whether anti-inflammatory drugs can be used for treating a subset of patients with psychosis in the future. We appreciate our participants' donation of time and any inconveniences endured, and we will reimburse accordingly.

There are some small risks of taking part but be assured that measures are taken to minimise these risks where possible. For examples see below:
BLOOD SAMPLING: This involves the use of a needle which may cause temporary discomfort and bruising. Blood will be drawn by trained staff, and we will make sure you are as comfortable as possible in the process.
CHEST X-RAY: A single chest X-ray may be required to assess for TB in the lung. The type of radiation used here carries an extremely small risk (around 1 in 1.5 million) of causing cancer later down the line. To put this in perspective, the amount of radiation participants will be exposed to via X-ray is equivalent to that from natural sources of radiation in the UK every three to ten days.
Brain Scan: A number of participants will undergo a MRI brain scans if they're considered eligible.
• MRI scanners use strong magnets that can have effects on metal objects nearby. This means that several screening processes are necessary to deter risk of entering the scanner with any metal inside your body and on your person. Where necessary, participants will be denied access to MRI scanning if it is deemed potentially unsafe by a professional.
• MRI machines can be loud, so earplugs and headphones will be provided to help participants relax.
• Any discomfort relating to confined spaces should be reduced with the presence of mirrors to see outside of the scanner as well as constant communication availability with operating staff. If you are in any way distressed the operator will remove you immediately.
DRUG IV INFUSION: The 'Psychosis with Evidence of Inflammation' group will receive a single intravenous infusion of either tocilizumab (an anti-inflammatory drug) or normal saline (dummy drug). Following safety checks, this will be administered continuously over one hour at a clinical research facility under the supervision of a doctor, and other members of the study team.
SIDE EFFECTS: Even when precautions are taken all medications carry a chance of side effects. The following side effects have been observed in Rheumatoid Arthritis patients generally during the 2nd to 4th infusion (this study uses just one infusion):
• The most common side effects are respiratory and other infections (about 7%). To minimize the risk of infection, people who have a history of repeated infections or recent serious infection such as TB, HIV, Hepatitis B, Hepatitis C, VZV, and those with uncontrolled blood pressure and other serious physical illness will be excluded from the trial.
• Other common side effects include headache (7%), high blood pressure (6%), altered liver enzymes (6%), nausea (6%), and diarrhoea (5%). Serious allergic reactions such as shortness of breath or swollen lips can occur during or after the infusion, but these are rare (0.1%). There is also a low risk of gastrointestinal perforation (roughly 0.2%-0.3% patients per year). Participants will receive information about how to seek help should any adverse effects occur. Any adverse

effects will be recorded at the time and at follow-up assessments.
PREGNANCY: Pregnant people will be also excluded from the trial as a precaution. This also means that participants who are sexually active will be asked to use approved effective contraception for 3 months after the infusion, and male participants should not donate sperm samples for 3 months after infusion.

Where is the study run from?
University of Bristol (UK)

When is the study starting and how long is it expected to run for?
April 2022 to November 2025

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Integrated Research Application System (IRAS)
301682

Central Portfolio Management System (CPMS)
51723

Protocol serial number
MR/S037675/1

Study information

Scientific Title
Psychosis Immune Mechanism Stratified Medicine Trial: The PIMS Trial

Acronym
PIMS

Study objectives

Our primary objective is to test whether interleukin 6 (IL-6), a pro-inflammatory cytokine, contributes to pathogenesis of psychosis, and to examine potential mechanisms by which IL-6 affects psychotic symptoms, mood, cognition, and behaviour.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 06/04/2022, Cambridgeshire East REC (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; +44 2071048265; CambridgeEast.REC@hra.nhs.uk), ref: 22/EE/0010

Primary study design
Interventional

Study design
Interventional double blind randomized parallel group placebo controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Psychosis

Interventions
The study includes two parts:
1. Intervention part: Approximately 60 participants with psychosis (intervention cohort) who have evidence of low-grade inflammation (i.e., IL-6 ≥0.7pg/ml) and inflammation-related symptoms (i.e., anhedonia and amotivation) will be recruited. Participants will be randomised into two groups to receive a single intravenous infusion of normal saline (placebo) or tocilizumab (a humanised monoclonal antibody that inhibits IL-6 signalling and is licensed in the UK for treatment of rheumatoid arthritis). The primary outcome will be anhedonia (i.e., reduced ability to experience or diminished motivation to engage in pleasurable activity). Data on the primary outcome, other psychiatric, and blood samples will be collected at baseline and 7, 14, and 28 days post-infusion. Cognitive and neuroimaging (optional) data will be collected at baseline and 14 days post-infusion.
2. Observational part: Approximately 30 participants with psychosis without low-grade inflammation (i.e., IL-6 <0.7pg/ml) and approximately 30 people with no history of mental illness will also be recruited. These participants will complete the same baseline assessments as the intervention cohort, allowing for comparison of the baseline characteristics of inflammation-related psychosis.

Procedure:
1) Participant Identification and Initial Screening
a) Secondary Care: Potential participants with psychosis will be identified by their clinical Early Intervention in Psychosis Service team. Consultant Psychiatrist, care co-ordinator (community psychiatric nurse), and/or the site Principal Investigator will confirm capacity to consent, risk inclusion criteria, diagnosis of psychotic disorder within three years of treatment onset, stable antipsychotic medication, and presence of positive symptoms. Referring NHS trust clinicians will document all relevant information in patient's clinical notes. If potentially eligible, the study will be introduced by the participant's consultant or care coordinator and the participant will be

given the Participant Information Sheet. If interested in taking part, the participant will next complete a consent for screening form and a screening questionnaire to determine eligibility. Then, an appointment will then be arranged with a member of the study team in coordination with the participant to complete a consent for study form and full eligibility assessment.
b) Advertisement: Healthy controls will be recruited through electronic and other advertisement methods including social media, job centres, and mental health charity organisations. Interested participants will complete a similar consent for screening form and screening questionnaire as patients to confirm their eligibility as healthy controls.
Potentially eligible participants will then be invited to an appointment to complete a consent for study form and full eligibility assessment.
Face-to-face assessments will take place at an appropriate University/NHS research facility or at suitable local facilities such as GP surgery, mental health team base, or at the participant's home. Neuroimaging will be completed in the Wolfson Brain Imaging Centre (WBIC) at the University of Cambridge, and at the Birmingham University Centre for Human Brain Health (CHBH). During the COVID-19 outbreak, to minimise risk to participants and study team members, appropriate measures will be taken during face-to-face visits to minimise risk of infection in line with University and NHS guidelines. These measures will include handwashing and use of hand sanitiser, face masks,
and other PPE as appropriate by study participants and research staff during the study visit and a social distance of 2 metres will be maintained throughout the visit, where possible.

2) Eligibility Assessment
After initial screening, potentially suitable participants will be invited to a full eligibility assessment. During this visit further information regarding the study will be provided to the participants, informed consent will be taken, inclusion and exclusion criteria will be applied, including an assessment of the individual's medical history and substance use history. Where necessary, the study team will consult PI to confirm eligibility. The Mini-International Neuropsychiatric Interview (MINI) will be used to confirm ICD-10 diagnosis of schizophrenia and related psychoses. The Positive and Negative Syndrome Scale (PANSS) will be used to confirm the presence of positive symptoms of psychosis in patients. The Temporal Experience of Pleasure Scale (TEPS) will be used to confirm eligibility on the basis of anticipatory and consummatory pleasure sum scores. A blood sample will be taken to establish evidence of immune activation (i.e., IL-6 ≥0.7pg/ml) in patients with psychosis, a key eligibility criteria. A MRI screening questionnaire will be administered to those willing and able to give consent for neuroimaging, as per WBIC/CHBH standard procedures, to establish eligibility for scanning.

3) Baseline Data Collection
Approximately 60 patients with psychosis and evidence of inflammation, 30 patients with psychosis and without evidence of inflammation, and 30 healthy participants will be assessed at baseline. This visit will be conducted by a member of the study team/CRN staff and will last approximately 2 hours, excluding time required for neuroimaging (approximately 1 hour). During this visit, participants will complete questionnaires recording sociodemographic information and psychiatric history. Validated psychiatric questionnaires and cognitive tests will be administered, MRI scan performed (optional) and all participants will provide blood samples. Blood samples will be used to measure biomarkers (including genetic) related to inflammation, stress and tryptophan metabolism, and for further tests for eligibility/safety to receive tocilizumab infusion. The assessment scales and questionnaires will be computerised where possible.
After the baseline assessment visit, participants without evidence of inflammation and healthy control participants will be debriefed and will exit the study. Those with psychosis and evidence of inflammation will be scheduled for the intervention visit within the next 14 days, given that all confirmatory tests are satisfactory.
Additional Safety Measures for the Intervention Group:

During the baseline data collection, safety tests for tocilizumab infusion including infection screen will also be carried out on participants with psychosis and evidence of inflammation. In particular, these participants will have a chest Xray to exclude pulmonary TB. Blood samples will be tested for TB, HIV, VZV, Hepatitis B, and C. Participants with normal test results will be eligible to continue in the study.

4) Randomisation and Blinding
Randomization will be done by an external agency. Participants will be randomly assigned to tocilizumab or normal saline group, ensuring two groups are comparable to each other on anhedonia severity and sex. A randomising agency will provide the randomisation code to the relevant hospital pharmacy in Bristol (i.e., United Hospital Bristol and Weston NHS Foundation Trust), Birmingham (i.e., University Hospitals Birmingham), and Cambridge (i.e., Cambridge University Hospitals NHS Foundation Trust) who will dispense tocilizumab or normal saline according to the randomisation schedule. Dispensing pharmacies will each keep a log of products dispensed. Infusions will be prepared and administered at clinical research facilities (CRFs) in Bristol (i.e., United Hospital Bristol and Weston NHS Foundation Trust), Birmingham (i.e., University Hospitals Birmingham), and Cambridge (i.e., Cambridge University Hospitals NHS Foundation Trust). Infusion packs will be prepared by trained staff not part of the core study team, ensuring blinding of treatment allocation. Infusion packs containing drug or placebo will be visually indistinguishable from each other, also ensuring that both participants and study team remain blind regarding treatment allocation. If necessary for a clinical reason, site PIs will un-blind the participant using sealed envelope and will inform their health professional whether the participant had received tocilizumab or normal saline.

5) Intervention Procedure (Day 0)
The intervention visit will take place at CRFs in Bristol, Birmingham, and Cambridge. The visit will last approximately two and half hours. On arrival, a member of study team will explain the schedule for this visit and confirm participants are happy to proceed. Interview to check it is safe to proceed with infusion, e.g., participants have not developed an infection. Female participants of childbearing age will be given a urine pregnancy test. Participants who are sexually active will be asked to use contraception for six weeks after infusion. Intravenous infusion: an unlabelled (i.e. double blind) infusion of tocilizumab (4mg/kg, max 800mg) or normal saline will be administered by a trained CRF staff under supervision of a designated study doctor. The infusion will be administered by CRF staff continuously over one hour and the participants will be supervised by a nurse or a member of the study team at all times.
Participants will remain in CRF under observation for a further one-hour period after the end of infusion. Plans for monitoring and managing potential side effects have been described above and in the protocol. All CRF sites are equipped with on site crash teams in case of emergency.

6) Follow-up
The follow-up assessments will take place approximately 7, 14, and 28 days after infusion. Similar to baseline assessment, these sessions will comprise completing questionnaires, and blood samples. Cognitive tasks and an MRI scan (where applicable) will be conducted once around 14 days post-infusion, i.e., at the second follow-up visit.
We will also record any side effects and change in current medications that patients take regularly.
These assessments will be conducted by a member of the study team and each will last approximately one hour, except the assessment around day 14 which will be more comprehensive and will last for approximately two hours, excluding time required for neuroimaging (approximately 1 hour). There be will be regular breaks in order to reduce burden on participants.

7) Final Safety Check and Exit from Study (Day 42)
Approximately 42 days after infusion, a member of the study team will contact participants to provide final debrief and answer any questions they may have. At this point participants will exit the study.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Tocilizumab

Primary outcome(s)
Current primary outcome measure as of 16/01/2023:
Anhedonia assessed using the anticipatory and consummatory pleasure scores of the Temporal Experience of Pleasure Scale (TEPS) at approximately day 14 post-infusion

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Previous primary outcome measure:
Anhedonia measured using the Temporal Experience of Pleasure Scale (TEPS) at baseline and after infusion around day 7, 14, and 28

Key secondary outcome(s)
Current secondary outcome measures as of 16/01/2023:
Clinical outcomes collected at baseline and after infusion around days 7, 14, and 28:
1. Positive and negative symptoms in psychosis measured via the Positive and Negative Syndrome Scale (PANSS) test and Scale for the Assessment of Negative Symptoms (SANS)
2. Depressive symptoms measured via the Calgary Depression Scale for Schizophrenia (CDSS)
3. Fatigue levels measured with the Multi-dimensional Fatigue Inventory (MFI)
4. General quality of life measured by the European Quality of Life-5 Dimensions Three-Level Version (EQ-5D-3L)
5. Subjective wellbeing measured using the Visual Analogue Scale for Subjective Wellbeing (VAS-W)

Cognitive outcomes collected at baseline and after infusion around day 14 :
6. Psychomotor speed assessed using CANTAB Reaction Time (RTI) test or a similar test (computerised) and with the Symbol Coding Test (pen and paper) or a similar test
7. Attention measured using CANTAB Rapid Visual Information Processing (RVP) test or a similar test (computerised)
8. Memory assessed with the CANTAB Paired Associates Learning (PAL) test or a similar test (computerised)
9. Executive function will be assessed using the CANTAB One Touch Stockings of Cambridge (OTS) test or a similar test (computerised) at baseline and 14 days post-infusion

Neuroimaging outcomes collected at baseline and after infusion around day 14:
10. Brain structure assessed using Whole Brain T1 Weighted Structural MRI performed using 3D volumetric spoiled gradient echo at baseline and 14 days post-infusion
11. Brain function assessed using a 1H-MRS measure of glutathione in the prefrontal cortex with 30x30x30 mm spectroscopic voxel at baseline and 14 days post-infusion

12. Brain oxidative stress levels assessed using a 10-min resting state fMRI scan with blood oxygenation-level-dependent (BOLD) images at baseline and 14 days post-infusion

Blood biomarker outcomes collected at baseline and after infusion around days 7, 14, and 28:
13. Levels of inflammatory proteins (including but not limited to cytokines, cytokine receptors, acute phase proteins) analysed using standard laboratory protocols
14. Biochemical assays (including but not limited to cortisol, cardiometabolic markers, tryptophan metabolites) analysed using standard laboratory protocols
15. Peripheral blood cellular immunophenotyping (including but not limited to white blood cell differential count, in depth cellular phenotyping of peripheral blood mononuclear cells, and cell /blood-based experiments/assays) analysed according to laboratory protocols

Genetic outcomes collected at baseline and after infusion around days 7, 14, and 28:
16. DNA sequencing analysed using standard laboratory protocols
17. RNA sequencing analysed using standard laboratory protocols
18. Epigenetic mechanisms assessed with methylation assays

Previous secondary outcome measures as of 16/01/2023:
Collected at baseline and after infusion around day 7, 14, and 28 (unless noted otherwise):
1. Clinical outcomes: positive and negative symptoms in psychosis which will be measured via the Positive and Negative Syndrome Scale (PANSS) test and Scale for the Assessment of Negative Symptoms (SANS); depressive symptoms measured via the Calgary Depression Scale for Schizophrenia (CDSS); Fatigue levels measured with the Multi-dimensional Fatigue Inventory (MFI); general quality of life as measured by the European Quality of Life-5 Dimensions Three-Level Version (EQ-5D-3L); and subjective wellbeing as measured using the Visual Analogue Scale for Subjective Wellbeing (VAS-W).
2. Cognitive outcomes: National Adult Reading Test (NART) for estimated premorbid IQ; psychomotor speed as seen on CANTAB Reaction Time (RTI) test or a similar test (computerised) and with the Symbol Coding Test (pen and paper) or a similar test; attention will be measured using CANTAB Rapid Visual Information Processing (RVP) test or a similar test (computerised); memory will be assessed with the CANTAB Paired Associates Learning (PAL) test or a similar test (computerised); and executive function will be assessed using the CANTAB One Touch Stockings of Cambridge (OTS) test or a similar test (computerised) at baseline and 14 days post-infusion.
3. Neuroimaging outcomes will be based on comparisons of brain structure, function, and oxidative stress levels, using the following imaging techniques: Whole Brain T1 Weighted Structural MRI performed using 3D volumetric spoiled gradient echo; 1H-MRS measure of glutathione in the prefrontal cortex with 30x30x30 mm spectroscopic voxel; and a ten-minute resting state fMRI scan with blood oxygenation-level-dependent (BOLD) images at baseline and 14 days post-infusion.
4. Blood Biomarker outcomes: will be assessed in comparison with baseline reports within and between groups. These measures will be recorded using assays to detect inflammatory proteins (including but not limited to cytokines, cytokine receptors, acute phase proteins); biochemical assays (including but not limited to cortisol, cardiometabolic markers, tryptophan metabolites); and peripheral blood cellular immunophenotyping (including but not limited to white blood cell differential count, in depth cellular phenotyping of peripheral blood mononuclear cells, and cell /blood-based experiments/assays).
5. Genetic outcomes will be determined via DNA sequencing, and epigenetic mechanisms will be assessed with methylation assays.

Previous secondary outcome measures:
Collected at baseline and after infusion around day 7, 14, and 28 (unless noted otherwise):
1. Clinical outcomes: positive and negative symptoms in psychosis which will be measured via the Positive and Negative Syndrome Scale (PANSS) test and Scale for the Assessment of Negative Symptoms (SANS); depressive symptoms measured via the Calgary Depression Scale for Schizophrenia (CDSS); Fatigue levels measured with the Multi-dimensional Fatigue Inventory (MFI); general quality of life as measured by the European Quality of Life-5 Dimensions Three-Level Version (EQ-5D-3L); and subjective wellbeing as measured using the Visual Analogue Scale for Subjective Wellbeing (VAS-W).
2. Cognitive outcomes: National Adult Reading Test (NART) for estimated premorbid IQ; psychomotor speed as seen on CANTAB Reaction Time (RTI) test or a similar test (computerised) and with the Digit Symbol Substitution Test (pen and paper) or a similar test; attention will be measured using CANTAB Rapid Visual Information Processing (RVP) test or a similar test (computerised); memory will be assessed with the CANTAB Paired Associates Learning (PAL) test or a similar test (computerised); and executive function will be assessed using the CANTAB One Touch Stockings of Cambridge (OTS) test or a similar test (computerised) at baseline and 14 days post-infusion.
3. Neuroimaging outcomes will be based on comparisons of brain structure, function, and oxidative stress levels, using the following imaging techniques: Whole Brain T1 Weighted Structural MRI performed using 3D volumetric spoiled gradient echo; 1H-MRS measure of glutathione in the prefrontal cortex with 30x30x30 mm spectroscopic voxel; and a ten-minute resting state fMRI scan with blood oxygenation-level-dependent (BOLD) images at baseline and 14 days post-infusion.
4. Blood Biomarker outcomes: will be assessed in comparison with baseline reports within and between groups. These measures will be recorded using assays to detect inflammatory proteins (including but not limited to cytokines, cytokine receptors, acute phase proteins); biochemical assays (including but not limited to cortisol, cardiometabolic markers, tryptophan metabolites); and peripheral blood cellular immunophenotyping (including but not limited to white blood cell differential count, in depth cellular phenotyping of peripheral blood mononuclear cells, and cell /blood-based experiments/assays).
5. Genetic outcomes will be determined via DNA sequencing, and epigenetic mechanisms will be assessed with methylation assays.

Completion date
30/11/2025

Eligibility

Key inclusion criteria
Inclusion Criteria for All Participants
1. Able and willing to give informed consent, including consent to share information with the participant’s General Practitioner (GP) and to access secondary care and GP records.
2. Able to understand written and spoken English.
3. Willing to consent to blood sampling.
4. Willing to abstain from strenuous exercise for 72 hours before the assessment visits.
5. Age: 18 - 40 years (inclusive) at the time of eligibility assessment.

Additional Inclusion Criteria for Neuroimaging
6. Able and willing to consent to MRI scanning.

Additional Inclusion Criteria for Healthy Controls
7. No current or lifetime psychiatric diagnosis.

Additional Inclusion Criteria for All Individuals with Psychosis
8. Diagnosis of psychosis: meet ICD-10 criteria for a diagnosis of schizophrenia and related psychoses (ICD-10 code F20, F22, F25, F28, F29) at the time of eligibility assessment and within three years of first diagnosis of psychotic disorder.
9. On stable treatment regime with no recent (within 2 weeks) initiation, cessation, or change in class of antipsychotic medication.
10. No indication of other reason for preclusion into research (e.g., risk to others) as determined by their clinical team.
11. Positive and Negative Syndrome Scale (PANSS) item score >=3 on P1 (delusions), P2 (conceptual disorganisation), P3 (hallucinatory behaviour), OR P6 (suspiciousness/persecution).

Additional Inclusion Criteria for Intervention Group
12. Evidence of immune activation: required at eligibility and at baseline visit to enter the study. Serum IL-6 level >=0.7pg/ml will be used as a measure of immune activation.
13. Inflammation-related symptom: Temporal Experience of Pleasure Scale (TEPS) anticipatory pleasure score <=41 (based upon item numbers 1, 3, 7, 11, 12, 14, 15, 16, 17, and 8) and consummatory pleasure score <=36 (based upon item numbers 2, 4, 5, 6, 8, 9, 10, and 13).
14. COVID-19 immunity: evidence of COVID-19 immunity required prior to infusion. Immunity will be confirmed before randomisation using evidence of vaccination and antibody titre test.

Additional Inclusion Criteria for Patients with Psychosis and No Inflammation
15. No evidence of immune activation: required at eligibility and at baseline visit to enter the study. Serum/plasma IL-6 level <0.7pg/ml will be used to confirm no evidence of immune activation.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
40 Years

Sex
All

Key exclusion criteria
Exclusion Criteria for All Participants
1. Pregnancy (confirmed by urine pregnancy test) or breast feeding.
2. Body mass index (BMI) >35 kg/m² (i.e., WHO obesity class II or above).
3. Current or lifetime diagnosis of antisocial personality disorder, autism or other

neurodevelopmental disorder, major traumatic brain injury (determined by Chief Investigator).
4. Currently active diagnosed eating disorder likely to compromise ability to take part (determined by Chief Investigator).
5. History of alcohol or substance use disorder (abuse/dependence) within six months prior to eligibility assessment (nicotine and caffeine dependence are not exclusionary).
6. Current use of medication likely to compromise interpretation of immunological data (including, but not limited to, antibiotics, regular non-steroidal anti-inflammatory drugs, oral /injectable corticosteroids – or any other substances to be determined by the Chief Investigator).
7. Known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other opportunistic infections.
8. Current or past infection including tests for TB, Hepatitis B, Hepatitis C, VZV or HIV confirmed by blood test. Chest X-ray will be also done to exclude TB.
9. Any major episode of infection requiring hospitalisation or treatment with IV antibiotics within 4 weeks of eligibility assessment.
10. Unstable cardiac, pulmonary, renal, hepatic, endocrine, hematologic, or active infectious disease, including current or prior malignancy.
11. Diverticulitis, inflammatory bowel disease, or uncontrolled gastric/duodenal ulcer.
12. Rheumatic autoimmune disease, mixed connective tissue disease, scleroderma, polymyositis, or significant systemic involvement secondary to rheumatoid arthritis.
13. Current and active ischemic heart disease, e.g., unstable angina.
14. Uncontrolled hypertension defined as systolic blood pressure >170 or diastolic blood pressure >110.
15. History of severe allergic or anaphylactic reactions to human, humanized or murine monoclonal antibodies.
16. No history of chicken pox infection or no history of varicella zoster vaccination.

Additional Exclusion Criteria for Neuroimaging
17. Contraindications to MRI scanning.

Date of first enrolment
01/10/2022

Date of final enrolment
01/02/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
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Study participating centre
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Study participating centre
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Study participating centre
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Study participating centre
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Steelhouse Lane
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B4 6NH

Study participating centre
University Hospitals Bristol and Weston NHS Foundation Trust
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BS1 3NU

Study participating centre
Cambridge University Hospitals NHS Foundation Trust
Cambridge Biomedical Campus
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CB2 0QQ

Study participating centre
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Queen Elizabeth Hospital
Mindelsohn Way
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Sponsor information

Organisation
University of Bristol

ROR
https://ror.org/0524sp257

Funder(s)

Funder type

Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

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 available upon request from Professor Golam Khandaker (golam.khandaker@bristol.ac.uk). Anonymised data and metadata will be available upon reasonable request for scientific, non-commercial research for five years after the trial manuscript has been published and following an application to the PIMS consortium describing the purpose of analysis. Data will only be shared for participants who have given consent for their data to be used for secondary research and will be fully anonymised.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		24/03/2023	10/05/2023	Yes	No
HRA research summary			28/06/2023	No	No
Other files	Data management plan	21/11/2022	28/11/2022	No	No
Participant information sheet	for control participants version 1.3	10/02/2022	11/07/2022	No	Yes
Participant information sheet	for patients version 1.3	10/02/2022	11/07/2022	No	Yes