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IVIG and rituximab in antibody-associated psychosis - SINAPPS2

Submission date	Recruitment status	[X] Prospectively registered
10/04/2017	Recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
02/05/2017	Ongoing	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
11/03/2025	Mental and Behavioural Disorders	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Psychosis is a mental health condition that causes people to see reality differently, causing hallucinations or delusions. There is some evidence that, rarely, psychosis may be caused by a particular kind of antibody in the blood that affects the brain. Antibodies are molecules which the body makes to fight infections. There is some evidence that getting rid of these antibodies may improve the symptoms of psychosis. Immunotherapy could be helpful for patients with psychosis. Immunotherapy is a type of treatment that aims to boost the body's natural defences to fight cancer. The trial combines the rapid-action treatment (IVIG) to induce symptom remission (stop it from returning), with a longer-action therapy (rituximab) to maintain remission. The aim of this study is to examine if immunotherapy is an effective treatment for antibody-associated psychosis, either in first episode psychosis (FEP) or relapse following remission, alongside antipsychotic medication if required.

Who can participate?
Adults aged 18 to 70 years old who have had an episode of psychosis within the last two weeks.

What does the study involve?
After a screening and baseline examination to assess the severity of their symptoms and to follow adverse events, participants are randomly allocated to one of two groups. Those in the first group receive IVIG (two grams per kilogram over four days) followed by two infusions of one gram of rituximab around day 30 (14 days after their first infusion). Those in the second group receive the same treatment but with a placebo (a dummy) medication. Participants undergo a number of assessments including a physician examination, laboratory tests, clinical and cognitive (mental) tests to assess if immunotherapy can help treat psychosis.

What are the possible benefits and risks of participating?
Participants may benefit from improvement in psychosis. There is a risk of discomfort when giving blood. Participating in this study may increase the number of clinic/hospital appointments participants attend and may require an inpatient stay in hospital of up to 4 days.

Where is the study run from?
1. Addenbrooke's Hospital (lead centre) (UK)

2. John Radcliffe Hospital (UK)
3. Queen Elizabeth Hospital (UK)
4. King's College Hospital (UK)

When is the study starting and how long is it expected to run for?
July 2015 to March 2027

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

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2016-000118-31

ClinicalTrials.gov (NCT)
NCT03194815

Protocol serial number
CPMS 32531

Study information

Scientific Title
A randomised phase II double-blinded placebo-controlled trial of intravenous immunoglobulins and rituximab in patients with antibody-associated psychosis (SINAPPS2)

Acronym
SINAPPS2

Study objectives
Immunotherapy is an effective treatment for antibody-associated psychosis, either in FEP or relapse following remission, alongside antipsychotic medication if required.

Ethics approval required
Old ethics approval format

Ethics approval(s)
South Central - Oxford C Research Ethics Committee, 06/12/2016, ref: 16/SC/0584

Study design
Randomized; Interventional; Design type: Treatment, Drug, Psychological & Behavioural, Immunotherapy

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Antibody-associated psychosis

Interventions
Participants are given a participant information sheet and asked to provide informed consent.

Participants first undergo screening assessments. This takes around 2 hours to complete and involves a physician review of medical and medication history, a physical exam, blood samples (for safety monitoring), and urine sample pregnancy tests (for women of childbearing potential). The severity of selected symptoms are assessed using the PANSS scale, a medical scale used for measuring symptom severity of participants with schizophrenia, separated into positive, negative and general symptoms. This takes around 30-40 minutes and is completed by a member of the research team. A short PANSS interview for selected symptoms is conducted (items on P1, G9, P3, P2, G5, N1, N4, N6. Recording and assessment of adverse events start from the point of informed consent and are assessed at the baseline visit

Within four weeks of the screening visit, participants return for a 30-minute baseline visit. This involves a physician review since the screening visit, weight and height assessment, and one blood sample is taken for future research purposes. Assessments of current symptoms are also carried out using clinical questionnaires. The severity of symptoms is assessed by PANSS interview (all items). Participants undergo other clinical and cognitive assessments including:
1. Global Assessment of Functioning (GAF): a brief numeric scale (1 through 100) used by mental health clinicians and physicians to rate subjectively the social, occupational, and psychological

functioning of adults, usually takes around 3 minutes and is completed by a member of the research team
2. Clinical Global Impression (CGI): A 7-point scale that provides a brief, stand-alone assessment of symptom severity, treatment response and the efficacy of treatments in treatment studies of participants with mental disorders, usually takes around 2 minutes and is completed by the clinician
3. Young Mania Rating Scale (YMRS): An 11-item scale used to assess symptoms of mania, usually takes around 10 minutes and is completed by a member of the research team
4. Brief Assessment of Cognition (BACS): A set of tests that assesses the aspects of cognition found to be most impaired and most strongly correlated with outcome in participants with schizophrenia (memory and executive function), usually takes around 30 minutes and is completed by the participant
5. Antipsychotic Non-Neurological Side Effects Rating Scale (ANNSERS): A scale used to assess the side effects associated with both first- and second-generation antipsychotic drugs, usually takes around 10 minutes and is completed by a member of the research team.
There are also be an adverse event review and concomitant medication review.

Following this visit, participants are randomly allocated to either receiving either the active or placebo treatment.

Active treatment group: Participants receive one cycle of intravenous immunoglobulin (IVIG) or placebo infusion on day 1 of treatment, and this lasts up to six hours a day for up to 4 days. Between 28 and 35 days after IVIG/placebo participants receive their first infusion of rituximab and intravenous methylprednisolone premedication prior to rituximab or equivalent 0.9% saline volume for patients receiving placebo, this lasts for up to four hours. This is preceded by paracetamol and piriton (for both groups) to reduce infusion reactions. After a further two weeks (+/- two days), participants receive a second infusion of rituximab and intravenous methylprednisolone premedication prior to rituximab or equivalent 0.9% saline volume for patients receiving placebo, preceded by paracetamol and piriton (for both groups). At the second treatment visit (first rituximab treatment), a blood sample for safety monitoring purposes is taken and participant undergo a short PANSS interview assessment (severity of selected symptoms; items P1, G9, P3, P2, G5, N1, N4, N6 only). At all three treatment visits includes assessments of both adverse events and concomitant medications.

Placebo group: Participants receive the same intervention as the active treatment group but with placebos to match IVIG and Rituximab.

After treatment has finished, monthly telephone or visit assessments are carried out at months two, four, five, seven, eight, ten, 11 (if more time is required to follow up to remission then the follow up assessments will continue to months 13,14,16,17) to review severity of symptoms and check the participant's condition. These follow up phone calls should last around 15 minutes and includes an assessment of severity of selected symptoms by a short PANSS interview (items on P1, G9, P3, P2, G5, N1, N4, N6 only), plus assessment of both adverse events and concomitant medications.

Following treatment, every three months (3,6,9,12 [15,18 if needed]) participants are be asked to come to a clinic to see a member of the research team. During these visits participants undergo a physician review and physical assessment, their height and weight are measured, have a monitoring blood sample taken (at month six and 12 (and 18 if required) only), and they complete a full PANSS, CGI, GAF, YMRS, BACS, and ANNSERS assessments. This includes assessments of both adverse events and concomitant medications take takes around two hours to complete.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Immunoglobulin, rituximab

Primary outcome(s)
Time to start of symptomatic remission sustained for 6 months is measured using the Positive and Negative Syndrome Scale (PANSS) at baseline, 3, 6, 9 and 12 months (also done at months 15 and 18 if needed).

Key secondary outcome(s))
1. Time to first treatment response is measured using the PANSS at monthly intervals out to month 12 (out to month 18 if needed).
2. Relapse rate is measured using the PANNS at monthly intervals out to month 12 (out to month 18 if needed).
3. Number of adverse effects is measured using the Adverse Event CRF at 3, 6, 9 and 12 months (also done at months 15 and 18 if needed).
4. Number of serious infections is measured using adverse event data at three, six, nine and twelve months (also done at month 15 and 18 if needed).
5. Proportion of patients reaching 20%, 30% and 40% reduction in PANSS total score using measured using the PANSS score at 3, 6, 9 and 12 months (also done at month 15 and 18 if needed).
6. Symptom severity (schizophrenia) is measured using the Clinical Global Impression (CGI) score in at baseline and month 12
7. Symptoms of mania are measured using the Young Mania Rating Scale (YMRS) at baseline and month 12
8. Side effects associated with both first- and second-generation antipsychotic drugs are measured using the Antipsychotic Non-Neurological Side-Effects Rating Scale (ANNSERS) at baseline and month 12
9. Cognition is measured using the Brief Assessment of Cognition in Schizophrenia (BACS) at baseline and month 12
10. Social, occupational, and psychological functioning is measured using the Global Assessment of Functioning scale (GAF) at baseline and month 12

Completion date
31/03/2027

Eligibility

Key inclusion criteria
1. Acute psychosis >2 weeks. This may either be the first episode or relapse after remission (remission defined as PANSS≤3 on PANSS items P1, G9, P3, P2, G5, N1, N4, N6 for previous six months)
2. Serum or CSF neuronal membrane autoantibodies at pathological levels (including NMDAR, LGI1 and other)
3. Aged 18-70 years

4. Psychosis symptomatic as defined by PANSS ≥4 on P1, G9, P3, P2, G5, N1, N4, N6.
5. Patient or legal representative is willing and able to provide informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
70 years

Sex
All

Key exclusion criteria
1. Duration of current episode of psychosis greater than 24 months
2. Alternative co-existing severe neurological disease, including tumour, hippocampal sclerosis with refractory epilepsy, probable dementia with evidence of atrophy on brain imaging, moderate or severe learning disability
3. Any evidence of a current acute encephalopathy (for instance coma, seizures)
4. Hepatitis B, Hepatitis C or HIV positivity; severe hypogammaglobulinaemia
5. Previous malignancy (to be usually excluded unless agreed with CI)
6. Pregnant, breast feeding or inadequate contraception if female
7. Hypersensitivity or absolute contra-indication to any study medication, murine proteins or excipients
8. Live vaccine within last three months
9. Previous treatment with rituximab in the past 12 months
10. Severe infection and severe heart failure
11. Any other medical illness or disability that, in the opinion of the investigator, would compromise effective study participation
12. Concurrent enrolment in other CTIMPs

Date of first enrolment
12/10/2017

Date of final enrolment
31/03/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Addenbrooke's Hospital (lead site)
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
John Radcliffe Hospital
Headley Way
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United Kingdom
OX3 9DU

Study participating centre
Queen Elizabeth Hospital
Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2GW

Study participating centre
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Suite 5
First Floor
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Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
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Queens Medical Centre
Derby Road

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NG7 2UH

Study participating centre
Oxford Health NHS Foundation Trust
Littlemore Mental Health Centre
Sandford Road
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Study participating centre
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Study participating centre
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G42 9LL

Study participating centre
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EX2 5DW

Study participating centre
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Glossop Road

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S10 2JF

Sponsor information

Organisation
Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge

ROR
https://ror.org/04v54gj93

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research 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 are/will be available upon request from a Scientific Advisory Board, led by Prof Peter Jones, will oversee all requests for data sharing from the trial.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	07/06/2019	10/06/2019	Yes	No
HRA research summary			28/06/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes