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The efficacy of xanomeline-trospium in treating cognitive impairment in patients with a psychotic disorder

Submission date
07/08/2025

Recruitment status
Recruiting

Registration date
13/11/2025

Overall study status
Ongoing

Last Edited
26/11/2025

Condition category
Mental and Behavioural Disorders

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

Plain English summary of protocol

Background and study aims
Psychosis is a mental health condition where people may experience symptoms such as hearing voices or experiencing beliefs or perceptions that others may not have. Many people with psychosis also have difficulties with concentration, memory, and other thinking skills - these are called cognitive symptoms. Current treatments for psychosis work by blocking dopamine D2 receptors in the brain. These medicines can help with hallucinations and delusions but do not usually improve cognitive symptoms.
Xanomeline–trospium is a new treatment being tested that works differently from standard antipsychotics, by activating muscarinic receptors rather than blocking dopamine receptors. This study will compare xanomeline–trospium with two commonly used antipsychotics (risperidone and lurasidone) to find out which is more effective at improving cognitive symptoms in people with early psychosis.

Who can participate?
Adults with early psychosis who are considering changing their current medication can take part. A separate group of healthy volunteers will also take part to provide comparison data, but they will complete assessments only and will not receive study medication.

What does the study involve?
Participants with early psychosis will be randomly assigned (like flipping a coin) to take either xanomeline–trospium or one of the two standard antipsychotics (risperidone or lurasidone) for 6 weeks. Neither participants nor the research team will know which treatment has been given until the end of this phase.
During the 6-week treatment period, participants will attend visits at the start (baseline), at 3 weeks, and at 6 weeks. At these visits, they will complete tests to assess memory and thinking, and assessments of symptoms, daily functioning, and quality of life. At some visits, they will also have brain scans and give blood samples.
After 6 weeks, participants will be told which treatment they received, and if they were receiving

xanomeline-trospium, they can decide whether they would like to continue in the study for another year in an open-label setting. If they choose to continue with the study, there will be an additional visit after one year, and three three-monthly safety calls.

What are the possible benefits and risks of participating?
Participation will help researchers assess whether xanomeline-trospium helps thinking, memory, and other symptoms of psychosis, more than standard antipsychotics. The information collected will help develop better treatments for psychosis. Participants will receive reimbursement for their time and to cover travel expenses.
Like all medicines, the study drugs can cause side effects. Xanomeline–trospium can cause nausea, vomiting, sweating, and constipation. Risperidone and lurasidone can cause movement problems, weight gain, drowsiness, and hormonal changes. Although these are the most common side effects, all medicines can also have other side effects, which will be monitored throughout the trial.
Some of the assessments may feel mentally or emotionally demanding and giving blood samples and the brain scans may be uncomfortable. The brain scans are optional, so participants can choose not to take part in this part of the study.

Where is the study run from?
There will be a study site at the University of Oxford, Oxford (UK) in collaboration with Oxford Health NHS Foundation Trust, and at King's College London, London (UK) in collaboration with South London and Maudsley (SLaM) NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
November 2025 to August 2030

Who is funding the study?
The Wellcome Trust (UK)

Who is the main contact?
1. Dr Robert McCutcheon, robert.mccutcheon@psych.ox.ac.uk
2. Dr Bodyl Brand, Michael Sinden or Lucy Cureton, focus@psych.ox.ac.uk

Contact information

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Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1010141

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
18770

Study information

Scientific Title
The efficacy of xanomeline-trospium in treating cognitive impairment in psychosis: A randomised, double-blind active-controlled clinical trial

Acronym
FOCUS

Study objectives
Primary objectives:
To compare the overall change in cognitive performance between patients who have been treated for 6 weeks with xanomeline-trospium versus a D2 antagonist.

Secondary objectives:
1. To compare improvement on measures of symptoms, functioning and side effects between patients who have been treated for 6 weeks with xanomeline-trospium versus D2 antagonist.
2. To compare the longer-term effects of treatment with xanomeline-trospium compared to a D2 antagonist.
3. To determine the change in biomarkers that occur following treatment with xanomeline-trospium compared to a D2 antagonist.
4. To assess if baseline biomarkers predict symptomatic improvement following treatment with xanomeline-trospium and D2 antagonists.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 10/11/2025, South West - Central Bristol Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 2071048367; centralbristol.rec@hra.nhs.uk), ref: 25/SW/0096

Study design
Double-blind randomized controlled parallel-group trial

Primary study design
Interventional

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Schizophrenia, schizoaffective disorder, or schizophreniform disorder

Interventions
Early psychosis participants are randomised in a 1:1 ratio in this Phase III trial to receive either xanomeline–trospium or a dopamine D2 antagonist (risperidone or lurasidone). Randomisation is stratified by site, baseline cognition status, and biological sex, and is performed centrally using the University of Oxford’s secure online Sortition randomisation system with randomly permuted block sizes to ensure allocation concealment.

Arm 1 – Xanomeline–trospium
Administered orally as capsules containing xanomeline tartrate and trospium chloride drug

beads. Dosing is initiated at 50 mg/20 mg twice daily for the first 2 days, increased to 100 mg/20 mg twice daily for days 3–7, then titrated to 125 mg/30 mg twice daily from day 8 (week 2). Participants unable to tolerate the highest dose may reduce to 100 mg/20 mg twice daily. Xanomeline–trospium is administered for 6 weeks during the double-blind phase. Participants may choose to continue in a 52-week single-blind extension, during which xanomeline–trospium is prescribed and managed as part of trial procedures at the end-of-double-blind dose, with adjustments as needed for safety and tolerability.

Arm 2 – Dopamine D2 antagonist (risperidone or lurasidone)
Allocation to risperidone or lurasidone is based on prior treatment history and clinical contraindications.
Risperidone: Initiated at 1 mg twice daily for the first 2 days, followed by 2 mg twice daily for the remainder of week 1 (days 3 to 7). On day 8 (week 2), the dose will be increased to 3 mg twice daily, unless the participant experienced adverse events from their previous dose. Participants who increased to 3 mg twice daily have the option to return to 2 mg twice daily, depending on tolerability, until day 21.
Lurasidone: Initiated at 37 mg twice daily for the first 2 days, followed by 55.5 mg twice daily for the remainder of week 1 (days 3 to 7). On day 8 (week 2), the dose will be increased to 74 mg twice daily, unless the participant experienced adverse events from their previous dose. Participants who increased to 74 mg twice daily have the option to return to 55.5 mg twice daily, depending on tolerability, until day 21.

All medication is taken twice daily for 6 weeks during the double-blind treatment phase. Participants may continue for a further 52 weeks in a single-blind extension. In this extension, those in arm 1 will continue to receive trial medication provided by the trial, while those in arm 2 will have their medication prescribed and managed as per usual care by their clinical team.

Follow-up
After the screening visit and the baseline visit, follow-up visits and assessments occur at 3 weeks, 6 weeks, and 58 weeks for those in the extension, with additional safety calls as specified in the protocol.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Xanomeline tartrate, trospium chloride, risperidone, lurasidone

Primary outcome(s)
Cognitive performance measured using the CANTAB composite score from baseline (Visit 2) to 6 weeks post-baseline (Visit 4)

Key secondary outcome(s))
1. Psychosis symptom severity measured using the Positive and Negative Syndrome Scale (PANSS) total and subscale scores from baseline (Visit 2) to 3- and 6-weeks post-baseline (Visit 3 and Visit 4)
2. Functional capacity measured using the Virtual Reality Functional Capacity Assessment Tool (VRFCAT) from baseline to week 6

3. Individual cognitive domains of the CANTAB measured using individual CANTAB tests from baseline to 6 weeks post-baseline
4. Global clinical severity measured using the Clinical Global Impression – Severity/Improvement scale (CGI-S/I) from baseline to 3- and 6-weeks post-baseline
5. Patient-rated global severity measured using the Patient Global Impression – Severity /Improvement scale (PGI-S/I) from baseline to 3- and 6-weeks post-baseline (Visit 3), and 6 weeks post-baseline (Visit 4)
6. Negative symptom severity measured using the Brief Negative Symptom Scale (BNSS), from baseline, to 3- and 6-weeks post-baseline
7. Subjective cognitive functioning measured using the Subjective Scale to Investigate Cognition in Schizophrenia (SSTICS), from baseline (Visit 2) to 3- and 6-weeks post-baseline
8. Depression symptoms measured using the Calgary Depression Scale for Schizophrenia (CDSS) from baseline to 3- and 6-weeks post-baseline
9. Subjective well-being measured using the Subjective Well-being under Neuroleptics (SWN) scale from baseline (Visit 2) to 3- and 6-weeks post-baseline
10. Work and social adjustment measured using the Work and Social Adjustment Scale (WSAS), from baseline (Visit 2) to 3- and 6-weeks post-baseline
11. Daily functioning measured using the Specific Level of Functioning Scale (SLOF) and the Social and Occupational Functioning Assessment Scale (SOFAS) from baseline (Visit 2) to 6 weeks post-baseline (Visit 4)
12. Quality of life measured using the Recovering Quality of Life scale (ReQoL), from baseline (Visit 2) to 6 weeks post-baseline (Visit 4)
13. Treatment acceptability assessed using the Theoretical Framework of Acceptability – Treatment Acceptability Scale (TFA-TAS), from baseline to 3- and 6-weeks post-baseline
14. Side effects monitored using the Glasgow Antipsychotic Side-Effect Scale (GASS) supplemented with five items from the UKU Side Effect Rating Scale (UKUSERS) at baseline (Visit 2), 3 weeks post-baseline (Visit 3), and 6 weeks post-baseline (Visit 4)

Follow-up phase (participants in follow-up only):
Longer-term effects of treatment measured assessing the change in PANSS, VRFCAT, CANTAB (composite and subtests), CGI-S, CGI-I, PGI-S, PGI-I, BNSS, SSTICS, CDSS, TFA-TAS, SWN, WSAS, SLOF, SOFAS, and ReQoL scores from baseline to 58 weeks post-baseline (Visit 5)

Biomarkers:
Biomarkers (MRI, MEG, and blood-based measures) assessed at baseline (Visit 2), 6 weeks post-baseline (Visit 4), and 58 weeks post-baseline (Visit 5)

Completion date
31/08/2030

Eligibility

Key inclusion criteria
General inclusion criteria:
1. Individuals aged 18 to 55 years, willing and able to provide written informed consent
2. In the Investigator’s opinion, is able and willing to comply with all trial requirements
3. Able to understand and communicate in English
4. Body mass index ≥18 and ≤40 kg/m2

Additional inclusion criteria for early psychosis participants:
1. The participant meets DSM-5 criteria for schizophrenia, schizoaffective disorder, or

schizophreniform disorder, as confirmed through the Mini International Neuropsychiatric Interview (MINI).
2. The participant has previously been treated with an antipsychotic.
3. The participant is within 10 years of first experiencing psychosis.
4. The participant is wishing to either commence an antipsychotic (if not currently receiving treatment), or switch from their current antipsychotic treatment and this is clinically indicated.
5. Attitude to antipsychotic medication is rated 4 or more on the Kemp Clinician Rating Scale (CRS).
6. Participants of childbearing potential (*) and male participants (assigned sex at birth) whose partner is of childbearing potential must confirm that they are using effective contraception, or that their partner is using effective contraception throughout the trial, in accordance with the requirements outlined in the protocol**.
7. The participant is willing to allow their General Practitioner and consultant, if appropriate, to be notified of participation in the trial.

Additional inclusion criteria for control participants:
1. No diagnosis of psychiatric disorder other than previous episode(s) of depression or anxiety.
2. The participant is willing and able to undergo MRI/MEG scans.

*A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
** Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include: 1) combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral; intravaginal; transdermal); 2) progestogen-only hormonal contraception associated with inhibition of ovulation (oral; injectable; implantable); 3) intrauterine device (IUD); 4) intrauterine hormone-releasing system (IUS); 5) bilateral tubal occlusion; 6) vasectomised partner; 7) sexual abstinence (abstinence should only be used as a contraceptive method if it is in line with the subjects' usual and preferred lifestyle.
Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception). The participant agrees to use an acceptable method of contraception for the full duration of the trial and for 30 days after any trial drug administration, unless surgically sterile or postmenopausal.

Participant type(s)
Healthy volunteer, Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
55 years

Sex
All

Total final enrolment
0

Key exclusion criteria
General exclusion criteria:
1. Pregnancy or breastfeeding.
2. The participant has a current diagnosis of 'Substance or medication induced psychotic disorder' or 'Psychotic disorder due to another medical condition' as determined through the MINI.
3. Current active suicidal ideation within the last 2 weeks, defined as a score of 1 or higher on CDSS question 8, followed by an assessment by the treating clinician who determines it is not safe for the patient to participate in the trial*
4. Meeting DSM-V criteria for substance use disorder, except for nicotine (mild, moderate, and severe allowed) well as alcohol or cannabis abuse (mild allowed).
5. Positive urine drug screen, except for cannabis provided that cannabis abuse (moderate or severe) or dependency has been ruled out, as determined through the MINI.
6. Participant has participated in another clinical trial in which the participant received an experimental or investigational drug or agent within 2 months before Visit 1. Participants who have participated in Type A studies (e.g. trials of standard and within-label treatments including antipsychotic medication) or non-CTIMP studies (e.g. studies of exercise therapy) must have completed the intervention but may be included if permitted by the protocol of the other trial.
7. The participant refuses any mandatory safety checks during the trial, specifically, refusal of: assessment of suicidality, pregnancy test (early psychosis participants of child-bearing potential only); safety blood test (early psychosis participants only); reporting of Adverse Events (AEs) (early psychosis participants only).
8. Any other significant factor which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial.

Additional exclusion criteria for early psychosis participants:
1. The participant meets modified Andreasen criteria for symptomatic remission AND displays no cognitive deficits at the screening visit.
2. Known hepatic impairment (mild, moderate or severe) and/or transaminase elevations levels exceeding the upper limit of normal 3 times or more and bilirubin greater than 2 times the upper limit of normal.
3. Abnormal ECG results at screening (QTC ≥450 ms for males and ≥460 ms for females)
4. In addition to abnormal transaminase levels and eGRF levels any other lab values that, based on the investigator's assessment, may deem the participant unsuitable for inclusion.
5. Known renal dysfunction and/or estimated glomerular filtration rate (eGRF) level below 60 ml /min/1.73 m2.
6. History or high risk of urinary retention, angioedema, gastric retention, or narrow-angle glaucoma.
7. History of serious constipation requiring treatment in the last 6 months
8. History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, or oncologic disease or any other condition that, in the opinion of the investigator, would jeopardise the safety of the subject or the validity of the study results.
9. Experienced any adverse effects related to trospium chloride previously, or allergy to any

component of trospium chloride tablets
10. Contraindication to treatment with lurasidone AND risperidone. If the participant has a contraindication to just one of these medications, they can still participate in the trial. In that case, if allocated to the standard antipsychotic arm, they will use the medication for which they do not have a contraindication.

Date of first enrolment
01/11/2025

Date of final enrolment
30/06/2029

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Warneford Hospital
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Study participating centre
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Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Research organisation

Funder Name
Wellcome Trust

Alternative Name(s)
Wellcome, WT

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not expected to be made available