ISRCTN10534853 https://doi.org/10.1186/ISRCTN10534853

A study to investigate the safety and processing by the body of the drug AUT00206 in patients with schizophrenia, and to explore the effects of AUT00206 on relevant central biomarkers

Submission date
02/02/2022

Recruitment status
No longer recruiting

Registration date
08/02/2022

Overall study status
Completed

Last Edited
10/12/2024

Condition category
Mental and Behavioural Disorders

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[X] Results
[ ] Individual participant data

Plain English summary of protocol

Background and study aims
Schizophrenia is a psychotic illness that affects nearly 5 million people in the EU, USA, and Japan. Symptoms of schizophrenia include hearing voices or seeing things that are not real, unusual beliefs and confused thinking. Overall, the total cost to society in England is estimated at £11.8 billion per year, and the cost to the public sector is about £7.2 billion. Currently, there are no medicines that specifically treat schizophrenia.
AUT00206 (the study medicine) is an experimental new medicine with the potential to treat schizophrenia. It acts at sites on nerve cells (called voltage-gated potassium channels) that help to control electrical signalling in parts of the brain involved in learning and behaviour. So, it is hoped that it will be a useful treatment for schizophrenia.
This study aims to investigate the safety, tolerability, processing by the body, and response of the body to AUT00206 after repeated doses in patients with stable but symptomatic schizophrenia, taking one or two established antipsychotic drugs. The results of this study, assuming they are supportive, will help direct the onward development of AUT00206, including further studies examining its potential for effectiveness on symptoms in patients with schizophrenia.

Who can participate?
Adult men aged 18-50 years with schizophrenia, who were diagnosed no more than 5 years before the start of the study.

What does the study involve?
16 participants will take the study medicine and 8 will take a dummy medicine. A computer will decide who takes which at random. The study medicine and dummy medicine look the same, so neither the participants nor researchers will know which one medicine is being taken (the research team will be able to find out if necessary). The medicine will be taken as follows: a single dose of 2000 mg on the first day; twice daily doses of 800 mg (1600 mg each day) for the next 26 days; and a single dose of 800 mg on the last day. Participants will stay at Hammersmith

Medicines Research (HMR) for 8 days and 7 nights in a row. Then they will leave HMR and continue to take the study medicine at home as directed. Participants will be asked to return to HMR after about 1, 2, and 3 weeks after they have been discharged, for outpatient visits, and again about 2 weeks after the last dose, for a final checkup. At these visits, the study team will measure brain activity, using EEGs and participants will be asked to do some tasks on a computer tablet to test memory, reaction time, and concentration. The study team will also look at the outside and inside of participants' ears using an otoscope (a small magnifying glass with a light on it) and carry out some audiology (hearing) assessments. There will also be optional PET and MRI scans at one of the follow-up visits.

What are the possible benefits and risks of participating?
There is no medical benefit from taking part in the study. There were no important side effects in participants who have taken AUT00206 in previous studies. Some people had headaches, drowsiness, abdominal pain, or nausea. The study medicine has also been thoroughly tested in laboratory animals, and there were no concerns for testing the study medicine in humans. Some animals had small increases in liver and thyroid weight, which returned to normal after treatment stopped. Blood tests will be done during the study to monitor participants' liver and thyroid function. As with any new medicine that only a few people have taken, we don’t yet know all its side effects.

Where is the study run from?
Hammersmith Medicines Research (UK)

When is the study starting and how long is it expected to run for?
March 2016 to April 2019

Who is funding the study?
Autifony Therapeutics Limited (UK)

Who is the main contact?
hmr@hmrlondon.com
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Contact information

Type(s)
Public

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT03164876

Clinical Trials Information System (CTIS)
2016-002704-63

Integrated Research Application System (IRAS)
215896

Protocol serial number
AUT031206

Study information

Scientific Title
A randomised, double-blind, placebo-controlled study of the safety, pharmacokinetics and exploratory pharmacodynamics of AUT00206 for 28 days as adjunctive therapy in patients with recently diagnosed schizophrenia

Study objectives
No formal hypothesis was included in this Phase I study

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 30/01/2017, London - Central Research Ethics Committee (Health Research Authority, 3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)201048007; sharon.northey1@nhs.net), REC ref: 17/LO/0066

Primary study design
Interventional

Study design
Phase Ib interventional single-center randomized double-blind placebo-controlled repeated-dose study

Study type(s)
Treatment

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

Interventions
Participants will be randomly assigned 2:1 by an independent statistician using SAS to take either AUT00206 or AUT00206 placebo oral capsules as follows:
1. A single dose of 2000 mg on the first day
2. Twice daily doses of 800 mg (1600 mg each day) for the next 26 days

3. A single dose of 800 mg on the last day
Participants will stay at Hammersmith Medicines Research (HMR) for 8 days and 7 nights in a row at the start of the study before being discharged to continue to take the study medicine at home as directed. Participants will be asked to return to HMR at 1, 2, and 3 weeks after they have been discharged (2, 3, and 4 weeks from the start of the study), for outpatient visits, and again about 2 weeks after the last dose (6 weeks from the start of the study), for a final check-up.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
AUT00206

Primary outcome(s)
1. Pharmacokinetic (PK) profile of AUT00206 after single oral doses measured using blood samples taken before and at several timepoints during the 28-day dosing period – at 0.5, 1, 2, 4, 6, 8, 12 and 16 h after morning dosing on Day 1. Pre-dose samples will be taken before morning dosing on Days 2–6 and on Days 14, 21 and 28 (before morning dosing, if possible)
2. Safety measured using the following at frequent intervals during the study:
2.1. Vital signs (blood pressure, heart rate, tympanic temperature, and respiratory rate) recorded before each morning and evening dose administered during residence, and at 4 h after the morning dose on Days 1–5 and pre-morning dose on Day 6, 14, 21, 28 and at follow up visit.
2.2. 12-lead electrocardiogram (ECG) (single measurements) will be recorded before each morning and evening dose administered during residence, and at 4 h after the morning dose on Days 1–5 and pre-morning dose on Day 21 and follow up.
2.3. Physical examinations on day -2 and on Day 6, 14,21, 28 and at follow up
2.4. Laboratory safety tests (haematology, biochemistry, and urinalysis) on Day 1, 5,14,21 and at follow up
2.5. Suicidal ideation with some intent to act measured using the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening, Day -1, Day 6
2.6. Adverse events (AEs) reported throughout the study

Key secondary outcome(s)
Secondary outcome measures:
The effects of repeated doses of AUT00206 on Mismatch Negativity (MMN) as a biomarker for schizophrenia measured using MMN at baseline (day -2) and Day 1, Day 4 or 6, Day 14, Day 21 and Day 28 during the study whilst subjects receive treatment

Exploratory outcome measures:
1. The effects of repeated doses of AUT00206 on several clinical rating scales measured using the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression (CGI) scale, and Hospital Anxiety and Depression Scale (HADS) at screening, baseline, and 6 weeks
2. The effects of repeated doses of AUT00206 on the electrical activity of the brain and cognition assessed using EEGs and cognitive tests at baseline and 2, 3, 4, and 6 weeks and some optional assessments which include Audiology at baseline and 2, 3, 4, and 6 weeks, and fMRI, and PET scans at one of the visits at baseline and 2, 3, 4, or 6 weeks

Completion date
03/04/2019

Eligibility

Key inclusion criteria
1. Aged 18–50 years
2. Schizophrenia diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5); no more than 5 years (before screening) since first contact, diagnosis, and treatment with the psychiatric services for a psychotic illness. Subjects up to 5 years and 6 months post-diagnosis may be included if considered otherwise suitable, at the discretion of the investigator.
3. One positive symptom >3, or two or more positive symptoms =3, AND one negative symptom >3, or two or more negative symptoms =3 on the PANSS
4. Medically and psychiatrically stable (in the opinion of the investigator) and no significant relapse of schizophrenia (i.e. requiring hospitalisation) for the 2 months before admission
5. On a stable dose of one or two antipsychotic drugs (excluding clozapine) for 1 month before screening
6. Agree to use appropriate contraception
7. Sufficient understanding of the nature of the trial and any hazards of participating in it. Ability to communicate satisfactorily with the investigator and to participate in, and comply with the requirements of, the entire trial.
8. Willingness to give written consent to participate after reading the information and consent form, and after having the opportunity to discuss the trial with the investigator or his delegate
9. Capacity to provide informed consent, as judged by an investigator

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
Male

Total final enrolment
24

Key exclusion criteria
1. Female
2. Severely underweight, or morbidly obese, as judged by the investigator
3. Clinically relevant abnormal history, physical findings, ECG, or laboratory values at the pre-trial screening assessment that could interfere with the objectives of the trial or the safety of the subject

4. Presence of acute or chronic illness or history of chronic illness sufficient to invalidate the subject's participation in the trial or make it unnecessarily hazardous
5. Impaired endocrine, cardiac, pulmonary, thyroid, haematological, hepatic, respiratory, neurological, immunological or renal function, or another major disease (e.g. cancer) deemed clinically significant at the time of the study
6. Type 1 diabetes or type 2 diabetes requiring therapeutic intervention (type 2 diabetes controlled by diet alone is permitted if HbA1c <7%)
7. History of epilepsy or seizures (except febrile seizures in childhood)
8. Surgery (eg stomach bypass) or medical condition that might significantly affect the absorption of medicines
9. Homicidal ideation or intent, as judged by an investigator; suicidal ideation, with some intent to act, within 6 months before admission, as judged by an investigator, or based response in the C-SSRS (positive response to questions 4 or 5 of the suicidal ideation section); or history of suicidal behavior within the year before admission
10. Moderate or severe depression or generalised anxiety as indicated by a score of ≥11 out of 21 in either subscales of the Hospital Anxiety and Depression Scale (HADS)
11. Current use of CNS drug that could potentially interfere with the mode of action of AUT00206 or certain drugs which have significant interactions with CYP3A4, CYP2C9, and 2C19
12. Presence or history of severe adverse reaction to any drug or a history of sensitivity to the study medicine excipients, or modulators of voltage-gated potassium channels
13. Participation in another clinical trial of a new chemical entity or a prescription medicine within the previous 30 days, or 5 half-lives of the study medicine (whichever is longer)
14. History of drug or alcohol dependence in the year before admission
15. Uncontrolled hypertension or hypertension treated with a prohibited medicine
16. Corrected QT interval (QTcB) <330 msec or >450 msec at the screening examination, unless judged not clinically significant by an investigator
17. Likelihood that the subject will not comply with the requirements of the protocol
18. Positive test for hepatitis B, hepatitis C or HIV
19. Loss of more than 400 ml blood during the 3 months before the admission, e.g. as a blood donor
20. Objection by a General Practitioner (GP), or another doctor responsible for their treatment, to the patient entering the trial

Additional exclusion criteria for PET and MRI only:
1. Exposure to radiation, such that in combination with this trial, exposure would be more than 10 mSv within the previous 12 months (PET exclusion only)
2. Presence of a cardiac pacemaker or other implanted electronic device
3. Contradictions to having an MRI scan, such as (but not limited to) ferromagnetic foreign bodies, pacemaker, shrapnel, etc. (MRI exclusion only)

Date of first enrolment
20/04/2017

Date of final enrolment
20/02/2019

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Hammersmith Medicines Research Limited
Cumberland Avenue
London
United Kingdom
NW10 7EW

Sponsor information

Organisation
Autifony Therapeutics (United Kingdom)

ROR
https://ror.org/005mj6e76

Funder(s)

Funder type
Industry

Funder Name
Autifony Therapeutics Ltd

Results and Publications

Individual participant data (IPD) sharing plan
Data generated or analysed during this study will be included in the subsequent results publication. While individual data will not be shared, summaries of group data will be published in a publicly accessible registry. Subsequent publications may include references to select anonymised datasets.

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		01/09/2022	20/12/2022	Yes	No
HRA research summary			28/06/2023	No	No