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Safety, blood levels and effects of AUT00201

Submission date 01/10/2021	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 11/10/2021	**Overall study status** Completed	
Last Edited 10/12/2024	**Condition category** Other	

Plain English summary of protocol

Background and study aims
This is a study of AUT00201, an experimental new medicine with the potential to treat a range of neurological disorders including certain forms of epilepsy, Fragile-X syndrome and schizophrenia. The researchers are doing this study to find out the blood levels and side effects of the study medicine in healthy volunteers (both men and women). This signalling in brain circuits is believed to be dysfunctional in certain neurological and neuropsychiatric disorders, including schizophrenia, Fragile X Syndrome, age-related hearing loss, and certain epilepsy and ataxia syndromes and it is hoped this new drug will be a new treatment option in future. AUT00201 (the study medicine) is an experimental new medicine that 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.

Who can participate?
Healthy male and female volunteers aged 18 – 45 years and 18-65 years, respectively

What does the study involve?
The study will involve four parts: Part A1, A2, A3 and Part B
Part A is divided into three subgroups: Part A1, A2 and A3
Part A1(men) - The first dose of the study medicine will be given in Session 1. The researchers plan to give higher doses in later sessions. It will take 12 weeks to finish the study
Part A2 (women) - The first dose will be decided after reviewing the results from earlier sessions in Part A1 (men) and to give higher doses in later sessions. It will take 12 weeks to finish the study
Part A3 (men) - A dose of the study medicine will be given with a meal and fasted and it will take 8 weeks to finish the study.
Part B (men) - Doses will be given for up to 14 days.
The study will last 10 weeks and there will be four groups of eight participants. In each study session participants will:
1. Take a dose of study medicine or placebo (a dummy medicine that looks the same as the study medicine but has no active ingredient) by mouth, as either a single dose in the morning; or two single doses – one dose in the morning and one in the evening - or both morning and evening in Part B
2. Give many blood samples
3. Have numerous safety assessments

4. Stay on the ward for 4 days and 3 nights in Part A and stay on the ward for up to 17 days and 16 nights in a row in Part B
5. Participants will have a final follow-up visit after the last dose of the study medicine.

What are the possible benefits and risks of participating?
There is no medical benefit from taking part in the study. No one has ever taken the study medicine before, so its side effects are not known. However, it's been thoroughly tested in laboratory animals at higher doses than the researchers plan to give anyone in this study.

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

When is the study starting and how long is it expected to run for?
June 2019 to December 2020

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

Who is the main contact?
Alice.Sharman@autifony.com

Contact information

Type(s)
Public

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT04158453

Clinical Trials Information System (CTIS)
2019-002160-26

Integrated Research Application System (IRAS)
266557

Protocol serial number

AUT011201

Study information

Scientific Title
A randomised, double-blind, placebo-controlled, single and repeated dose-escalation study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of AUT00201 in healthy male and female volunteers

Study objectives
This first-time-in-human (FTIH) study will investigate the safety, tolerability, and PK of AUT00201 after single and multiple ascending oral doses in healthy male and female subjects. The results of this study will be used to select doses for subsequent studies in patients which may be used to treat rare neurological disorders.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 30/08/2019, Office for Research Ethics Committees Northern Ireland (ORECNI) (Unit 4, Lissue Industrial Estate West, Rathdown Walk, Moira Road, Lisburn, BT28 2RF, Northern Ireland; +44 (0)28 95361400; RECB@hscni.net), ref: 19/NI/0141

Primary study design
Interventional

Study design
Phase I single-center placebo-controlled blinded randomized interventional study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Phase I study in healthy volunteers of a treatment to improve/or normalize symptoms and deficits in patients with rare neurological disorders associated with reduced Kv3 channel function

Interventions
Subjects will be numbered consecutively, in the order in which they arrive on the ward and are entered into the trial. Subject numbers will be allocated to treatment sequences (active or placebo) according to the randomisation schedule prepared by an independent statistician using a SAS program.

Part A1 is a double-blind, placebo-controlled, crossover comparison of single rising oral doses of AUT00201 in healthy men; enrollment of up to three groups of 8 men:

Part A, Group 1, Session 1: 6 AUT00201 Active, 2 AUT00201 matching placebo
Part A, Group 1, Session 2: 6 AUT00201 Active, 2 AUT00201 matching placebo
Part A, Group 1, Session 3: 6 AUT00201 Active, 2 AUT00201 matching placebo
Part A, Group 1, Session 4: 6 AUT00201 Active, 2 AUT00201 matching placebo

Part A, Group 2, Session 1: 6 AUT00201 Active, 2 AUT00201 matching placebo
Part A, Group 2, Session 2: 6 AUT00201 Active, 2 AUT00201 matching placebo
Part A, Group 2, Session 3: 6 AUT00201 Active, 2 AUT00201 matching placebo
Part A, Group 2, Session 4: 6 AUT00201 Active, 2 AUT00201 matching placebo

Part A, Group 3, Session 1: 6 AUT00201 Active, 2 AUT00201 matching placebo
Part A, Group 3, Session 2: 6 AUT00201 Active, 2 AUT00201 matching placebo
Part A, Group 3, Session 3: 6 AUT00201 Active, 2 AUT00201 matching placebo
Part A, Group 3, Session 4: 6 AUT00201 Active, 2 AUT00201 matching placebo

PART A2: 8 women were enrolled in a single group
Part A2, Group 1, Session 1: 6 AUT00201 Active, 2 AUT00201 matching placebo
Part A2, Group 1, Session 2: 6 AUT00201 Active, 2 Aut00201 matching placebo

PART A3: up to two groups of 8 men (food interaction)
Part A3, Group 1, Session 1: 6 AUT00201 Active, 2 Aut00201 matching placebo
Part A3, Group 1, Session 2: 6 AUT00201 Active, 2 Aut00201 matching placebo

PART B: multiple ascending dose in men:
Group 1 - 6 AUT00201 Active, 2 Aut00201 matching placebo
Group 2 - 6 AUT00201 Active, 2 Aut00201 matching placebo
Group 3 - 6 AUT00201 Active, 2 Aut00201 matching placebo
Group 4 - 6 AUT00201 Active, 2 Aut00201 matching placebo

All subjects will be dosed orally. Whether subjects receive either a single dose or two single doses (one in the morning and one in the evening) of AUT00201 or placebo, and whether the dose is taken fed or fasted will be determined based on the pharmacokinetic data as it becomes available.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
AUT00201

Primary outcome(s)
PART A1
The tolerability of single oral doses of AUT00201 in healthy men is measured by collecting the percentage of subjects with treatment-related adverse events from Day 1 until the subject’s last visit

PART A2
The tolerability of single doses of AUT00201 in healthy women is measured by collecting the percentage of subjects with treatment-related adverse events from Day 1 until the subject’s last visit

PART A3
The tolerability of single oral doses of AUT00201 with food in healthy men is measured by

collecting the percentage of subjects with treatment-related adverse events from Day 1 until the subject's last visit.

PART B
The tolerability of repeated oral doses of AUT00201 in healthy men is measured by collecting the percentage of subjects with treatment-related adverse events from Day 1 until the subject's last visit

Key secondary outcome(s)

PART A1
1. Pharmacokinetic (PK) profile of AUT00201 after single oral doses of AUT00201 in healthy men is measured from blood samples taken before and frequently up to 144 h
2. Effect of food on the bioavailability of single oral doses of AUT00201 in healthy men measured from blood samples taken before and frequently up to 144 h
3. Safety of AUT00201 in healthy men measured by collecting clinically significant changes to laboratory assessments (routine haematology, biochemistry and urinalysis), physical examinations, 12-lead ECG, 5-lead telemetry, 3-lead Holter monitoring, vital signs (supine and standing), and C-SSRS will be done frequently until the subject's last visit. EEGs will be performed at baseline and 4 h post-dose and around 24 h

PART A2
1. Pharmacokinetic (PK) profile of AUT00201 after single oral doses of AUT00201 in healthy women measured from blood samples taken before and frequently up to 144 h
2. Safety of AUT00201 in healthy women measured by collecting clinically significant changes to laboratory assessments (routine haematology, biochemistry and urinalysis), physical examinations, 12-lead ECG, 5-lead telemetry, 3-lead Holter monitoring, vital signs (supine and standing), and C-SSRS will be done frequently until the subject's last visit. EEGs will be performed at baseline and 4 h post-dose and around 24 h

PART A3
1. Pharmacokinetic (PK) profile of AUT00201 after single oral doses of AUT00201 in healthy men measured from blood samples taken before and frequently after dosing up to 144 h
2. Effect of food on the bioavailability of single oral doses of AUT00201 in healthy men measured from blood samples taken before and frequently after dosing up to 144 h
3. Safety of AUT00201 in healthy men measured by collecting clinically significant changes to laboratory assessments (routine haematology, biochemistry and urinalysis), physical examinations, 12-lead ECG, 5-lead telemetry, 3-lead Holter monitoring, vital signs (supine and standing), and C-SSRS will be done frequently until the subjects last visit. EEGs will be performed at baseline and 4 h post-dose and around 24 h

PART B
1. Pharmacokinetic (PK) profile of AUT00201 after repeated oral doses of AUT00201 in healthy men measured from blood samples taken before each daily repeated morning dose, frequently up to 96 h
2. Effect of food on the bioavailability of repeated oral doses of AUT00201 in healthy men measured from blood samples taken before each daily repeated morning dose, frequently up to 96 h
3. Safety of repeated oral doses of AUT00201 in healthy men measured by collecting clinically significant changes to laboratory assessments (routine hematology, biochemistry and urinalysis) physical examination, 12-lead ECG,5 lead telemetry, 4-lead Holter monitoring, vital signs (supine and standing), and C-SSRS will be done frequently until the subject's last visit

Completion date
23/12/2020

Eligibility

Key inclusion criteria
1. Healthy male volunteer (groups other than Part A2) or healthy female volunteer (Part A2)
2. Aged 18–45 years (men) or 18–65 years (women)
3. A body mass index (BMI; Quetelet index) in the range 18.0–31.0
4. Sufficient intelligence to understand 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
5. 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
6. Agree to use effective contraception
7. Agree not to donate blood or blood products during the study and for up to 3 months after the administration of the trial medication
8. Registered with a General Practitioner (GP) in the UK
9. Willingness to give written consent to have data entered into The Overvolunteering Prevention System (TOPS)

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
57

Key exclusion criteria
1. Woman who is pregnant or lactating, or woman of child-bearing potential who is sexually active and not using a highly effective method of contraception (see section 11)
2. Clinically relevant abnormal history, physical findings, ECG, Holter, or laboratory values at the pre-trial screening assessment that could interfere with the objectives of the trial or the safety of the volunteer
3. Presence of acute or chronic illness or history of chronic illness sufficient to invalidate the volunteer’s participation in the trial or make it unnecessarily hazardous.
4. Family history of seizures and history of seizures or recent head trauma. History or presence of epilepsy, severe head injury, unexplained blackouts, childhood
febrile seizures, chronic pain or any other chronic neurological condition or any psychiatric

disorder (including but not limited to diagnosed anxiety disorders or
depression, family history of suicide, history of attempted suicide, etc)
5. Abnormal safety EEG at screening (Part A1 only)
6. Impaired endocrine, thyroid, hepatic, respiratory or renal function, diabetes mellitus, coronary heart disease, or history of any psychotic mental illness
7. Surgery (eg stomach bypass) or medical condition that might affect the absorption of medicines
8. Presence or history of severe adverse reaction to any drug
9. Use of a prescription medicine (except contraceptive implants in females) during the 28 days before the first dose of trial medication or use of an over-the-counter
medicine, herbal treatments or dietary supplements (including St John's Wort), with the exception of acetaminophen (paracetamol) or multivitamins, during the 7 days before the first dose of trial medication
10. Receipt of an investigational product (including prescription medicines) as part of another clinical trial within the 3 months (or 5 half-lives, whichever is longer)
before [first] admission to this study; in the follow-up period of another clinical trial at the time of screening for this study
11. Presence or history of drug or alcohol abuse, or intake of more than 21 units of alcohol weekly (for men) or 14 units of alcohol weekly (for women) or use of cigarettes or nicotine-containing products during the 3 months before the first dose until the end of the study
12. Blood pressure and heart rate in supine position at the screening examination outside the ranges: blood pressure 90–140 mm Hg systolic, 50–90 mm Hg diastolic; heart rate 40_100 beats /min. Borderline values (ie values that are ≤ 5 mm Hg outside the relevant range for blood pressure, or 5 beats/min for heart rate) will be repeated. Subjects can be included if the repeat value is within range or still borderline, but deemed not clinically significant by the investigator
13. QT value, measured at the screening visit, greater than 450 msec for men or 470 msec for women on 12-lead ECG, using Fridericia's formula (QTcF) for correction. Triplicate measurements will be made, and a mean QTcF value higher than 450 msec for men or 470 msec for women will lead to exclusion. A repeat (in triplicate) is allowed on one occasion for the determination of eligibility
14. Positive result for suicidal ideation or behaviour using the C-SSRS, including a positive response to items 3 to 5; or a history of suicidal behaviour in the past year
15. Possibility that the volunteer will not cooperate with the requirements of the protocol
16. Evidence of drug abuse on urine testing
17. Positive test for hepatitis B, hepatitis C or HIV
18. Loss of more than 400 mL blood during the 3 months before the trial, e.g. as a blood donor
19. Unsatisfactory venous access
20. Vegetarians or vegans who are not willing to take gelatine of animal origin, or on a restricted diet for medical reasons, e.g. lactose or gluten-free diet
21. Objection by GP to volunteer entering trial

Date of first enrolment
10/10/2019

Date of final enrolment
23/12/2020

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Hammersmith Medicines Research Limited
Cumberland Ave
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 Limited

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			26/07/2023	No	No

Other unpublished results	Sponsor report. Some information in this file has been redacted. version 1	31/08/2021	05/11/2021	No	No