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PET study to assess the distribution of RO7308480 in the brain

Submission date	Recruitment status	[X] Prospectively registered
01/12/2022	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
10/02/2023	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
04/12/2023	Mental and Behavioural Disorders	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
The study medicine (RO7308480) is an experimental medicine for treating social anxiety disorder. People with social anxiety disorder have intense fear or discomfort in social situations. This can lead to difficulties in relationships, work or school life. Current treatments for social anxiety disorder don't work well for all patients, or have troublesome side effects.

Studies in animals have shown that by activating sites in the brain called GABAA receptors, animals had a decrease in anxiety-like behaviours. We hope RO7308480 will reduce the symptoms of social anxiety disorder by attaching to these sites.

We'll test single doses of RO7308480 in healthy volunteers to find out its blood levels, side effects, and to measure how much RO7308480 binds to GABAA receptors. To find out, we'll use a brain scan called a PET (positron emission tomography) scan, which makes images of the brain.

Who can participate?
Healthy volunteers aged 23 – 55 years

What does the study involve?
The study is in 2 parts. Part 1 will have up to 5 groups of up to 3 participants and Part 2 will have up to 3 groups of up to 3 participants. Participants will have 2 study sessions. Eligible participants (up to 24 healthy men and women, aged 23–55 years) will take a single dose of RO7308480 by mouth. Participants will have 3 PET scans, and an MRI (magnetic resonance imaging) scan at a separate screening visit. The MRI uses a strong magnetic field to take pictures of the brain.

Participants will take up to 7 weeks to finish the study. They'll make 3 outpatient visits, and have 2 study sessions. They'll stay on the ward for 1 night in Session 1, and for 3 nights in Session 2.

What are the possible benefits and risks of participating?
Benefits:
Participants will not have any benefit from participating in the study.
Risks:

The study is divided into 2 parts (called Parts 1 and 2). Doses from 1mg up to 25mg of RO7308480 will be tested in Part 1.
Like other medicines that enter the brain, the study medicine could affect participants' mood and behaviour, but we haven't seen those side effects in animal studies. Some medicines that enter the brain may increase the risk of people taking their own life, so we'll ask participants often if they've had any such thoughts, or if they've ever tried to take their own life.
Participants will have 3 PET scans, using either [11C]RO7285378 or [11C]flumazenil as a radioactive tracer. To date, over 500 people worldwide have been given [11C]flumazenil. [11C] RO7285278 is a new tracer. So far, it has been tested in 18 healthy volunteers and no side effects were reported. The proposed doses of PET ligands to be administered have been optimised to provide the lowest radiation exposure while maintaining an adequate quality of the data acquired.
In this study, we'll monitor the participants closely, and we won't increase the dose of RO7304840 unless the previous dose causes no important side effects. If a participant is withdrawn, we ask them to consent to a final follow up. We document their consent using an information and consent form (ICF), which has been approved by the HRA's Generic Review Committee (GRC; REC ref: 18/GR/0054).
During their stay, participants must follow HMR's 'house rules'. Our information leaflet is given to volunteers at screening and has been approved by the GRC (REC ref: 18/GR/0104).
If a participant, or their partner, becomes pregnant during the study, we ask to contact their GP about the pregnancy – we document that using a generic ICF that has been approved by the HRA' s GRC (REC ref: 18/GR/0055 or 21/GR/16).
If we find any medically important problem at screening, our physician will tell the participant in person, and pass on the results to the participant's GP, using a letter template, which has been approved by the GRC (REC ref: 18/GR/0101).
We contact participants' GPs to inform them that their patient has volunteered to take part in a study, and provide the GP with a study summary. Our GP letter templates have been approved by the GRC (REC refs: 18/GR/0098 and 18/GR/0099); therefore, we've not attached copies of those letters to this application. Participants give consent for us to contact their GP when they sign the ICF.

Where is the study run from?
HMR London (UK)

When is the study starting and how long is it expected to run for?
November 2022 to June 2024

Who is funding the study?
F. Hoffmann-La Roche Ltd (Switzerland)

Who is the main contact?
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Contact information

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Scientific

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Clinical Trials Information System (CTIS)
2022-002958-12

Integrated Research Application System (IRAS)
1006931

Protocol serial number
BP43580

Study information

Scientific Title
A phase I non-randomized, open label, adaptive, parallel group, human positron emission tomography (PET) study to assess the occupancy of brain γ1 and γ2 containing GABAA receptors of RO7308480 using [11C]RO7285378 and [11C]flumazenil following single oral doses in healthy participants.

Study objectives
Current study hypothesis as of 27/06/2023:

Primary objectives:
Part 1 - To assess the relationship between RO7308480 plasma concentration and brain occupancy of GABAA receptor subtypes (containing the γ1 subunit) after selected single oral doses of RO7308480 using [11C]RO7285378 PET tracer
*Part 2 - To assess the relationship between RO7308480 plasma concentration and brain

occupancy of GABAA receptor subtypes (containing the γ2 subunit) after selected single oral doses of RO7308480 using [11C]flumazenil PET tracer

Secondary objective:
To find out if single doses of RO7308480 have any important side effects in healthy participants when taken by mouth.

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Previous study hypothesis:

Primary objectives:
*Part 1 - To find out if RO7308480 enters the brain and binds specifically to a site called GABAA γ1 subunit-containing receptors after a single oral dose.
*Part 2 - To find out if RO7308480 can bind to a site in the brain called a GABAA γ2 subunit-containing receptors after a single oral dose.

Secondary objective:
To find out if single doses of RO7308480 have any important side effects in healthy participants when taken by mouth.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 07/02/2023, London - Chelsea (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, UK; +44 207 104 8356; chelsea.rec@hra.nhs.uk), ref: 22/LO/0876

Primary study design
Interventional

Study design
Interventional non randomized

Study type(s)
Other

Health condition(s) or problem(s) studied
Social anxiety disorder

Interventions
Participants will receive a single dose of RO7308480 capsule, orally on Day 1. Multiple dose levels of RO7308480 will be tested in Part 1 and Part 2 of the study.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)

RO7308480

Primary outcome(s)
1. Pharmacodynamic (PD): Occupancy of brain GABAA γ1 and GABAA γ2 subunit containing receptors by RO7308480 measured using 1 baseline and 2 post-dose PET scans to assess GABAA receptor occupancy. The baseline PET scan will be carried out on Day -7 or predose on Day 1. The second and third PET scans will be approximately 1.5-2.5 hours and 24-36 hours post-dose. The timing of the on-treatment PET scans may or may not be adjusted after the review of the results from the previous groups.
2. Pharmacokinetic (PK): RO7308480 plasma concentrations measured using blood samples for plasma concentration of RO7308480 will be taken before and after each on-treatment PET scan.

Key secondary outcome(s)
Safety and tolerability of single oral doses of RO7308480, as judged by adverse events, vital signs, physical, and neurological exams, ECG parameters, clinical laboratory results, and C-SSRS. Vital signs, medical examination (including weight), laboratory safety tests, ECGs and adverse events will be assessed frequently until the subject's final visit, 10-14 days after their dose of RO7308480. Serious adverse events (SAEs) will be assessed up to 2 weeks after the last dose of RO7308480. If the Investigator learns of an SAE at any time after the follow up period that they considered reasonably related to study treatment or study participation, the Investigator will notify the Sponsor.

Completion date
27/06/2024

Eligibility

Key inclusion criteria
1. Participants aged 23- 55 years
2. Body mass index 18-32 kg/m²
3. In good health, as judged by medical history, medical examination, vital signs, ECG and clinical laboratory tests
4. Able to communicate with study personnel
5. Reliable, willing, and likely to comply with the protocol
6. Willing to comply with the contraception requirements of the protocol
7. Consent to inform their GP of their participation in the study, and to enter their details into the over-volunteering database (TOPS).

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
23 Years

Upper age limit
55 Years

Sex
All

Key exclusion criteria
1. Not healthy (clinically significant abnormality in our screening tests, which include ECG, vital signs, physical examination, MRI scan and laboratory safety tests of blood and urine);
2. Abuse of alcohol or drugs;
3. Serious reaction to any medicine;
4. Taken certain medicines (ones that could affect the breakdown of the study medicine or that affect the central nervous system or blood flow) during the 30 days before dosing; taken any medicine (except paracetamol), herbal remedies or dietary supplements during the 2 weeks before dosing; taken isotretinoin 2 years prior to screening;
5. History of ophthalmologic conditions that might affect the corneal surface (such as keratoconus, severe dry eye disease and/or corneal dystrophy); wear prescription contact lenses on a daily basis, unless they are not willing to switch to prescription glasses during the study, including the follow-up visit;
6. Have had any condition or operation that might affect the way the body absorbs medicines; have had any clinically significant disease; history of seizures or convulsion 'fits' (other than single benign febrile convulsion of childhood);
7. Objection by GP on medical grounds — because they might increase the risk, or confound the assessment of receptor occupancy
8. Tried to commit suicide or homicide, had suicidal or homicidal thoughts; mental illness might compromise consent;
9. Pregnant or breastfeeding; unwilling to comply with the contraception requirements of the protocol — because of the potential risk to the unborn or breastfed baby;
10. Claustrophobia; any condition which would make it difficult to lie still for very long;
11. Metal in the body (eg pacemaker, mechanical heart valve, replacement hip joint, shrapnel); have worked as a metal worker, machinist or welder — due to increased risk from MRI scans
12. Exposure to ionising radiation as part of a research study, such that combined with the exposure from this study their effective dose in a 12 month period would exceed 10 mSv.
13. Unsatisfactory venous access or contraindication for arterial cannulation;
14. Participants who have donated 500 mL of blood or blood products or had significant blood loss within 3 months prior to screening.
15. participants who use 5 or more cigarettes per day or equivalent amount of tobacco or nicotine products — because participants must be able comfortably to abstain from smoking during the study.
16. Alanine aminotransferase and total bilirubin above the upper limit of normal (ULN) (added 27 /06/2023)

Criteria are designed to select healthy young participants, who are robust enough to recover quickly from any adverse effects of RO7308480.

Date of first enrolment
15/02/2023

Date of final enrolment
11/06/2024

Locations

Countries of recruitment
United Kingdom

Study participating centre
HMR
Cumberland Avenue
London
United Kingdom
NW10 7EW

Sponsor information

Organisation
F. Hoffmann-La Roche Ltd

Funder(s)

Funder type
Industry

Funder Name
F.Hoffmann-La Roche Ltd.

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available due to participant-level data not being a regulatory requirement

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No