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A study to investigate the safety, tolerability, disposition in the body, effects of RO7308480 on the body, and its changes in midazolam disposition in the body following oral administration in healthy participants

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Registration date 08/11/2023	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 08/11/2023	**Condition category** Other	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol

Background and study aims

Social anxiety disorder (also known as social phobia) is a disorder in which people have intense fear or discomfort around social situations, but they desire social contact. This can lead to difficulties in relationships and work or school life as well as everyday activities. Current treatments for social anxiety disorder don't work well for all participants with social anxiety disorder or have troublesome side effects.

RO7308480 is an experimental new medicine that is being developed for treating social anxiety disorder. An experimental drug means that Health Authorities (like the European Medicines Agency) have not approved RO7308480 for the treatment of social anxiety disorder or any other disease.

The study will be conducted in two parts i.e., Part 1 and Part 2.

The purpose of Part 1 of this study is to compare the safety and tolerability of different dose levels of RO7308480 (i.e., the study drug) with a drug that looks like the study drug but contains no active medication (placebo), to determine how well it is tolerated by the participants and to measure how the body absorbs, distributes, and gets rid of it (this is called "pharmacokinetics"). In addition, the effect of RO7308480 on the pharmacokinetics of a microdose of midazolam will be investigated.

The purpose of Part 2 of this study is to collect data regarding the effects of the drug on body (pharmacodynamics) for two different doses of RO7308480 and to compare the results with those for a similar drug (lorazepam) and with placebo.

Who can participate?

Healthy participants with age between 18 years to 55 years.

What does the study involve?
Participants will either be enrolled in Part 1 or Part 2 of the study.
Participants will need to be a part of Part 1 of the study for about 8 weeks (including the screening period and the safety follow-up visit). The study will have three periods:

1. Screening Period: Participants will be screened to check if they are eligible to participate in the study. Screening period will take up place up to 4 weeks before first treatment administration.
2. In-Clinic Period: There will be an in-house stay at the clinic for 20 days and 19 nights during this period. During this time participants will receive study treatment (RO7308480 or placebo) for 14 days (Day 1 to Day 14) and two doses of midazolam two weeks apart, 2 days prior (Day -2) to the first dose of RO7308480 administration and on Day 14.
3. Ambulatory Visit: Participants will have to revisit the clinic about 4 times after getting discharged for check-ups after the study treatment is completed. The final visit will be 2 weeks after the last treatment day.

Participants will need to be part of Part 2 of the study for about 12 weeks (including the screening period and the safety follow-up visit). The study will have four periods:

1. Screening Period: Participants will be screened to check if they are eligible to participate in the study. Screening period will take place up to 4 weeks before first treatment administration.
2. In-Clinic Period: There will be four in-house stays at the clinic for 3 days and 2 nights each time during this period. During each stay participants will receive one single dose of study treatments (low dose RO7308480, or high dose RO7308480, or lorazepam, or placebo).
3. Wash-out period: There will be a break (called a “wash-out period”) of 10 to 14 days between the treatments when the previous drug is expected to be eliminated from the body. There will be three wash-out periods after the first, second, and third dose of study treatment.
4. Ambulatory visit: Participants will have to revisit the clinic 2 weeks post the last treatment day for check-ups.

What are the possible benefits and risks of participating?
Participants will not receive any benefit from participating in this study. But the information learned from this study may be useful to treat future patients with social anxiety disorder.
Participants may have side effects from the drug or procedures used in this study, and they can be mild to severe, and they can vary from person to person.
Risks Associated with RO7308480: Like other medicines that enter the brain, the study medicine (RO7308480) could affect participants’ mood and behaviour, but these side effects have not been seen in animal studies. Some medicines that enter the brain may increase the risk of people taking their own life, so often participants will be asked if they’ve had any such thoughts, or if they’ve ever tried to take their own life.

Risks Associated with Lorazepam:
Side effects most frequently associated with lorazepam are sleepiness (sedation), somnolence, confusion, weakness, resistance of muscle to stretch (reduced muscle tone), decreased attention and unsteadiness. There may also be side effects that are not known at this time.

Risks associated with study procedures
Magnetic resonance imaging (MRI) Scan (Part 2 only):
A MRI scan is a medical procedure using powerful magnets, radio waves, and a computer to make detailed images of the organs in the body so participants with an artificial heart valve, metal plate, pin, or other metallic objects in their body (including gunshot or shrapnel) may not be eligible. The risks or side effects associated with undergoing an MRI scan are minimal for

most participants. MRI scanners are quite closed in and may be unpleasant for people who have a fear or strong dislike of enclosed spaces.

There may be a risk in exposing an unborn child to study the drug, and all risks are not known at this time. Women who are pregnant, become pregnant, or are currently breastfeeding, cannot participate in this study.

Where is the study run from?
F. Hoffmann-La Roche (Switzerland)

When is the study starting and how long is it expected to run for?
June 2023 to December 2023

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

Who is the main contact?
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Contact information

Type(s)
Public, Scientific, Principal investigator

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Clinical Trials Information System (CTIS)
2023-504794-20-00

Protocol serial number
BP43804

Study information

Scientific Title
A phase I randomized, investigator and participant blind, adaptive, multiple-ascending dose, parallel and four-way crossover, placebo-controlled study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and drug interactions (with midazolam) of RO7308480 following oral administration in healthy participants

Study objectives
The purpose of this study is to assess the safety, tolerability, pharmacokinetics, and interaction potential of multiple ascending oral doses of RO7308480 and to investigate the pharmacodynamic (PD) effects of a single oral dose(s) of RO7308480 or lorazepam in healthy participants.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 23/10/2023, Comité de Protection des Personnes SUD-EST IV (Centre Léon Bérard 28, rue Laennec, Lyon Cedex 08, 69373, France; +33 4 78 78 27 61; cppse4@lyon.unicancer.fr), ref: Nil known

Study design
Phase I randomized single center investigator and participant-blind adaptive placebo-controlled study
Part 1: Randomised multiple-ascending dose (MAD) and drug-drug interaction (DDI) study with parallel design
Part 2: Randomised four period four treatments four sequence cross-over design

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Healthy participants

Interventions
Part 1: MAD and DDI:
Participants enrolled in multiple dose groups will be randomized in a 3:1 ratio to receive RO7308480 or matching placebo, orally, once daily (QD) for 14 days. Participants will also receive 2 microdoses of midazolam. First dose will be given 2 days prior to the first dose of RO7308480 (or matching placebo) administration and the second dose will be given on Day 14, after the last RO7308480 (or matching placebo) administration.

Part 2: (Proof of Mechanism (POM)): Participants will randomized in 1:1:1:1 sequence to receive one of the four-treatments i.e., RO7308480 low dose oral capsule; RO7308480 high dose oral capsule; lorazepam oral tablet and placebo) in four periods. Participants will receive a single dose of one of the four treatments on Day 1 in each cross-over period. Each period will be followed by a wash-out period of 10 to 14 days after which the participant will be administered the second treatment.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
RO7308480, Lorazepam, Midazolam

Primary outcome(s)
1. Part 1: Number of Participants with Adverse Events (AEs) and Severity of AEs Graded on a Scale From Mild, Moderate or Severe From Screening up to Follow-up Visit (up to Approximately 8 Weeks)
2. Part 2: Difference in Regional Amygdala Activity During Emotional Face Matching Task from Placebo Measured by Functional Magnetic Resonance Imaging (fMRI) on Day 1

Key secondary outcome(s))
1. Part 1: Plasma Pharmacokinetics (PK) Parameters of RO7308480 (and its Metabolite[s] as Appropriate) Measured Using Specific and Validated Liquid Chromatography–Mass Spectrometry /Mass Spectrometry (LC-MS/MS) from Day 1 up to Day 22
2. Part 1: Urine PK Parameters of RO7308480 (and its Metabolite[s] as Appropriate) Measured Using Specific and Validated LC-MS/MS on Multiple Time-Points from Day 1 up to Day 15
3. Part 1: Plasma PK parameters of RO7308480 (and its Metabolite[s] as Appropriate) Measured Using Specific and Validated LC-MS/MS on Day 1 vs Steady-State-Cmax, AUCtau From Day 1 up to Day 22
4. Part 1: Plasma PK parameters of Midazolam With and Without Concomitant Administration of RO7308480 Measured Using Specific and Validated LC-MS/MS on Multiple Time-Points from Day -2 (2 Days Prior to the First Dose of RO7308480 [or Matching Placebo]) up to Day 15
5. Part 2: Number of Participants with Adverse Events (AEs) and Severity of AEs Graded on a Scale From Mild, Moderate or Severe From Screening up to Follow-up Visit (Approximately 12 Weeks)

Completion date
31/12/2023

Eligibility

Key inclusion criteria
1. Participants who are overtly healthy (defined by absence of evidence of any active or chronic disease).
2. Body mass index (BMI) of 18.5 to 30 kilogram metered square (kg/m^2) inclusive.
3. Affiliated with a social security scheme.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit

55 years

Sex
All

Key exclusion criteria
1. Any condition or disease detected during the medical interview/physical examination that could relapse during or immediately after the study, or would render the participant unsuitable for the study, place the participant at undue risk, or interfere with the ability of the participant to complete the study, as determined by the Investigator.
2. History or evidence of any medical condition potentially altering the absorption, metabolism, or elimination of drugs. This includes a surgical history of the gastrointestinal tract affecting gastric motility or altering the gastrointestinal tract.
3. Use of any psychoactive medication, or medications known to have effects on central nervous system (CNS), or blood flow taken within 4 weeks prior to dosing with RO7308480.
4. Use of any psychoactive medication, or medications known to have effects on CNS or blood flow taken within 4 weeks (or within 5 × the elimination half-life of the medication, whichever is longer) prior to dosing with RO7308480.
5. History of convulsions (other than benign febrile convulsions of childhood) including epilepsy, or personal history of significant cerebral trauma or CNS infections (e.g., meningitis).
6. Part 2 only: abnormalities in the brain known at time of screening which would adversely affect the MRI data analysis.
7. Part 2 only: any condition or disease detected during the medical interview/physical examination which are contraindications for lorazepam such as acute narrow-angle glaucoma, hypersensitivity to benzodiazepines or to any of the other ingredients, acute pulmonary insufficiency: respiratory depression; sleep apnea (risk of further respiratory depression), obsessional states (inadequate evidence of safety and efficacy), severe hepatic insufficiency (may precipitate encephalopathy) and/or myasthenia gravis.
8. Participation in an investigational drug or device study within 90 days (or within 5 times the elimination half-life of the investigational drug, whichever is longer) prior to screening, as calculated from the day of follow-up from the previous study, or more than 4 times per year.
9. Dietary restrictions that would prohibit the consumption of standardized meals.
10. Sensitivity to any of the study treatments, or components thereof, or drug or other allergy that contraindicates the participation in the study.
11. Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and/or total bilirubin outside of normal range (with the exception of Gilbert’s syndrome with total bilirubin < 2.5 x upper limits of normal (ULN)).
12. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert’s syndrome with total bilirubin < 2.5 x ULN).
13. History of suicidal behavior or any risk of suicidal behavior in the opinion of a certified clinician or as evidenced by a “yes” to questions 4 and/or 5 of columbia-suicide severity rating scale (C-SSRS) taken at screening.
14. Coffee (including caffeinated soft drinks or tea) consumption > 5 cups per day or methylxanthine (e.g., Coca-Cola) containing drinks > 1 liter/day or > 250 grams/day of chocolate.
15. Participants under judicial supervision, guardianship, or curatorship.
16. Part 2 only: any contraindication to MRI as determined by a standard questionnaire for radiography screening and safety, including but not restricted to claustrophobia, pacemaker, artificial heart valves, cochlear implants, presence of foreign metal objects in head or body, intracranial vascular clips, tattoos with MRI-incompatible ink etc., or any brain/head

abnormalities restricting MRI eligibility. Any sensorial impairment such as deafness or reduced visual acuity, which cannot be corrected in the MRI scanner.
17. Part 2 only: participant likely not able to remain motionless for the time required for an MRI.

Date of first enrolment
16/11/2023

Date of final enrolment
31/08/2024

Locations

Countries of recruitment
France

Study participating centre
Biotrial
7-9 rue Jean-Louis Bertrand, Rennes Cedex
Rennes
France
35042

Sponsor information

Organisation
F. Hoffmann-La Roche Ltd

Funder(s)

Funder type
Industry

Funder Name
F. Hoffmann-La Roche

Alternative Name(s)
Hoffman-La Roche, F. Hoffmann-La Roche Ltd.

Funding Body Type
Private sector organisation

Funding Body Subtype

For-profit companies (industry)

Location
Switzerland

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