A Randomized, investigator/subject blind, adaptive, single and multiple ascending dose, placebo-controlled study to investigate safety, tolerability , pharmacokinetics, pharmacodynamics, food effect and taste of RO7017773 following oral administration in healthy participants.

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Part 1, 2 and 3;To assess the safety and tolerability of single and multiple ascending doses of RO7017773 in healthy participants.To investigate the PK of RO7017773 in plasma and urine.To investigate the PD effects of RO7017773 treatment on specific...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Communication disorders and disturbances
Study type	Observational invasive

Summary

ID

NL-OMON46688

Source
ToetsingOnline

Brief title
Study for Safety, Tolerability, PK, PD, Food Effect, Taste of RO7017773

Condition

- Communication disorders and disturbances

Synonym
Autism Spectrum Disorder

Research involving
Human

Sponsors and support

Primary sponsor: F. Hoffmann-La Roche Ltd
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Autism, Autism spectrum disorder (ASD), Drug research

Outcome measures

Primary outcome

Part 1, 2 and 3;

Incidence and severity of AEs.

Changes in vital signs, physical findings, ECG parameters, and clinical

laboratory results during and following RO7017773 administration.

Change in suicide risk (using Columbia Suicide Severity Rating Scale).

Secondary outcome

All parts

PK parameters of RO7017773.

Change from baseline in spontaneous brain electrical activity by qEEG

part 2a

PK parameters of RO7017773 in fasted and in fed state.

Study description

Background summary

Autism spectrum disorder is a complex, heterogeneous neurodevelopmental disorder characterized by impairments in social communication and interaction, as well as repetitive behaviors and restricted interests (Diagnostic and Statistical Manual of Mental Disorders [DSM 5]). The estimated prevalence of ASD in the United States is 1 in 68 children (CDC, 2014), and it is estimated that 1% of the world*s population have ASD (WHO, 2013). No approved pharmacological treatment exists for the core social communication and social interaction deficits and repetitive behavior of ASD, and this disorder continues to be an area of high unmet medical need. Current treatments for associated symptoms of ASD may include antipsychotics (risperidone and aripiprazole) used for the treatment of irritability associated with ASD symptoms. Multiple lines of evidence suggest that an imbalance between excitatory/inhibitory neurotransmission in favor of excitation could arise from dysfunction of the GABAergic signaling system (the main inhibitory neurotransmitter system in the brain), early in development and is a central characteristic of the neurobiology of autism, leading to some of the impairments observed in individuals with ASD. GABAA alpha-5 receptors are thought to play a major role in cognition since they are predominantly expressed in the hippocampus in rodents and humans, which is important for learning and memory processes. RO7017773 is a selective gamma-aminobutyric acid type A (GABAA) alpha- 5 subunitcontaining receptor positive allosteric modulator. RO7017773 is being developed for the treatment of the two core domains of Autism spectrum disorder (ASD); social communication deficits and repetitive behaviors. RO7017773 has the potential to normalize GABAergic signaling in key brain regions implicated in ASD without the sideeffects of non-specific GABA modulators (e.g. benzodiazepines).

Study objective

Part 1, 2 and 3;
To assess the safety and tolerability of single and multiple ascending doses of RO7017773 in healthy participants.
To investigate the PK of RO7017773 in plasma and urine.
To investigate the PD effects of RO7017773 treatment on specific quantitative electroencephalography (qEEG) parameters (not applicable for Part 2b).

Part 2a
To assess the effect of food on the PK of a single dose of RO7017773.

Study design

This study will be conducted in three parts in healthy participants.
Part 1 will be a randomized, Investigator/participant blind, adaptive, placebo controlled SAD study to explore the safety, tolerability, PK and PD of single doses of orally administered RO7017773 in the fasted state.

Part 2 will be split into two parts both following single doses of orally administered RO7017773;
Part 2a will be a randomized, Investigator/participant blind, single-dose, two-period (fasted,fed) fixed sequence study in healthy participants to explore the effect of food on PK parameters.
Part 2b will be a randomized, open-label, single-dose study to assess the taste of RO7017773.

Part 3 will be a randomized, Investigator/participant blind, adaptive MAD, placebo-controlled study with the purpose of evaluating the safety, tolerability, PK and PD of multiple doses of orally administered RO7017773.

Study burden and risks

This is the first study with RO7017773 in humans, designed to assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of single (Part 1) and multiple ascending doses (Part 3), food effect (Part 2a) and taste (Part 2b) following oral administration of RO7017773 to healthy participants. For this study, healthy male and female participants aged 18 to 55 (inclusive) were chosen because of the absence of
potentially confounding disease processes, which will lead to a clearer and more consistent assessment of drug disposition and biological activity. In addition, healthy participants are unlikely to require concomitant medication which could interfere with the study drug or its pharmacodynamic effects. The study is adaptive in nature. Ascending doses are planned in order to establish the safety and tolerability at low dose levels before proceeding to higher dose levels. Dose levels may be adjusted (increased, decreased, or repeated) or intermediate doses may
be used depending on the emerging safety, PK and Neurocart and EEG (up to predicted Tmax) data at each dose level. To ensure participants' safety additional monitoring/assessments have been implemented based on the findings reported in pre-clinical studies. During the conduct of
the study, participants will be hospitalized at the clinical research unit for the entire treatment duration and for at least 48 hours after the last dose. Safety and tolerability will be monitored closely throughout the study. Tolerability will be assessed by recording adverse events (e.g. change in appetite and signs of hypoactivity and drowsiness), cognition assessments and close observation of the participants.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Able and willing to provide written informed consent and to comply with the study protocol according to ICH and local regulations.
2. Participants 18 to 55 years of age inclusive, at the time of signing the informed consent.
3. Healthy, as judged by the Investigator. Healthy status will be defined as the absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination, vital signs, 12-lead ECG, hematology, blood chemistry, serology and urinalysis.;4. Body mass index (BMI) within the range 18 to 30 kg/m2 (inclusive).
5. Male and female participants
The contraception and abstinence requirements are intended to prevent exposure of an embryo to the study treatment. The reliability of sexual abstinence for male enrollment eligibility needs to be evaluated in relation to the duration of the clinical study and the

preferred and usual lifestyle of the participant. Periodic abstinence and withdrawal are not acceptable methods of contraception.
e) Female Participants
A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and the following condition applies:
* Women of non-childbearing potential (WONCBP), as defined in Appendix 5 who:
* Have a negative pregnancy test (blood) within the 21 days prior to the first study drug administration.
f) Male Participants
During the treatment period and for at least 28 days after the last dose of study drug, agreement to:
* Remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom, with partners who are women of childbearing potential (WOCBP, as defined in Section 1 of Appendix 5), or pregnant female partners, to avoid exposing the embryo.
*Refrain from donating sperm 28 days.

Exclusion criteria

1. Any condition or disease detected during the medical interview/physical examination that 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. History of any clinically significant gastrointestinal, renal, hepatic, bronchopulmonary, neurological, psychiatric, cardiovascular, endocrinological, hematological or allergic disease, metabolic disorder, hypofertility, cancer or cirrhosis.
4. Use of any psychoactive medication, or medications known to have effects on CNS or blood flow taken within 4 weeks prior to first dosing (or within 5 times the elimination half-life of the medication) prior to first dosing (whichever is longer).
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. History or current significant ophthalmologic or neurologic condition that would adversely affect the eye movement assessments.
7. A history of clinically significant hypersensitivity (e.g., drugs, excipients) or allergic reactions.
8. Any major illness within one month before the screening examination or any febrile illness within one week prior to screening and up to first study drug administration.
9. Abnormal blood pressure, defined as confirmed (based on the average of >/=3 consecutive measurements) systolic blood pressure (SBP) greater than 140 or less than 90 mm Hg, and diastolic blood pressure (DBP) greater than 90 or less than 50 mm Hg.
10. Abnormal pulse rate, defined as confirmed (based on the average of >/=3 consecutive

measurements) resting pulse rate greater than 100 or less than 40 bpm.
11. History or presence of clinically significant ECG abnormalities before study drug administration (e.g. PQ/PR interval >210 ms, QTcF > 450 ms (>470 ms females) or cardiovascular disease (e.g., cardiac insufficiency, coronary artery disease, cardiomyopathy, congestive heart failure, family history of congenital long QT syndrome, family history of sudden death).
12. Clinically significant abnormalities in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis). In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility.
13.ALT and bilirubin > 1.5 X ULN (isolated bilirubin > 1.5 X ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%).
14. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).;15. Participants who, in the Investigator's judgment, pose a suicidal or homicidal risk, or any participant with a history of suicidal or homicidal attempts.
16. Have used or intend to use over-the-counter or prescription medication including herbal medications within 30 days prior to dosing.
17. Participants likely to need concomitant medication during the study period (including for dental conditions).
18. Participation in an investigational drug or device study within 90 days prior to screening, as calculated from the day of follow-up from the previous study, or more than 4 times a year.
19. Positive test for drugs of abuse or alcohol.
20. For, female participants, a positive pregnancy test.
21. Show evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies.
22. Positive result on hepatitis B (HBV) or hepatitis C (HCV), presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening or within 3 months prior to starting study treatment.
23. Dietary restrictions that would prohibit the consumption of standardized meals.
24. Consumption of any prohibited medications and food before study start and during the study.
25. Any suspicion or history of alcohol abuse and/or suspicion of regular consumption of drug of abuse or previous history of or treatment for a dependence disorder.
26. Sensitivity to any of the study treatments, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates the participation in the study.
27. Participants who regularly smoke more than 5 cigarettes daily or equivalent and unable or unwilling not to smoke during the in-house period.
28. Participants who have donated over 500 mL of blood or blood products or had significant blood loss within 3 months prior to screening.
29. Participants under judicial supervision, guardianship or curatorship.
30. Contraindications for MRI scans (including but not restricted to claustrophobia, pacemaker, artificial heart valves, cochlear implants, presence of foreign metal objects in head or body, intracranial vascular clips, etc.) or any brain/head abnormalities restricting MRI eligibility. Any sensorial impairment such as deafness and reduced visual acuity which cannot be corrected in the fMRI scanner.
31. Contraindication to TMS-EEG (including, but not restricted to, a history of epilepsy or

febrile seizures, having metal objects in brain or skull, having a cochlear implant or implanted deep brain stimulator, abnormal sleeping pattern (e.g., working night shifts), resting motor threshold (rMT) of more than 83% of the maximum stimulator output as measured using TMS-EMG during screening.
32. Fulfillment of any of the MRI contraindications on the standard radiography screening questionnaire.

Study design

Design

Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-12-2017
Enrollment:	184
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	RO07017773
Generic name:	n/a

Ethics review

Approved WMO

Date:	16-11-2017
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-12-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-01-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-01-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-06-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	31-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-08-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-10-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-002764-40-NL
CCMO	NL63769.056.17