A Non-Randomized, Open Label, Adaptive, Single Center, Positron Emission Tomography (PET) Study to Assess Distribution of RO7248824 in the Central Nervous System Following Single Intrathecal Doses of [89Zr]-Labeled RO7248824 in Healthy Male Participants

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Ethical review	Approved WMO
Status	Completed
Health condition type	Neurological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON52457

Source
ToetsingOnline

Brief title
Pet study to assess distribution of RO7248824 in the cns

Condition

- Neurological disorders NEC

Synonym
Angelman syndrome

Research involving
Human

Sponsors and support

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

Intervention

Keyword: central nervous system, Distribution, RO7248824

Outcome measures

Primary outcome

To quantify the [89Zr]DFO-RO7248824 distribution within the central nervous

system (CNS) following a single intrathecal (IT) administration of

[89Zr]DFO-RO7248824 mixed with 10 mg RO7248824

Secondary outcome

To assess the safety and tolerability of single IT administrations of

[89Zr]DFO-RO7248824 mixed with 10 mg RO7248824

Study description

Background summary

RO7248824 is a new compound that may potentially be used for the treatment of Angelman syndrome. Angelman syndrome is a rare genetic disorder that is present at birth. People with AS have developmental problems that become noticeable by the age of 6 to 12 months. Other common signs and symptoms usually appear in early childhoods like walking and balance disorders, gastrointestinal issues, seizures, and little to no speech. There is currently no cure for AS. People with AS have genetic changes leading to a shortage of a protein called UBE3A especially in the brain. In animal studies RO7248824 was able to increase the UBE3A protein. It is hoped that treatment with RO7248824 will also increase the level of UBE3A protein in people with AS, which could help to reduce the symptoms of AS. The only way that RO7248824 can reach the brain is by an injection into the fluid surrounding the spine, known as cerebrospinal fluid or

CSF in short.

Study objective

The new compound RO7248824 is being developed for the treatment of Angelman syndrome (AS). The purpose of this study is to find out how RO7248824 spreads in the brain and spine after injection into the spinal canal (intrathecal administration). This information is important for the design of clinical trials for people with AS and to learn more about how other similar types of drug can travel to the brain and spinal cord. It will also be investigated how safe RO7248824 is and how well it is tolerated when it is administered to healthy male volunteers.

Study design

Participation from screening until the follow-up visit will last up to 12 weeks (3 months).

The volunteer will be given one single dose of 10 mg RO7248824 mixed with a maximum of 100 µg of the labeled form of RO7248824 through an intrathecal injection. The dose of tracer may be adapted during the study. If this happens, the volunteer will be informed about this prior to receiving the dose.

The study will be performed in 2 parts, Part 1 and Part 2. the volunteer can participate in 1 part only.
• In Part 1, RO7248824 will be administered in a similar way as in another study ongoing in parallel. The dose of the labeled form of RO7248824 (which determines the amount of radioactivity the volunteer will receive) is selected to obtain good quality PET images and to restrict the amount of radioactivity to acceptable limits and can be adapted if needed.
• Depending on the results from Part 1, different procedures for injection of RO7248824, and/or different variations of the PET/CT scans may be tested in Part 2. For each new procedure for injection, the dose of the labeled form of RO7248824 could be adapted if needed to obtain good quality PET/CT images.
Which part of the study the volunteer participate in will depend on when the volunteer is enrolled.

Intervention

The volunteer will be given one single dose of 10 mg RO7248824 mixed with a maximum of 100 µg of the labeled form of RO7248824 through an intrathecal injection. The dose of tracer may be adapted during the study.

During an intrathecal injection, a thin needle is placed in a space between two vertebrae in the lower back and the study compound will be injected into the fluid of the spinal cord sac. We also call this fluid cerebrospinal fluid

(CSF). This intrathecal injection is popularly known as an epidural. The procedure will be performed by a specialist in the UMCG.

Study burden and risks

Intrathecal injection

• In this study the volunteer will undergo an epidural, also known as an intrathecal injection. The anesthetist will ask the to sit down and to arch the back. With a very thin needle, the anesthetist just pierces the spinal membranes and an amount of cerebrospinal fluid is taken. The study compound is also administered via this thin needle.
• The skin where the epidural will be done is anesthetized beforehand. In principle, people will therefore experience little pain during the epidural. Some people experience a feeling of faintness when they get an injection.
• The spot where the volunteer got the epidural can sometimes be a little sensitive. This will disappear after a while. If the volunteer have back pain in a different place, this may be because the volunteer have been in the same position for a long period of time during the procedure. This pain usually disappears within a few days.
• While performing the epidural, the needle may sometimes touch a spinal nerve. This can give a shock to the leg.
• Sometimes someone gets a bad headache after an epidural. The headache can start immediately after the procedure, but also 24 hours afterwards. Usually this headache disappears on its own within a week.
* If the volunteer does not respond to the standard *treatment* of bed rest, fluid intake and time or pain medications and medications against vomiting and nausea per the responsible doctor*s advice, the responsible doctor may decide to perform an *epidural blood patch*. During this procedure a small volume of the blood (approximately 15-20 milliliters that will be drawn from a vein in the arm) will be injected in the epidural space of the spinal cord (space just outside the meninges around the spinal cord) using an epidural needle. This will be performed by an anesthesiologist under sterile conditions and with local anesthesia. The volunteer will have to be in a sitting position with the legs together. Relief of headache usually occurs swiftly after this procedure, sometimes directly after administration of the blood patch, although a transient sensation of *fulness* in the back is common. In some instances more than 1 attempt may be required for relief of headache. After the procedure the volunteer has to lie down on the back for another 1.5 - 2 hours to decrease the risk of leakage of CSF.
* The volunteer may be asked to keep bed rest up to 3 days after the procedure to reduce the risk of headache after an epidural. If you are taking pain medications for the headache, your doctor may instruct you to taper them to avoid the possibility of a rebound headache from sudden medication withdrawal.
• In rare cases, an epidural can cause infection or bleeding in the back. These complications can lead to damage to the spinal nerves. Nerve damage often causes pain, but can also result in movement and sensory disturbances.

Fortunately, these complications are rare.

Blood draw
• During this study, small amounts of blood will be drawn from a vein and by finger prick and used for tests that allow the responsible doctor to see how the volunteer is doing. Drawing blood may cause pain and there is a small risk of bruising or infection at the place where the needle is inserted. Very rarely, a blockage of the vein or a small nerve injury can occur, resulting in numbness and pain. However, this will resolve with time. Some people experience dizziness, upset stomach, or fainting when their blood is drawn.
• On Day 1, when several blood samples will be taken, we may use a cannula inserted in the arm using a small needle. There is a small chance of infection by placing the cannula in the arm, but every medical precaution will be taken to avoid an infection.
• In total, we will take less than 500 milliliters of blood from the volunteer. This amount does not cause any problems in adults. To compare: a blood donation involves 500 mL of blood being taken each time.

ECG
• The volunteer will have small, soft pads, placed stuck temporarily on different parts of the body. There is no pain or discomfort during an ECG; however the area of skin in which the ECG pads will be stuck may need to be shaved, and the pads may cause a skin reaction such as redness or itching. Taking the pads off may cause localized irritation to the skin and/or hair loss, similar to having a plaster taken off.

PET scan / CT scan / MRI scan
• PET/CT and MRI scans are quite *closed in* and may be unpleasant for people who have a fear (or strong dislike of) enclosed spaces. Because an MRI scanner uses strong magnets, the volunteer cannot have any metal implants in the body to have an MRI scan. People with a pacemaker, Implantable Cardioverter Defibrillator (ICD) or with metal splinters, metal plate, pin, or other metallic objects in their body may not be eligible for this study. If the volunteer has certain tattoos, he/she might feel a little discomfort when they have their MRI scan. Study personnel will ask questions to make sure the volunteer can safely have an MRI scan. The MRI scan itself makes loud noises. The volunteer will therefore receive earplugs and headphones. That muffles the sound and protects the hearing. Sometimes the volunteer can listen to music. Study personnel will ask questions to make sure the volunteer can safely have the MRI and PET/CT scans.

Exposure to radiation
• This study involves using X-rays (PET/CT scan) and a radioactive tracer. The additional amount of radiation (radiation burden) the volunteer will be exposed to in this study is slightly less than 10 millisieverts. This is equivalent to approximately 4 years of naturally occurring background radiation in the Netherlands (~2.5 mSv per year). Background radiation is the radiation that

everyone is exposed to from sources such as the air we breathe, food we eat, cosmic rays from the sun and space, as well as the ground and buildings around us.
• Scientists disagree on whether radiation doses at these low levels are harmful. A possible effect that could occur at doses associated with this study is a slight increase in the risk of developing cancer later in life.

Coronavirus test
•Samples for the coronavirus test will be taken from the back of the nose and throat using swabs. Taking the samples only takes a few seconds, but can cause discomfort and can give an unpleasant feeling. Taking a sample from the back of the throat may cause the volunteer to gag. When the sample is taken from the back of the nose, the volunteer may experience a stinging sensation and the eyes may become watery.
• Participation in this study may expose you to viruses (including but not limited to the seasonal flu, SARS-CoV-2, and common cold) and bacteria that exist in the environment. While PRA will take all the possible steps to provide safe and clean facilities, PRA cannot guarantee you will not be exposed to these viruses and bacteria during the course of the study. Neither PRA nor the Sponsor are responsible for any diagnosis or treatment related thereto. We do not expect that participation in this study increases your risk of getting exposed to viruses.

Contacts

Public
F. Hoffmann-La Roche Ltd

Grenzacherstrasse 124
Basel 4070
CH
Scientific
F. Hoffmann-La Roche Ltd

Grenzacherstrasse 124
Basel 4070
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

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. Aged 25 to 55 years at the time of dosing
3. Overtly healthy (defined by absence of evidence of any active or chronic disease) as determined by medical evaluation including:
- A detailed medical and surgical history
- A complete physical and neurological examination
- Vital signs
- 12-lead ECG
- Hematology
- Coagulation
- Blood chemistry
- Serology and urinalysis
4. Fluent in the language of the Investigator and study staff, and able to communicate with the study staff
5. Body mass index of 18 to 30 kg/m2 at screening
6. Male participants only who, for 3 months after the dosing of RO7248824, agree to:
- Remain abstinent or use contraceptive barrier measures such as a condom, with a female partner of childbearing potential, or pregnant female partner, to avoid exposing the embryo
- Refrain from donating sperm
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 (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of preventing drug exposure.

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 presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study treatment; or interfering with the interpretation of data
3. History or presence of clinically significant cardiovascular disease in the opinion of the Investigator, including, but not limited to: left ventricular ejection fraction < 40%, (assessed by echocardiogram/multiple-gated acquisition scan [ECHO/MUGA]) congestive heart failure Class IV New York Heart Association (NYHA), left ventricular outflow obstruction (aortic stenosis, idiopathic hypertrophic subaortic stenosis), symptomatic coronary artery disease, prior myocardial infarction,
congestive heart failure requiring hospitalization, prior cerebrovascular accident
4. History or presence of an abnormal ECG that is clinically significant in the Investigator's opinion (e.g., PQ/PR interval > 220 ms, QTcF > 450 ms)
5. Uncontrolled arrhythmias or history of clinically significant arrhythmias including: ventricular arrhythmias or risk factors for ventricular arrhythmias (such as clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia); second- or third-degree atrioventricular block; family history of sudden unexplained death or long QT syndrome; congenital hypertrophic or dilated cardiomyopathy

For the complete overview see the protocol

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	29-03-2021
Enrollment:	26

Type:	Actual

Ethics review

Approved WMO Date:	27-08-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-03-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-05-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-07-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-08-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-08-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-02-2022
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-03-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2019-003786-18-NL
CCMO	NL74259.000.20

Study results

Date completed:	01-08-2022
Results posted:	27-10-2023

First publication
26-05-2023

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek

URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File
File