A single-center randomized, adaptive, investigator/participant blind, single oral ascending dose, placebo-controlled Phase I study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of RO7189752 in healthy male participants.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Central nervous system infections and inflammations
Study type	Interventional

Summary

ID

NL-OMON45777

Source
ToetsingOnline

Brief title
Entry-into-Human study of RO7189752

Condition

- Central nervous system infections and inflammations

Synonym
Multiple sclerosis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: PD, PK, RO7189752

Outcome measures

Primary outcome

To evaluate the safety and tolerability of single oral ascending doses of

RO7189752 in healthy male participants.

Secondary outcome

To investigate the PK of RO7189752 in plasma and urine, and if appropriate, its

metabolite(s) after single oral doses.

To assess the PD of RO7189752 after single oral doses.

Study description

Background summary

RO7189752 is a new compound that may eventually be used for the improvement of disabling neurological symptoms experienced by patients with multiple sclerosis (MS).

Multiple sclerosis is a long-lasting inflammatory disease of the central nervous system, which concerns about 2.5 million patients worldwide, and often affects young adults. In the beginning, most patients experience recurring episodes of disability (relapses). To date, it is not possible to predict how the disease will progress, but the majority of MS patients develop some level of disability within 15 to 20 years after having been diagnosed with the

disease. Multiple sclerosis is a disease in which the insulating covers of nerve cells (myelin sheaths) in the brain and spinal cord are damaged. This damage disrupts the ability of parts of the nervous system to communicate, resulting in a range of signs and symptoms that can amount to substantial disability. Symptoms include numbness, visual changes (e.g., blurred or double vision), speech impairment, muscle weakness, bladder incontinence, and severe fatigue. Although the exact cause of MS is not known, it is thought to be a disease, where the person*s own immune system attacks the myelin sheath.

Currently MS cannot be healed. Drugs that are already available for MS are more or less effective in reducing (or eliminating) the number of relapses, but do not primarily improve disability or slow disability worsening. RO7189752 aims to address the latter and to improve patients* quality of life by improving their overall neurological functioning. There is scientific data to suggest that RO7189752 may result in benefits for MS patients, as it is expected to help building back the myelin sheath.

Study objective

The purpose of this study is to investigate how safe the new compound RO7189752 is and how well it is tolerated when it is administered as a drink to healthy male volunteers. RO7189752 has not been administered to humans before. It has been previously tested in the laboratory and in animals. RO7189752 will be tested at various dose levels.

It will also be investigated how quickly and to what extent RO7189752 is absorbed and eliminated from the body (pharmacokinetics). In addition, the effect of RO7189752 on the body will be investigated (pharmacodynamics).

The effects of RO7189752 will be compared to the effects of a placebo.

Study design

This study will be performed in a maximum of 48 healthy male volunteers. The study will consist of up to 6 groups of 8 volunteers each. The volunteer can participate in one of these groups.

Participation from screening until the follow-up visit will last between 2 and 7 weeks, depending on the timing of the screening and follow-up visit.

The study will consist of 1 period during which the volunteer will stay in the research center for 5 days (4 nights).

Day 1 is the day of administration of the study compound. The volunteer is expected at the research center at 14:00 h in the afternoon on Day -2, which is 2 days prior to Day 1. The volunteer will leave the research center on Day 3 of

the study. This will be followed by 1 or 2 days during which the volunteer will visit the research center for a short visit. These short visits will take place on Day 4, and if considered necessary by the responsible doctor and Sponsor based on pharmacokinetic results from the study, on Day 6.

Optionally, the volunteer may choose to stay in the research center for the rest of Day 3. The volunteer will then stay overnight until the morning of Day 4, and then leave after all tests planned on Day 4 have been conducted.

One to 3 weeks after administration of the study compound volunteers health will be checked for the last time during the follow-up visit.The timing of the follow-up visit will depend on the pharmacokinetic results from the study.

Intervention

RO7189752 or placebo will be given as a drink of 100 milliliters (mL) in the morning of Day 1 at 30 minutes (approx. 5 minutes) after the start of a standardized breakfast. The breakfast has to be completed entirely within 30 minutes. After administration of the study compound, the vial will be rinsed twice with 50 mL of water, which the volunteer will also is required to drink.

The volunteer is not allowed to drink anything else during the first 2 hours after dosing. Water will be allowed from 2 hours after dosing. A standardized lunch will be provided 4 hours after dosing.

Whether the volunteer will receive RO7189752 or placebo will be determined by chance. Per group, 6 volunteers will receive RO7189752 and 2 volunteers will receive placebo. Neither the volunteer, nor the responsible doctor knows if RO7189752 or placebo will be administered; a double-blinded study. However, if it is important for volunteers health to know if he has received RO7189752 or placebo, for example in case of a serious side effect, this information can be looked up during the study.

For safety reasons, initially 2 volunteers will receive the study compound in each group. One volunteer will receive RO7189752, and 1 will receive placebo. After administration, the safety and tolerability of the study compound in these 2 volunteers will be closely monitored. If there are no concerns about the safety and tolerability 24 hours after administration, then the remaining 6 volunteers (5 will receive RO7189752 and 1 will receive placebo) of the same group will receive the study compound.

The study will consist of up to 6 groups of 8 volunteers each. It is planned that subjects within each group receive the same dose level of RO7189752 and that the dose level will be increased from one group to the next group. However, it is possible that a dose level is repeated or even that a lower dose is investigated. In that case, the additional group will consist of at least 3 volunteers receiving RO7189752 and 1 volunteer receiving placebo. In this case,

all volunteers will receive the study compound at the same time.

Further, based on results obtained during the study, there is a possibility to split the total daily dose into 2 sub-doses such that the second administration of the study compound will take place 8 to 12 hours after the first administration of the study compound.

The starting dose for the first group will be 20 milligrams (mg). The highest total daily dose of RO7189752 will not exceed 1500 mg per day. The dose for the next group will only be increased if the lower dose of the previous group was found to be well tolerated and in case of no objection by the Medical Research Ethics Committee. The study will be discontinued if, in the opinion of the investigators, unacceptable side effects appear.

Study burden and risks

All potential drugs cause adverse effects; the extent to which this occurs differs. As RO7189752 will be administered to humans for the first time in this study, adverse effects (or so-called *side effects*) of RO7189752 in humans have not been reported to date.

The volunteer may have side effects from the study compound or procedures that are used in this study. However, the Sponsor, the responsible doctor, and other doctors do not know all of the side effects that could occur. Side effects can vary from mild to very serious and may vary from person to person. Many side effects go away soon after volunteer stops what is causing them. The volunteer should talk to the responsible doctor about any side effects he has while taking part in the study. Everyone taking part in the study will be watched carefully for any side effects and cared for as appropriate. The responsible doctor may give the volunteer medications to help lessen side effects.

Possible side effects due to the study compound
Allergic reactions can occur with any drug and this can be in the form of itching, difficulty breathing, a skin rash and/or drop in blood pressure. If the volunteer does experience any such reaction, the volunteer should tell the responsible doctor immediately so that the volunteer can receive the appropriate treatment.

As stated earlier, RO7189752 is a new compound that has not yet been tested in humans. For this reason, the side effects in humans are not known at this time.

RO7189752 was well tolerated by animals. In animal studies with RO7189752 the following adverse effects were observed in some animals:

Effects concerning the heart and/or blood vessels
•In some animals receiving different single doses of RO7189752, changes in the electrical activity of the heart were observed, which became slightly more

distinct at higher doses. At the highest dose administered, slight and sporadic increases in heart rate and irregular heartbeats were observed. However, the doses used in this study are much lower than those given to animals, which is why such effects are not expected to occur in humans.
The electrical activity of the heart will be regularly monitored during the study by recording a heart tracing (ECG) and by 48-hour telemetry monitoring (for a period of 24 hours after administration of the study compound), and your blood pressure will be measured at regular intervals.

Effects concerning the liver
•During an animal study of 4 weeks with daily administration of the study compound, in some animals, changes in liver function and increases in the volume and weight of the liver were seen at different doses of the study compound. However, since the breakdown of the study compound in human liver cells differs from the breakdown observed in animals, these effects are not expected to occur in the current study in which single doses will be given to humans.
The liver function will be regularly monitored during the study by taking blood samples for routine laboratory tests.

Effects concerning the thyroid
•During an animal study of 4 weeks with daily administration of the study compound, increases in the volume and weight of the thyroid were observed at some doses. These effects are not expected to occur in the current study in which single doses will be given to humans.
The thyroid function will be regularly monitored during the study by taking blood samples for routine laboratory tests.

Effects for the unborn child
•Since the study compound may harm the unborn child, female volunteers will not be allowed to be included into the study. Male volunteers with female partners who can become pregnant or are pregnant must agree to use 2 methods of contraception.

Effects concerning the testicles
•In some animals, an enlargement at the site of sperm production in the testicles was observed; however, this effect fully resolved after treatment was stopped. No other side effects concerning the testicles were observed and the function of the male reproductive system in animals was not impaired in any way.

Effects concerning some laboratory values
•In animals, a decrease in white blood cells was observed at all study compound dose levels. White blood cells are the blood cells which protect the body against infections and foreign invaders. However, the decrease did not vary at different doses and remained within normal values.

•In different animal species, either minimal increases of cholesterol or

minimal decreases of triglycerides and cholesterol were observed. Cholesterol and triglycerides are the lipids in blood and body tissues. However, the changes of these in animals were considered minor and not harmful.
The laboratory values, including white blood cells and lipids, will be regularly monitored during the study by taking blood samples for routine laboratory tests.

The study compound might have other side effects that are not known at this time. If new information is discovered that might change volunteers decision to stay in the study, the volunteer will be informed about it by the responsible doctor.

Possible discomforts due to procedures
Blood sampling
During this study, small amounts of blood will be drawn from a vein and used for tests that allow the responsible doctor to see how the volunteer is doing. Drawing blood may cause pain where the needle is inserted, 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 days when several blood samples will be taken, a cannula (small plastic tube) will be inserted in the arm using a small needle. This cannula may remain in place for the day and will be taken out before the volunteer goes to bed at night. 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 about 200 mL 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.

Heart tracing (ECG) and telemetry
Electrodes (small, plastic patches) will be placed temporarily on different parts of volunteers body. There is no pain or discomfort during an ECG; however the area of skin in which the ECG patches will be stuck may need to be shaved, and the patches may cause a skin reaction such as redness or itching. Taking the patches off may cause localized irritation to the skin and/or hair loss, similar to having a plaster taken off.

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

-Healthy male subjects
-18-45 yrs, inclusive
-BMI: 18.0-30.0 kg/m2, inclusive
-Non-smoking or light-smoking

Exclusion criteria

Suffering from hepatitis B, hepatitis C, cancer or HIV/AIDS. In case of participation in another drug study within 90 days before the start of this study or being a blood donor within 60 days from the start of the study. In case of donating more than 1.5 liters of blood in the 10 months prior the start of this study.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-08-2018
Enrollment:	48
Type:	Actual

Ethics review

Approved WMO Date:	06-07-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-07-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-08-2018
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	EUCTR2018-001249-15-NL
CCMO	NL66585.056.18