A SINGLE-CENTER, RANDOMIZED, INVESTIGATOR/SUBJECT-BLIND, ADAPTIVE SINGLE-ASCENDING-DOSE (SAD), PLACEBO-CONTROLLED, PARALLEL STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS (INCLUDING THE EFFECT OF FOOD AND THE EFFECT OF ITRACONAZOLE ON THE PHARMACOKINETICS OF A SINGLE ORAL DOSE OF RO7034067), AND PHARMACODYNAMICS OF RO7034067 FOLLOWING ORAL ADMINISTRATION IN HEALTHY SUBJECTS

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This study is not intended to improve your health, but is necessary for the further development of RO7034067 .The study will be performed in 3 parts, Parts 1, 2 and 3. This document only refers to Part 1/2/3 of the study . Part 1:A single dose will...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Muscle disorders
Study type	Interventional

Summary

ID

NL-OMON42781

Source
ToetsingOnline

Brief title
RO7034067 SAD/FE/DDI study

Condition

- Muscle disorders

Synonym
spinal muscular atrophy

Research involving
Human

Sponsors and support

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

Intervention

Keyword: RO7034067, spinal muscular atrophy

Outcome measures

Primary outcome

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

RO7034067 in healthy male subjects.

Secondary outcome

* To investigate the single dose oral pharmacokinetics (PK) of RO7034067 (and

its metabolite(s) if appropriate), in plasma and urine.

* To investigate the pharmacodynamic (PD) effect of single ascending oral doses

of RO7034067 on SMN2 mRNA splicing modification and SMN protein increase.

* To explore the pharmacokinetic/pharmacodynamic (PK/PD) relationship of single

ascending oral doses of RO7034067 on SMN2 mRNA splicing modification and SMN

protein increase.

* To assess the effect of food on the PK of a single oral dose of RO7034067.

* To investigate the effect of multiple oral doses of itraconazole on the

pharmacokinetics of a single oral dose of RO7034067 in healthy male subjects

* To assess the safety and tolerability of a single oral dose of RO7034067 in

combination with itraconazole in healthy male subjects

Study description

Background summary

RO7034067 is a new investigational compound that may eventually be used for the treatment of spinal muscular atrophy (SMA).

SMA is a genetic disease that affects the control of muscle movement. It is caused by a loss of specialized nerve cells, called motor neurons, in the spinal cord and the part of the brain that is connected to the spinal cord (the brainstem). The loss of motor neurons leads to weakness and wasting (atrophy) of muscles used for activities such as crawling, walking, sitting up, and controlling head movement. In severe cases of SMA, the muscles used for breathing and swallowing are affected. There are many types of SMA distinguished by the pattern of features, severity of muscle weakness, and age when the muscle problems begin. SMA affects 1 in 11,000 live births and is the leading genetic cause of mortality in infants and young children.

The survival motor neuron (SMN) protein is important for the maintenance of motor neurons. In SMA, genes responsible for giving instructions to the body to produce the SMN protein are not working correctly. This results in a shortage of SMN protein levels in the body and thereby, a loss of motor neurons. RO7034067 is thought to repair one of these genes (SMN2) and thereby restoring SMN protein levels in the body.

RO7034067 is not registered as a drug and has not been given to humans before.

If you participate in Part 3 of this study, in addition to RO7034067, you will also receive the antifungal compound itraconazole, which is a registered drug.

If you participate in Part 1 of this study, in addition to RO7034067, you may

receive the mouth wash solution Listerine®.

Study objective

This study is not intended to improve your health, but is necessary for the further development of RO7034067 .
The study will be performed in 3 parts, Parts 1, 2 and 3.
This document only refers to Part 1/2/3 of the study .

Part 1:
A single dose will be administered of RO7034067 or placebo (same formulation but then without the active ingredient RO7034067). The purpose of Part 1 is to investigate how safe RO7034067 is and how well RO7034067 is tolerated. Part 1 will also investigate how quickly and to what extent RO7034067 is absorbed into, distributed in, and eliminated from the body (this is called pharmacokinetics). In addition, the effect of RO7034067 on reparation of the SMN2 gene as well as on SMN protein levels in the blood will be investigated (this is called pharmacodynamics).

Part 1 will be performed in 6 groups (Groups 1 to 6) of which Group 1 will consist of 5 healthy male volunteers and the other groups of 4 healthy male volunteers each. Groups 2 to 6 may be expanded to a maximum of 16 healthy male volunteers each, based on emerging results from this study. You will participate in 1 of these 6 groups.

Part 2:
The purpose of Part 2 is to investigate the effect of food on the absorption, distribution and elimination of RO7034067 in the body (this is called pharmacokinetics) following a single dose of RO7034067. RO7034067 will be administered twice, once with and once without food.

Part 2 will be performed in 1 group of 6 healthy male volunteers; the group may be expended to to a maximum of 12 healthy male volunteers.

Part 3:
The purpose of Part 3 is to investigate the effect of multiple oral doses of itraconazole on the absorption, distribution and elimination of RO7034067 in the body (this is called pharmacokinetics) following a single dose of RO7034067. RO7034067 will be administered twice, once alone and once in combination with itraconazole. Itraconazole is known to inhibit proteins that are involved in metabolizing compounds like RO7034067. In addition, the Part 3 will investigate how safe the study compound RO7034067 is and how well the study compound is tolerated when it is given in combination with itraconazole.

Part 3 will be performed in 1 group of 8 healthy male volunteers; the group may be expended to a maximum of 12 healthy male volunteers.

Study design

Part 1: The actual study will consist of one period where they will stay for 6 days (5 nights) in the clinical research center in Groningen: the afternoon of Day-2 (two days before administration of study drug) on the morning of Day 4. This is followed by three days (Day 5, 7 and 10) to which one applies a short visit to the clinical research center in Groningen.
It can also be concluded that the volunteers should stay longer than three days in the clinical research center (until the morning of Day 7). In this case, the short visit will be scheduled on Day 5 and 7 will lapse.

Part 2: The actual study will consist of two periods of one every period for 6 days (5 nights) the volunteers will be staying in the clinical research center in Groningen: the afternoon of Day-2 (two days before administration of study drug) until tomorrow day 4. This is every period followed by three days (Day 5, 7 and 10) to which one applies a short visit to the clinical research center in Groningen. Each period can also be determined that the volunteers should stay longer than three days in the clinical research center (until the morning of Day 7). In this case, the short visit will be scheduled on Day 5 and 7 will lapse.

Part 3: In the first period they will stay for 4 days (3 nights) in the clinical research center in Groningen: the afternoon of Day 1 (the day before administration of study drug) on **the morning of Day 3. This is followed by 4 days (Day 4, 5, 7 and 10) to which one applies a short visit to the clinical research center in Groningen. It can also be concluded that the volunteers in the first period up to 3 days longer have to stay in the clinical research center (until the morning of Day 6). In this case, the short visit will be scheduled on Day 4 and 5 lapsed.

Second period
In the second period will be only stay for two days (one night) in the clinical research center in Groningen: the afternoon of Day 1 (the day before administration of study drug) on **the morning of Day 1. Then it will be for seven days (6 nights) stay in the clinical research center in Groningen: the afternoon of Day 3 until the morning of Day 9. This is followed by five days (Day 10, 11, 13, 15 and 18) which one a short visit the clinical research center in Groningen.Er can also be concluded that the free will keepers in the second period up to 3 days longer have to stay in the clinical research center (until the morning of Day 12). In this case, the short visit will be scheduled on Day 10 and 11 lapse.

Intervention

Part 1:
cohort 1 (0.6 mg): 5 (3 active + 2 placebo)

cohort 2 (2 mg): 4 (3 active + 1 placebo)
cohort 3 (6 mg): 8 (6 active + 2 placebo)
cohort 4 (20 mg): 8 (6 active + 2 placebo)
cohort 5 (60 mg): 8 (6 active + 2 placebo)
cohort 6 (200 mg): 8 (6 active + 2 placebo)

Part 2:
cohort 7: 12 subjects

Part 3:
cohort 8: 8 subjects

Study burden and risks

Pain, minor bleeding, bruising, possibly an infection.

Contacts

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GB
Scientific
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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 volunteers
18 - 45 years, inclusive
BMI 18 - 30 kilogram/meter2, inclusive
non smokers or less then 6 sigarettes per day

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:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-12-2015
Enrollment:	93
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	itraconazol
Generic name:	itraconazol
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	RO7034067
Generic name:	RO7034067

Ethics review

Approved WMO Date:	30-11-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-12-2015
Application type:	First submission
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	EUCTR2015-004605-16-NL
CCMO	NL55759.056.15