A Single Center, Non-Randomized, Open-Label, One-Sequence, Two-Period Within-Subject Study to Investigate the Effect of Itraconazole on the Pharmacokinetics of Multiple Doses of Balovaptan in Healthy Volunteers

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

Summary

ID

NL-OMON46113

Source
ToetsingOnline

Brief title
Balovaptan-itraconazole DDI study.

Condition

- Other condition

Synonym
Autism Spectrum Disorders (ASD)

Health condition

autisme spectrum stoornissen (ASS)

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Balovaptan, DDI, Itraconazole, PK

Outcome measures

Primary outcome

To investigate the effect of itraconazole treatment on the PK of balovaptan and its major metabolites M2 (as applicable) and M3, at steady state.

Secondary outcome

To explore the safety and tolerability of balovaptan when given alone and in combination with itraconazole in healthy subjects.

Tertiary/Exploratory:

Relationship between the CYP3A4 genotype, among others*, and steady state balovaptan exposure, and the influence of the CYP3A4 genotype, among others, on the effect of itraconazole on balovaptan PK.

The plasma exposure of itraconazole and hydroxy-itraconazole.

* The relationship between other genotypes and PK of balovaptan may also be

explored

Study description

Background summary

Balovaptan (also known as RO5285119) is a new investigational compound that may eventually be used for the treatment of Autism Spectrum Disorders (ASD), a diverse neurodevelopmental disorder. This disorder is typically characterized by social deficits, communication difficulties, repetitive behaviors, and in some cases, learning disabilities. Vasopressin is a hormone that regulates blood pressure and the retention of water in the kidneys. Vasopressin is also present in the brain and may play a role in autism. Balovaptan reduces signaling via vasopressin and is in development for treatment of ASD. Balovaptan is not yet registered as a drug but has been given to adults with ASD before at doses of up to 10 mg for a period of 12 weeks and to healthy volunteers at doses of up to 52 mg for a period of two weeks.

Itraconazole, an approved drug for the treatment of fungal infections, is known to interfere with the activity of the liver enzyme CYP3A. This enzyme is involved in the breakdown of balovaptan in the body and may therefore interfere with the presence of balovaptan in the body. In a previous study involving itraconazole and a single dose of balovaptan, the blood levels of balovaptan were increased by at least 3.1-fold. Therefore, itraconazole will be expected to increase the blood levels of balovaptan in this study.

Study objective

The purpose of the study is to investigate how quickly and to what extent balovaptan is absorbed and eliminated from the body (pharmacokinetics) when it is administered alone or in combination with itraconazole. It will also be investigated to what extent balovaptan is tolerated by volunteers if administered alone or in combination with itraconazole.

Study design

This study will be performed in 14 to 18 healthy male or female volunteers, divided into 2 groups: Group A (Group 1) and Group B (Group 2).

In Period 1 the volunteer will stay in the research center for 12 days (11 nights). Day 1 is the first day of administration of the study compound. The volunteer is expected at the research center at 14:00 hr in the afternoon prior to the day of first administration of the study compound (Day -1). the volunteer will leave the research center on Day 11.

There will be a period of at least 7 days between the last administration of study compound in Period 1 and the first administration of study compound in Period 2.

The volunteer is expected to return to the research center at 14:00 hr in the afternoon on Day -1 of Period 2. In Period 2 the volunteer will stay in the research center for 22 days (21 nights). Then the volunteer will leave the research center on Day 21 of Period 2.

Between 14 to 21 days after volunteers last dose in Period 2, volunteers health will be checked for the last time.

Intervention

Balovaptan will be given once daily, at a dose of 5 mg, for the initial 4 volunteers (Group A). Based on the results from Group A, the dose of balovaptan may either:

- remain at 5 mg once daily in a second group of 10 volunteers (Group B), or
- be increased to 10 mg once daily a second group of 14 volunteers (Group B)

Balovaptan will be given as an oral tablet with 240 milliliters (mL) of water after consumption of a standardized breakfast.

Itraconazole will initially be given twice daily at a dose of 200 mg (in total 400 mg a day), a typical dose for this medication. When given together with balovaptan (5 or 10 mg) once daily, itraconazole will be given once daily at a dose of 200 mg (in total 200 mg a day). On those days, balovaptan will be given first and then itraconazole. Itraconazole will be given as capsules with 240 mL of water after consumption of a standardized breakfast (morning) or snack (evening).

One of the investigators will inspect volunteers hands and mouth after each intake of study compound.

The study will consist of two periods. We refer to the table below to see the days at which the volunteer will receive the study compounds:

Period 1:
Day -1 - none
Day 1 to 10 - balovaptan once daily
Day 11 - none
Day 12 to 16 - none

Period 2:
Day -1 - none
Day 1 to 4 - itraconazol twice daily

Day 5 - itraconazol once daily
Day 6 to 20 - balovaptan once daily and itraconazol once daily
Day 21 - none

Study burden and risks

The study compound may cause side effects. Balovaptan has had limited testing in humans. Side effects that were observed in clinical trials with balovaptan are listed below. However, it is not clear whether balovaptan has been the cause of these side effects. On the other hand, there may be side effects that are not known at this time.

The most common side effects reported are listed below.

Side Effects Reported in Previous Clinical Trials with Balovaptan:
Aggression
Anxiety, nightmares, and insomnia
Arthralgia (joint pain)
Back pain
Bronchitis
Diarrhea
Digestion troubles
Dizziness
Dysgeusia (affecting sense of taste)
Dyspepsia (indigestion)
Fatigue
Headache
Irritability
Muscle pain
Nasopharyngitis (runny nose and sore throat)
Nausea
Runny nose
Skin lesion
Syncope (fainting) after standing up quickly
Taste alteration
Upper respiratory tract infection

Also, should the volunteer experience lightheadedness or dizziness when standing up or even fainting, or should the volunteer experience muscle ache or cardiovascular symptoms, such as chest pain, palpitations, or breathlessness, the volunteer should inform the study doctor as soon as possible.

Itraconazole
The most common side effects of itraconazole are the following: gastrointestinal disturbances, nausea, vomiting, diarrhea, abdominal pain, and rash. Other adverse effects include itching, angioedema, anaphylaxis fatigue, headache, dizziness, hypertension, decreased libido, impotence, and somnolence.

Itraconazole is rarely associated with hepatotoxicity.

Tests
Drawing blood and/or insertion of the indwelling cannula may be painful or cause some bruising.

To monitor the heart rate, electrodes (small, plastic patches) will be pasted at specific locations on the chest and abdomen. Prolonged use of these electrodes can cause skin irritation (rash and itching).

This study includes a test exploring how well the body manages blood pressure control when standing up quickly after about 15 to 20 min in a supine position. The blood pressure and pulse rate will be measured several times while in a supine position as well as 3 minutes after having moved into a standing position. Should the volunteer experience dizziness, sweating, or any pre-fainting symptoms the volunteer should tell the site staff and do not hesitate to interrupt the test by moving back into a sitting or supine position. After the volunteer moved from supine to standing position a study nurse will be with the volunteer until the end of the test.

This test will be performed at screening and should the volunteer experience pre-fainting symptoms or fainting, the volunteer will not be enrolled into this study. After enrollment, the test is also scheduled for study Day 9 in Period 1 and study Days -1, 4 and 16 in Period 2.

Procedures: pain, minor bleeding, bruising, possible infection

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 and female subjects
-18 to 65 years, inclusive, at screening
-BMI: 18 to 30 kg/m2, inclusive, at screening
-Non-smoking
-Women of childbearing potential and men must use contraceptive methods

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

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-06-2018
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Itraconazole Teva
Generic name:	Itraconazole Teva
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-06-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-06-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-08-2018
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	EUCTR2018-001454-10-NL
CCMO	NL66074.056.18