Single-center, open-label study with 14C-radiolabeled ACT-246475 to investigate its mass balance, pharmacokinetics, and metabolism following single subcutaneous administration to healthy male subjects.

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

Summary

ID

NL-OMON46067

Source
ToetsingOnline

Brief title
ACT-246475 ADME study

Condition

- Myocardial disorders

Synonym
Acute myocardial infarction (heart attack)

Research involving

Human

Sponsors and support

Primary sponsor: Idorsia Pharmaceuticals Ltd
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: ACT-246475, ADME, PK

Outcome measures

Primary outcome

•To investigate the rate and routes of elimination of ACT-246475 and its mass balance in urine and feces.

•To investigate the PK of total 14C-radioactivity in whole blood and plasma.

•To investigate the PK of ACT-246475 in plasma.

•To identify and quantify the metabolites of ACT-246475 in plasma, urine, and feces.

•To evaluate the safety and tolerability of 16 mg ACT-246475 including 3.7 MBq (100 µCi) 14C-radiolabeled ACT-246475 in healthy male subjects.

Secondary outcome

n/a.

Study description

Background summary

ACT-246475 a new compound that may eventually be used for the treatment of acute myocardial infarction (heart attack). On average it takes between 2 and 4 hours for treatment to start after the first symptoms of an heart attack are noticed. While quick treatment of suspected heart attacks could prevent death, and reduce damage to the heart. During a heart attack one of the blood vessels

of the heart becomes obstructed with a blood clot, and if this is not treated quickly, the heart muscle can die, leading to permanent damage or even death. Platelets are a type of blood cell responsible for blood clotting. Platelets form blood clots in case of damage to the blood vessels. ACT-246475 reduces platelet activation in the blood. In case of a heart attack, reducing the formation of blood clots at the start of a (suspected) heart attack during the first symptoms could prevent or reduce damage.

ACT-246475 is in development and it is not registered as a drug but has been given to humans before.

Study objective

This study will be performed in 6 healthy male volunteers.

The purpose of this study is to investigate how quickly and to what extent ACT-246475 is absorbed, distributed, metabolized (broken down) and eliminated from the body (pharmacokinetics). ACT-246475 will be labelled with 14 Carbon (14C) and is thus radioactive (also called radiolabeled). In this way ACT-246475 can be traced in blood, urine and feces. It will also be investigated how safe ACT-246475 is and how well it is tolerated when it is administered to healthy male volunteers.

Study design

The study will consist of 1 period during which the volunteer will stay in the research center location Martini Hospital for at least 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 prior to the day of administration of the study compound (on Day -1).

The duration of the stay in the research center will depend on the amount of radioactivity left in urine and feces at the end of the study (Day 4). The amount of radioactivity in urine and feces will be measured daily from Day 1 onwards. If, from Day 4 onwards, the radioactivity levels in urine and feces are below the pre-defined levels, the volunteer is allowed to leave the research center. The volunteer should be aware that when the radioactivity levels are still above the pre defined levels on Day 4, the stay in the research center will be extended with a maximum of 6 days (until Day 10).

On the day that the volunteer leaves the research center volunteers health will be checked for the last time.
The volunteer will be contacted by telephone for a last safety follow-up call, 30 to 32 days after administration of the study compound on Day 1. During this phone call the volunteer will be asked how he is feeling and if anything

happened to him since he has left the research center.

Intervention

The volunteer will receive a single dose of 16 mg/3.7 MBq radiolabeled ACT-246475 as an injection of 1 milliliter under the skin (subcutaneous) in the upper leg. The volunteer must remain in a sitting position from approximately 5 minutes before until 4 hours after administration of the study compound, except for the measurement of the vital signs and ECG, which will be conducted when the volunteer is lying down, or during blood sampling or for going to the toilet.

Study burden and risks

The study compound may cause side effects. Because ACT-246475 is an investigational drug, all of it side effects may not be known. There may be rare and unknown side effects.

In the first study with the study compound administered subcutaneously, one volunteer suffered, after a single subcutaneous dose of 1.6 mg, from serious headache and hypotension, leading to hospitalization for additional exams and treatments, and the study was prematurely terminated. The volunteer recovered spontaneously.
In this study, apart from headache and hypotension, other complaints were also reported: diarrhea, weakness (asthenia), abdominal pain, belching (eructation), nausea, vomiting, chest pain, fatigue, feeling cold, inflammation of a vein (phlebitis) at the injection site, accommodation disorder, light sensitivity (photophobia), vision blurred, altered state of consciousness, hypersensitivity for and fear of (loud) sounds (phonophobia).

In a subsequent study in healthy volunteers with subcutaneous doses between 1 and 32 mg of ACT-246475 or placebo, the following complaints were reported: headache, dizziness, rhinorrhea, nausea and increased perspiration, without a relationship to the administered dose.

Tests
Drawing blood and/or insertion of the indwelling cannula may be painful or cause some bruising. In total, we will take about 493 milliliters of blood from the volunteer. This amount does not cause any problems in adults. To compare: a blood donation involves 500 milliliters of blood being taken each time.

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

Exposure to radiation

In this study radiolabeled ACT-246475 will be used. The amount of radioactivity in this dose will be approximately 3.7 MBq (MBq = megaBecquerel, this is a unit to express the amount of radioactivity in the study compound). The average environmental background radiation burden in The Netherlands is approximately 2.5 mSv per year (mSv = milliSievert, this unit indicates the burden on the human body; thus the effect on the human body of the amount of radioactivity administered). The additional radiation burden in this study due to the administration of approximately 3.7 MBq radiolabeled ACT-246475 is calculated to be 0.02 mSv. This is approximately 1% of the average annual radiation burden in The Netherlands.

If the volunteer participate in scientific research involving exposure to radiation more often, the volunteer should discuss with the responsible doctor whether participation at this moment would be safe.

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
-45-65 yrs, inclusive at screening
-BMI: 18.0-28.0 kg/m2 (inclusive) at screening.
-Non-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

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-07-2018
Enrollment:	6
Type:	Actual

Ethics review

Approved WMO

Date:	21-06-2018

Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-06-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-09-2018
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	EUCTR2017-004622-15-NL
CCMO	NL66246.056.18