Non-blinded, non-randomized study to investigate the pharmacokinetics, including absolute bioavailability of BAY 2433334 following administration of a 25 mg oral dose and a 50 µg intravenous [13C7,15N]-labeled BAY 2433334 microdose in healthy male participants

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Embolism and thrombosis
Study type	Interventional

Summary

ID

NL-OMON49790

Source
ToetsingOnline

Brief title
PK and absolute bioavailability of BAY 2433334

Condition

- Embolism and thrombosis

Synonym
coronary artery disease

Research involving
Human

Sponsors and support

Primary sponsor: Bayer AG
Source(s) of monetary or material Support: Pharmaceutical industry.

Intervention

Keyword: BAY 2433334, Pharmacokinetics

Outcome measures

Primary outcome

To investigate the absolute bioavailability and pharmacokinetics of BAY 2433334

using a simultaneous oral unlabeled and i.v. [13C7,15N]-labeled microdose.

Secondary outcome

To investigate safety and tolerability of BAY 2433334.

Study description

Background summary

BAY 2433334 is a compound that may potentially be used for the prevention of blood clots in the heart, in blood vessels or in the brain as it can happen after heart attack or stroke, with an irregular heart rhythm or due to other reasons. Worldwide, disease of the heart or blood vessels is the leading cause of death in adults with an estimated 17.7 million deaths in 2015. BAY 2433334 is a blood thinner (an *anti-coagulant*) which can prevent the formation of blood clots in blood vessels (so-called *thrombo-embolic* disorders). These blood clots can travel through the bloodstream and block arteries which prevents blood from delivering oxygen and nutrients to the organs. When that happens in the heart, it is called a heart attack and when that happens in the brain it is called a cerebral infarction, also called stroke. All these conditions may ultimately result in death or permanent disability. BAY 2433334 aims to prevent the formation of blood clots (anticoagulation). It works by blocking a *blood clotting* protein (FXIa) from performing its function.

Study objective

The purpose of this study is to investigate how quickly and to what extent BAY 2433334 is absorbed, broken down, and eliminated from the body (this is called pharmacokinetics). The pharmacokinetics of BAY 2433334 administered as a tablet will be compared to the pharmacokinetics of BAY 2433334 administered as intravenous (iv; in the vein) infusion.

It will also be investigated how safe BAY 2433334 is and how well it is tolerated when it is administered to healthy male volunteers. Furthermore, the effect of your genetic information on your body*s response to BAY 2433334 will be investigated.

The iv infusion of BAY 2433334 will be a very low dose (microdose) which will be labeled with carbon-13 (13C7) and nitrogen-15 (15N). Carbon-13 and nitrogen-15 are isotopes. Isotopes are atoms of the same element with the same number of protons, but with a different number of neutrons in the atom nucleus. Carbon-13 and nitrogen-15 both have a neutron more than their normal elements. As a result, they are heavier and can be measured separately so that the absolute bioavailability can be determined (pharmacokinetics of BAY 2433334 tablet without isotopes compared to pharmacokinetics of BAY 2433334 iv infusion with isotopes). The carbon-13 and nitrogen-15 isotopes are not radioactive.

BAY 2433334 is an investigational compound. It is not approved for sale in any country. That means it can only be used in studies like this one. BAY 2433334 has been administered to healthy volunteers before. It has also previously been extensively tested in the laboratory and on animals.

The study will be performed in up to 16 healthy male volunteers.

Study design

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

Day 1 is the day of administration of the study compound. Volunteer is expected at the research center at 11:00 hrs in the morning one day prior to the day of administration of the study compound (Day -1). Volunteer will leave the research center on Day 4 of the study.

Volunteer will be tested for the presence of coronavirus at the visit on Day -5 or -4 and upon admission to the research center on Day -1. Until the test results are available, volunteer will be separated from other volunteers and only have very limited contact with study staff. This is to avoid virus spread from potentially infected volunteers to other volunteers or to the study staff because, until the results are available, it is not certain whether the volunteer is infected or not and can thus potentially infect others. The test results will be available within a few hours. If volunteer test positive for coronavirus, he cannot participate in the study. It may be decided that more

tests are needed (eg, if volunteer has COVID-19 symptoms).

Intervention

On day 1, the volunteers are administered 25 mg of BAY 2433334 followed 2 hours later by 50 µg of 13C7.15N-labeled BAY 2433334.

Study burden and risks

BAY 2433334 has been administered to in total 219 healthy men before in 7 previous clinical studies. These studies found no relevant effects of BAY 2433334 on several health parameters, including heart tracings (ECGs), blood pressure, and heart rate. BAY 2433334 was considered safe and well tolerated. Side effects that did occur were:
• Nausea
• Headache
• Dizziness
• Dry mouth
• Bitter taste sensation
• Fast or irregular heartbeat
• Tingling or pricking sensation (paresthesia) in hands and fingertips
• Sensation of cold in feet
• Sensation of *lump in the throat*

The side effects disappeared again after a few hours. Only the irregular heartbeat was observed over a longer period of approximately 1 day.

In previous clinical trials, single doses of 5 mg up to 150 mg of BAY 2433334 and multiple doses of 25 mg up to 100 mg BAY 2433334 were administered and were considered safe and well tolerated. Therefore, the single oral dose that will be used in this study (25 mg BAY 2433334) and the intravenous micro dose (50 µg BAY 2433334) are also expected to be safe and well tolerated.

BAY 2433334 has been studied extensively in the laboratory and in animals. Studies in animals showed effects of BAY 2433334 on the liver. Therefore, intensive monitoring is used in the human studies to make sure human volunteers do not develop similar signs or symptoms. In all the previous studies in humans, no changes in the liver function were found after administration of BAY 2433334.

The mode of action of BAY 2433334 is to slow down the clotting of blood. A risk of compounds that have a similar mode of action (blood thinners) is that they can result in spontaneous bleeding. As the working mechanism of BAY 2433334 is slightly different than that of other blood thinners, spontaneous bleedings with BAY 2433334 are less likely. The main risk associated with BAY 2433334 is assumed to be increased bleeding after trauma or surgery. So far, bleedings

have not been reported in previous studies when BAY 2433334 was administered to humans.

The study compound may also have side effects that are still unknown. In addition to unknown side effects, there is a (small) chance that an allergic reaction will occur. This can be caused by the study compound or the other ingredients used to make the formulation.
An allergic reaction is always possible with a drug you have not taken before. Unexpected serious allergic reactions can be life-threatening. Some things that may happen during an allergic reaction to any type of medication include rash, breathing difficulty, sudden drop in blood pressure, swelling of mouth/throat/eyes, fast pulse and/or sweating.

Possible discomforts due to procedures
On the day of administration of the study compound, blood is drawn using an indwelling venous cannula from a blood vessel in the forearm. This might sometimes cause mild pain, inflammation, swelling, hardening of the vein, blood clotting and bleeding into surrounding (bruising) at the insertion site. In rare cases, there may be inflammation and damage to blood vessels and/or damage to neighboring nerves. In sensitive individuals, blood draws may sometimes cause pallor, nausea, sweating, slow pulse, or drop in blood pressure with dizziness or fainting. On the day of administration of the study compound, blood will be sampled very frequently (20x) by using an indwelling cannula to determine the course of the concentration of BAY 2433334 in the blood over time. The use of adhesive bandages to cover blood draw sites may cause mild, temporary redness and itching of the skin.

For the intravenous administration, an extra indwelling cannula will be inserted on Day 1 in addition to the indwelling cannula used for blood sampling. Thus, the volunteers will have a cannula inserted in both arms during the 30-minute infusion of the study compound.

In total, we will take about 170 milliliters (mL) of blood from you.

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

A sample for the coronavirus test will be taken from the back of the nose and throat using a swab. Taking the sample 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 volunteer to gag. When the sample is taken from the back of the nose, volunteer may experience a stinging sensation and the eyes may become watery.

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 white male
• 18 to 45 years old at the time of the screening visit
• BMI is between 18 and 29.9 kilograms/meter2
• not regularly drink more than 17.5 units of alcohol per week. 17.5 units of alcohol is equal to approximately 12 glasses (285 mL) of beer or lager, 12 glasses (125 mL) of wine, or 17 small shots (25 mL) of spirits.
• do not regularly consume more than 1 L of methylxanthine or caffeine-containing beverages daily.
• did not donate more than 100 mL of blood or plasma within 4 weeks or 500 mL blood within 3 months before study compound administration. Blood donation is not allowed during the entire study, until 3 months after the last visit.
• not participated in any other drug study within 3 months preceding the

administration of the study compound.
• no history of COVID-19 infection, do not test positive in the SARS-CoV-2 test, and no contact with SARS-CoV-2-positive or COVID-19 patients within 4 weeks prior to admission to the research center.
• at screening the state of health must satisfy the study entry requirements.

Exclusion criteria

1. A history of relevant diseases of vital organs, of the central nervous system or other
organs.
2. Medical disorder, condition or history of such that would impair the participant*s ability to participate or complete this study in the opinion of the investigator.
3. Incompletely cured pre-existing diseases for which it can be assumed that the absorption, distribution, metabolism, elimination and effects of the study intervention will not be normal.
4. Known hypersensitivity to the study interventions (active substance or excipients of
the preparation).
5. Known severe allergies e.g. allergies to more than 3 allergens, allergies affecting the
lower respiratory tract - allergic asthma, allergies requiring therapy with corticosteroids, urticaria or significant non-allergic drug reactions.

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):	22-07-2020
Enrollment:	16

Type:	Actual

Ethics review

Approved WMO Date:	02-06-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-07-2020
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	EUCTR2019-004049-34-NL
CCMO	NL74123.056.20