Single center, open-label, non-randomized, non-placebo-controlled study to investigate the metabolism, excretion pattern, mass balance, safety, tolerability and pharmacokinetics after single administration of 200 mg [14C]rogaratinib (oral solution) in healthy male subjects

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Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON46572

Source
ToetsingOnline

Brief title
Rogaratinib (BAY1163877) human mass balance study

Condition

- Other condition
- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Tumors

Health condition

tumoren

Research involving
Human

Sponsors and support

Primary sponsor: Bayer AG
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: ADME, open-label, Rogaratinib, Tumors

Outcome measures

Primary outcome

-To determine the mass balance and routes of excretion of total radioactivity

after a single oral 200mg dose of [14C]rogaratinib given as a solution

-To quantify rogaratinib concentrations in plasma *

-To quantify total radioactivity in whole blood and plasma

Secondary outcome

Secondary objectives are not applicable in this study.

Other objectives of this study are: *

-To provide plasma and excreta samples for further metabolite profiling and

chemical structure identification (to be reported separately) *

-To provide additional information on the safety and tolerability of a single

oral dose of 200mg rogaratinib

Study description

Background summary

Rogaratinib is a new compound that may eventually be used for the treatment of tumors. Fibroblast growth factors (FGF) and fibroblast growth factor receptors (FGFR) are specific proteins that play an important role in cell proliferation, survival and migration. Rogaratinib is an inhibitor of FGFR1, 2, 3 and 4. In this way, rogaratinib may be used as a treatment of tumors. Rogaratinib is in development and it is not registered as a drug but has been given to humans before.

Study objective

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

Study design

A study to investigate the absorption, distribution, metabolism and excretion (ADME) of rogaratinib in healthy male volunteers. Rogaratinib is a new compound developed for the treatment of tumors

The volunteer will receive a single dose of 200 mg/3.7 MBq radiolabeled rogaratinib as an oral solution. Thereafter the volunteer is also required to drink an additional amount of 100 mL of non-sparkling water.

The study will consist of 1 period during which the volunteerr will stay in the PRA research center at the Martini Hospital location for up to 16 days (15 nights): from Day -1 up to Day 15.

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 15). The amount of radioactivity in urine and feces will be measured daily from Day 1 onwards. If, from Day 8 onwards, the radioactivity levels in urine and feces are below the pre-defined levels, the volunteer will be allowed to leave the

research center at an earlier day. From Day 8, this will be communicated with the volunteer on a daily and per person basis. If the radioactivity levels are still above the pre defined levels on Day 15, the volunteer will be required to come back to the research center after 7 days for a stay of 2 days (1 night). For this overnight stay, the volunteer is expected at the research center at 11:00 h in the morning and will leave the research center after 24 hours. If necessary, this procedure will then be repeated every 7 days until the radioactivity levels are below the pre-defined levels. For a maximum of 4 times the volunteer will visit the research center for a stay of 2 days (1 night).

Intervention

The volunteer will receive a single dose of 200 mg/3.7 MBq radiolabeled rogaratinib as an oral solution. Thereafter you are also required to drink an additional amount of 100 mL of non-sparkling
water.

Study burden and risks

Administration of a single dose of 200 mg of rogaratinib is not expected to cause any clinically relevant side effects, however they cannot be entirely excluded.

The side effects that are described in the following information have been observed after administration of multiple and higher doses of rogaratinib either in animal studies (which can be transposed to humans only to a limited extent), or in the 2 clinical studies in human subjects (studies 16443 and 16958) in which 118 patients with cancer have been treated to date.

In the animal studies, it was observed that the use of rogaratinib may cause abnormal calcium deposits in soft tissues of the body (for example in the lungs, stomach, trachea (breathing tube), skin and cartilage). This is known as soft tissue mineralization and this represents the most important potential risk associated with the use of rogaratinib.

Although soft tissue mineralization has not been observed in any patient treated with rogaratinib, it is known that the risk of this increases with abnormally high phosphate and abnormally high calcium in the blood. Therefore, the responsible doctor will monitor the levels of phosphate and calcium in volunteers blood and the overall health whilst you are receiving rogaratinib.

If the volunteers blood phosphate level is above normal, it might be necessary to take blood samples more often than once a week, for as long as the phosphate in the blood remains high. The responsible doctor can also give the volunteer other medicine called *phosphate binders* to reduce the blood phosphate level. This would reduce the risk of soft tissue mineralization.

Also, additional ECGs (heart trace) will be taken to monitor the heart function if volunteers blood calcium level is found to be abnormal. The results from blood samples and ECGs taken during the study will support the responsible doctor to determine whether the volunteer is at risk for soft tissue mineralization or cardiac side effects.

In the clinical studies in human subjects, mostly mild or moderate adverse events (untoward medical occurrences) were observed in patients during the treatment with rogaratinib. The very common adverse events (> 10 % of treated patients) were:
• An abnormally high level of phosphate in the blood
• Gastro-intestinal disorders such as diarrhea, nausea and constipation
• Nail disorders (nail deformity, discoloration and nail loss)
• Decreased appetite
• Feeling tired (fatigue)
• Anemia (decrease in the total amount of red blood cells or hemoglobin in the blood)
The high phosphate in the blood, the diarrhea and nail disorders are regarded to be caused by rogaratinib.

Furthermore, a detachment of retinal pigment epithelium (a layer of the light-sensitive structure in the eye) was found in some patients treated with rogaratinib. Therefore, eye examinations will be performed prior and after participation in the study to monitor volunteers eye health.

The data collected in the 118 patients to date, indicates that rogaratinib is removed from the body via the urine only in small amounts. Therefore, it is not expected that rogaratinib will significantly accumulate in the body in patients with impaired kidney function. To date, 2 patients have experienced impairment of their kidney function, which recovered back to normal within a few days after sufficient fluid intake. No kidney function impairment re-occurred in these patients after the treatment with rogaratinib was resumed. Currently, no difference in behavior of rogaratinib in the body is expected in patients with mild or moderate kidney impairment versus patients with healthy kidneys. The responsible doctor will monitor the values reflecting volunteers kidney function and the overall health continuously with regular blood samples and urine tests.

As rogaratinib is an experimental drug, it is also possible that more and/or other side effects may occur in humans that have not been observed before.

While on the study, the volunteer may experience diarrhea or vomiting. Therefore, oral intake of adequate amount of water is recommended.

The study drug contains lactose as a filler, but in such a small amount that no side effects are expected in patients with slight or moderate lactose intolerance. The volunteer should inform the responsible doctor if he is

subject to lactose intolerance. The doctor will then decide if the volunteer can be treated.

Up to now the results of 135 cancer patients, who received multiple dose administrations between 50 and 800 mg rogaratinib twice daily have been reported. In these patients the following complaints and abnormalities have been recorded: an increase in the concentration of phosphate in the blood, diarrhea, a decreased appetite, fatigue, nausea, constipation, anemia and dry mouth. Also, some reports have been made of increases in liver enzyme activities, decrease of the concentration of sodium in the blood, decrease of the number of neutrophil cells (a subgroup of the white blood cells) in the blood, lung infection, urine tract infection, alopecia (hair loss), arthralgia (joint pain), dysgeusia (distortion of the sense of taste), and stomatitis (inflammation of the mouth and lips). In 4 patients abnormalities in the retina have been observed. Because these studies involved patients with often advanced cancer, it is often not possible whether and in what degree complaints and abnormalities are related to the study compound or to the underlying disease or other treatments given. Because the study compound will be given once in the current study, the chance on above-mentioned or other complaints appears not high, but can certainly not be excluded.

Tests
Drawing blood and/or insertion of the indwelling cannula may be painful or cause some bruising. In total, we will take about 505 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 volunteers 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 rogaratinib 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 rogaratinib is calculated to be 0.1 mSv. This is approximately 4% of the average annual radiation burden in The Netherlands.

Procedures: pain, minor bleeding, bruising, possible infection

Contacts

Public
Bayer AG

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Scientific
Bayer AG

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Berlin 13353
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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
-21 to 65 years, inclusive
-BMI 18.5 and 32.0 kg/m2 (inclusive)
-Total body weight of 55 to 100kg (inclusive)
-non-smoking or light smokers (not more than 5 cigarettes daily)
-Use adequate contraception during the study and in the 3 months following dosing

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:	Completed
Start date (anticipated):	06-04-2018
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	Rogaratinib

Ethics review

Approved WMO Date:	13-03-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-04-2018
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	EUCTR2017-002777-19-NL
CCMO	NL65273.056.18

Study results

Date completed: 14-06-2018

Results posted: 29-01-2020

First publication
14-12-2018

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File