A two parts, open-label, single-dose mass balance and absolute bioavailability study with an oral regular dose of PHA-022121 and an oral (part 1) and intravenous (part 2) microtracer dose of 14C-PHA-022121 in healthy male subjects

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Ethical review	Approved WMO
Status	Completed
Health condition type	Congenital and hereditary disorders NEC
Study type	Interventional

Summary

ID

NL-OMON51216

Source
ToetsingOnline

Brief title
ADME with 14C PHA-022121 in healthy male subjects

Condition

- Congenital and hereditary disorders NEC

Synonym
Hereditary Angioedema

Research involving
Human

Sponsors and support

Primary sponsor: Pharvaris Netherlands BV
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: 14C, ADME, PHA-022121

Outcome measures

Primary outcome

Part 1:

The primary objective of this study is to characterize the absorption, metabolism and excretion of orally administered radiolabeled PHA-022121 in healthy male subjects.

Part 2:

The primary objective is to determine the absolute bioavailability of orally administered PHA-022121 in healthy male subjects.

Secondary outcome

Part 1:

The secondary objective of this study is to evaluate safety and tolerability of a single oral dose of radiolabeled PHA-022121 administered in healthy male subjects.

Part 2:

The secondary objectives are

- To evaluate the safety and tolerability of simultaneously administered unlabelled (orally) and radiolabeled (intravenously) PHA-022121 in healthy male subjects.

- To determine the mass balance after an intravenously (IV) dose of a microdose/microtracer dose of PHA-022121.

Optional after the results of study PHA022121-C003 and the mass balance data after IV dosing of a microdose/microtracer dose of PHA-022121 are available:

- To characterize the metabolism of intravenously administered radiolabeled PHA-022121 in healthy male subjects.

Study description

Background summary

PHA-022121 is a new compound that may potentially be used for the treatment of hereditary angioedema. With this disease, swellings occur (edema), most commonly in the limbs, the face (lips and tongue), the intestinal tract, the area of the abdomen near the urinary tract and genitals, and the airways. These swellings often lead to discomfort, pain, and nausea, and can become life threatening in case of airway blockade. It is estimated that hereditary angioedema affects on average 1 in every 50,000 people. PHA-022121 is able to influence a certain receptor, called bradykinin B2, and thereby has the ability to treat hereditary angioedema.

Study objective

In this study we will investigate how quickly and to what extent PHA-022121 is absorbed, transported, and eliminated from the body (this is called pharmacokinetics). PHA-022121 will first be given as a single oral dose, and then as an infusion in a vein. The dose of PHA-022121 that is administered in a vein is radioactively labelled with carbon 14 (14C). In this way, PHA-022121 can be traced in blood, urine, and feces. We will also compare the

pharmacokinetics of both administrations.

We also investigate how safe the new compound PHA-022121 is and how well it is tolerated when it is used by healthy male participants.

We also look at the effect of genetic information on the body*s response to PHA-022121. The responses to medicines can strongly vary among people and this may be explained by different genetic profiles. This part of the study is mandatory.

PHA-022121 has been used by humans before in previous drug studies. In addition, it has been extensively tested in the laboratory and on animals. PHA-022121 will be tested at a dose level of 20 milligram (mg).

Study design

The study will take a maximum of 5 weeks (Part 1) or 4 weeks (Part 2) from the screening until the end of study. For the study it is necessary that subjects stay in the research for 1 period of 5 days (4 nights) (Part 1) or 7 days (6 nights) (Part 2).

Day 1 is the day when subjects receive the study compound. Subjects are expected at the research center the day before the day of administration of the study compound. Subjects will leave the research center on Day 4 (Part 1) or Day 6 (Part 2) of the study.

Screening visit: Day -21 up to Day -2
Arrival: Day -1
Administration of study compound: Day 1
In-house stay: Day -1 up to Day 4 (Part 1) or Day 6 (Part 2)
Departure and follow-up: Day 4 (Part 1) or Day 6 (Part 2)

Intervention

Part 1:
Subjects will be given PHA-022121 as a drink of 0.4 mL. Because of the small volume, the drink will be administered via a syringe into the mouth. This will be followed by drinking 240 milliliters (mL) of water.

Subjects will receive the study compound in the morning after they have fasted for at least 10 hours (overnight). After intake of the study compound, fasting continues for 4 more hours.

Subject will receive a single dose of 20 mg 14C-labeled radioactive PHA-022121 one time.

Part 2:
The first dose of PHA-022121 will be given as a drink. Because of the small volume, the drink will be administered with a syringe into the mouth. This will be followed by drinking 240 milliliters (mL) of water.

The second dose of PHA-022121 will be radioactively labeled and is given 75 minutes after the first dose. This dose will be given as an intravenous infusion. The infusion takes 15 minutes.

Subjects will receive PHA-022121 twice:
1. 20 milligram PHA-022121 as a drink.
2. 20 microgram of 14C-labeled radioactive PHA-022121 with a total volume of 8 milliliter that will be given as an intravenous infusion.

Study burden and risks

Blood draw
Drawing blood may be painful or cause some bruising. The use of the indwelling cannula can sometimes lead to inflammation, swelling, hardening of the vein, blood clotting, and bleeding in the environment (bruising) of the puncture site. In some individuals, a blood draw can sometimes cause pallor, nausea, seating, low heart rate, or drop in blood pressure with dizziness or fainting.

In total, we will take approximately 321 mL (Part 1) or 359 mL (Part 2) of blood from the volunteer. This amount does not cause any problems in adults. To compare: a blood donation involves 500 mL of blood being taken each time. If the investigator thinks it is necessary for the safety of a participant, extra samples might be taken for possible additional testing. If this happens, the total amount of blood drawn may be more than the amount indicated above.

Heart tracing
To make a heart tracing, electrodes will be placed on arms, chest and legs. Prolonged use of these electrodes can cause skin irritation.

Meals/Fasting
If subjects have to fast for a prolonged time during the study, this may lead to symptoms such as dizziness, headache, stomach upset, or fainting.

Coronavirus test
Samples for the coronavirus test will be taken from the back of the nose and throat using swabs. Taking the samples 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 subjects to gag. When the sample is taken from the back of the nose, subjects 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)

Inclusion criteria

1. Subject must be a healthy male, between 18 to 65 years of age, extremes included, at screening.

2. Subject must have a body mass index (BMI; weight in kg divided by the square of height in meters) between 18.0 and 30.0 kg/m2, extremes included, and a body weight not less than 50.0 kg, inclusive, at screening.

3. Subject must sign an ICF indicating that he understands the purpose of the study including the procedures required, and is willing to participate in the study, including that he agrees to provide DNA samples for research, before starting of any screening activities.

4. During the study and for a minimum of 1 spermatogenesis cycle (defined as up

to and including 90 days after receiving the study drug), a male subject may be enrolled if he is willing and able to adhere to the contraceptive requirement as specified in 4.5 item 12 in the protocol.

5. Subject must be willing and able to adhere to the prohibitions and restrictions.

Further criteria apply.

Exclusion criteria

1. Subject has a history of current clinically significant medical illness including (but not limited to) cardiac arrhythmias or other cardiac disease, hematologic disease, lipid abnormalities, significant pulmonary disease, including bronchospastic respiratory disease, diabetes mellitus, hepatic or renal insufficiency (estimated creatinine clearance < 61 mL/min/1.73m2 at screening, calculated by MDRD formula), thyroid disease, neurologic or psychiatric disease, infection, or any other illness, that in the investigator*s and/or sponsor*s medical monitor opinion should exclude the subject or that could interfere with the interpretation of the study results.

2. Subject has one of the following laboratory abnormalities at screening as defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, 27 November, 2017 and in accordance with the normal ranges of the clinical laboratory if no gradings are available.
- Serum creatinine elevation grade 1 or greater (>1.1 x upper limit of normal range [ULN])
- Hemoglobin below LLN (reference of site);
- Platelet count below LLN;
- Absolute neutrophil count lowering grade 1 or greater (<=1,5 109/L);
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >=ULN;
- Total bilirubin>=ULN;
- Any other toxicity grade 2 or above, except for grade 2 elevations for triglycerides, low density lipoprotein (LDL) cholesterol and/or total cholesterol.

3. Clinically significant abnormal values for hematology, clinical chemistry or urinalysis at screening or at admission to the clinical site on Day -1 as deemed appropriate by the investigator.

4. Subject, at screening, has a positive test of human immunodeficiency virus (HIV) 1 and 2 antibodies, hepatitis B surface antigen (HBsAg), or hepatitis C antibodies.

5. Subject has a history of heart arrhythmias , tachycardia at rest or history

of risk factors for Torsade de Pointes syndrome (eg, hypokalemia, family history of long QT syndrome).

Further criteria apply.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	24-02-2021
Enrollment:	12
Type:	Actual

Ethics review

Approved WMO Date:	05-02-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-02-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-10-2021
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-10-2021
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	EUCTR2020-006083-83-NL
CCMO	NL76529.056.21

Study results

Date completed:	08-11-2021
Results posted:	04-05-2022

First publication
02-05-2022