# An open-label, single-sequence cross-over drug-drug interaction study to evaluate the effect of single and multiple oral doses of PHA-022121 on the pharmacokinetics of selective CYP1A2, CYP2C19, and CYP3A4 substrates in healthy subjects

Published: 20-10-2020
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The main purpose of this study is to investigate the effect of multiple doses of PHA-022121 on how quickly and to what extent a drug cocktail (a combination of agents consisting of caffeine, omeprazole, and midazolam) is absorbed, distributed,...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Congenital and hereditary disorders NEC |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON49587

**Source**
ToetsingOnline

**Brief title**
DDI of PHA-022121 on PK of CYP1A2, CYP2C19 and CYP3A4.

### 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:** Ministerie van OC&W,Pharmaceutical Industry

## Intervention

**Keyword:** DDI, Midazolam, Omeprazole, PHA-022121

## Outcome measures

### Primary outcome

The primary objective of this study is to determine the potential inhibitory/inducing effects of multiple doses of PHA 022121 on the single-dose pharmacokinetics (PK) of a cocktail, containing selective probe substrates of cytochrome P450 (CYP) enzymes (CYP1A2, CYP2C19 and CYP3A4) in healthy adult subjects.

### Secondary outcome

The secondary objectives of this study are to evaluate the safety and tolerability of PHA 022121 after multiple doses in the presence of a drug cocktail in healthy adult subjects and to assess steady-state PK of PHA-022121 and its active metabolite M2-D in the presence of a drug cocktail in healthy adult 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 (called edema), most commonly in the limbs, the face (lips and tongue), the intestinal tract, the area of the abdomen near the urinary and genital openings, 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**

The main purpose of this study is to investigate the effect of multiple doses of PHA-022121 on how quickly and to what extent a drug cocktail (a combination of agents consisting of caffeine, omeprazole, and midazolam) is absorbed, distributed, metabolized and eliminated from the body.

It will also be investigated how safe PHA-022121 is and how well it is tolerated after multiple doses in the presence of the drug cocktail.

Furthermore, the effect of the genetic information on the body*s response to PHA-022121 will be investigated. This part of the study is mandatory.

PHA-022121 has been administered to humans before. Caffeine, omeprazole, and midazolam are already available on the market in several dosages and formulations.

This study will be performed in 14 healthy male and female volunteers.

**Study design**

The actual study will consist of 1 period during which the volunteers will stay in the research center for 15 days (14 nights). Day 1 is the first day of administration of the study compound. They are expected at the research center at 14:00 h in the afternoon prior to the day of first administration of the study compound. The time of entry may be changed. If this happens the volunteers will be informed about it in advance. They will leave the research center on Day 14 of the study.

On Day 1, the drug cocktail will be given as an oral tablet of caffeine, an oral capsule of omeprazole, and an oral solution of midazolam together with 240 mL of non-carbonated water, after an overnight fast of at least 10 hours.

On Day 3 until Day 12, PHA-022121 will be given twice daily as oral capsules with 240 mL of non-carbonated water, 0.5 hours after finishing a standard meal (Day 4 until Day 11) or after an overnight fast (in the morning of Day 3 and Day 12) as explained above.

On the morning of Day 3 and Day 12, a combination of PHA-022121 and drug cocktail will be given. PHA-022121 will be given first with 120 mL of non-carbonated water and 30 minutes later, the drug cocktail will be given with 120 mL of non-carbonated water. The study compounds will be given after an overnight fast of at least 10 hours.

**Intervention**

Day Treatment How often
1 drug cocktail consisting of 50 mg caffeine, 10 mg omeprazole, and 1 mg midazolam once
3 20 mg PHA-022121 twice daily
drug cocktail consisting of 50 mg caffeine, 10 mg omeprazole, and 1 mg midazolam once
(30 minutes after PHA-022121)
4 to 11 20 mg PHA-022121 twice daily
12 20 mg PHA-022121 twice daily
drug cocktail consisting of 50 mg caffeine, 10 mg omeprazole, and 1 mg midazolam once
(30 minutes after PHA-022121)

**Study burden and risks**

The study compound may cause side effects.

The following side effects are most commonly observed:
• Sore throat/throat irritation
• Dizziness when standing
• Nausea
• Dry skin
• Diarrhea
• Abdominal pain

The study compound may also have (serious) 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 excipients.

If during the study more information becomes available regarding side effects that may be related to the study compound, the responsible doctor will inform the volunteers about this.

Possible discomforts due to procedures

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

In total, we will take about 350 milliliters 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. Based on the discretion of the responsible doctor, extra samples might be taken to guarantee the safety of the participants. If this happens, the total amount of blood drawn will be more than this.

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

Samples for the coronavirus test will be taken from the back of your 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 your throat may cause the volunteer to gag. When the sample is taken from the back of the nose, the 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

1. Subject must be a healthy male or female subject, 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 or she understands the purpose of the study including the procedures required, and is willing to participate in the study, including that he /she 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 approximately 90 days) after receiving the last dose of study drug, a male subject:
- who is sexually active with a woman of child-bearing potential and has not had a vasectomy, must agree to use a barrier method of contraception (eg, condom or partner with occlusive cap [diaphragm or cervical/vault caps]). In addition, their female partner should also use a highly effective method of birth control (eg, hormonal contraception , intra-uterine device) for at least the same duration.
- Who is sexually active with a woman who is pregnant must use a condom.
- Must agree not to donate sperm until 90 days after receiving the last study drug administration.

## 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 <90 mL/min at/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 4. 14, 2010 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 applies for male and female, respectively) lowering grad 1 or greater (<=6.5 mmol ; <=109 g/L );
- 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.

# Study design

## Design

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|---|---|
| Study type: | Interventional |
| Intervention model: | Crossover |
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 07-12-2020 |
| Enrollment: | 14 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Midazolam |
| Generic name: | n.a. |

| | |
|---|---|
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Omeprazole |
| Generic name: | n.a. |
| Registration: | Yes - NL intended use |

## Ethics review

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|---|---|
| Approved WMO Date: | 20-10-2020 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 18-11-2020 |
| 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 | EUCTR2020□004130□38-NL |
| CCMO | NL75390.056.20 |

# Study results

**First publication**
15-10-2021