An open-label, single-sequence crossover drug-drug interaction study to evaluate the effect of multiple oral doses of itraconazole on the pharmacokinetics of PHA-022121 in healthy 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-OMON49496

Source
ToetsingOnline

Brief title
DDI Itraconazole and PHA-022121 in healthy subjects

Condition

- Congenital and hereditary disorders NEC

Synonym
Hereditary Angioedema

Research involving
Human

Sponsors and support

Primary sponsor: Pharvaris BV
Source(s) of monetary or material Support: Ministerie van OC&W,Pharmaceutical industry

Intervention

Keyword: DDI, Itraconazol, PHA-022121

Outcome measures

Primary outcome

The primary PK parameters are Cmax, AUClast, and AUC* of the PHA-022121. All parameters will be analyzed on a logarithmic scale. AUC* will be rejected as primary parameter for a treatment if more than half of the subjects do not have a reliable value for that treatment.

Secondary outcome

NA

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, 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.

PHA-022121 is broken down by certain enzymes, among others by CYP3A4. Itraconazole (a medicine against fungi and yeast) is a strong inhibitor of the enzyme CYP3A4, and may thus have an impact on how long PHA-022121 stays in the body. Research into the effect of itraconazole on PHA-022121 is therefore

needed.

Study objective

The purpose of this study is to investigate the effect of multiple doses of itraconazole on how quickly and to what extent the new compound PHA-022121 is absorbed into the body and eliminated from the body (this is called pharmacokinetics). It will also be investigated how safe PHA-022121 is and how well it is tolerated when it is administered to healthy volunteers. PHA-022121 has been administered to humans before. It has furthermore been previously tested in the laboratory and on animals. Itraconazole is not a new compound; it is already more than 30 years available on the market as antifungal medication.

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

Study design

The study will consist of 1 period during which the volunteer will stay in the research center for 10 days (9 nights). The volunteer will then return to the research center for 1 day for a follow-up visit.

Day 1 is the first day of administration of the study compound. The volunteer is expected at the research center at 2:00 PM in the afternoon prior to the day of first administration of the study compound, so on Day -1. The volunteer will leave the research center on Day 9 of the study.

Intervention

PHA-022121 will be given twice as a solution via the mouth using a syringe. Then the volunteer will be given 240 milliliter (mL) of water which the volunteer should drink. Itraconazole will be given 7 times as a solution via the mouth, together with 120 or 240 mL of water. The planned treatments for the study are as follows:

Day Treatment How often
1 12 mg PHA-022121 Once
2 - -
3 200 mg (20 mL) itraconazole Twice
4 to 6 200 mg (20 mL) itraconazole Once daily
7 12 mg PHA-022121
200 mg (20 mL) itraconazole Once
Once
8 200 mg (20 mL) itraconazole Once

When the volunteer receives both PHA 022121 and itraconazole (Day 7), the volunteer will first receive itraconazole. One hour later, the volunteer will

receive a breakfast. Half an hour after the volunteer finished the breakfast, the volunteer will receive PHA-022121.

One of the investigators will inspect the volunteers hands and mouth after each study compound intake.

Study burden and risks

The study compound may cause side effects.

PHA-022121 has been studied extensively in the laboratory and in animals. PHA-022121 has furthermore been administered to humans in 1 completed clinical trial. In total, 52 volunteers have received single doses up to 22 mg of PHA-022121. Overall, PHA-022121 was considered safe and well tolerated. In this study, the reported side effects which were considered related to the study compound were: stomach cramps (once) and nausea (once).

Based on the way PHA-022121 is working, the following side effects may occur: increased blood pressure, reduced heart rate, and worsening of blood supply. Side effects of icatibant (another medication that influences the receptor bradykinin B2) which could potentially also occur for PHA-022121, include: dizziness, headache, nausea, rash, redness of the skin, itching, fever, and increased enzymes involved in the production of amino acids.

The study compound may also have side effects that are still unknown. In addition to unknown side effect, 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 volunteer about this.

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 60 years of age, extremes included, at screening.
2. Subject must have a body mass index 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 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) 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.
5. A female subject must be of non-childbearing potential at screening, defined as: - Postmenopausal. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level at screening (>33.4 IU/L) in the postmenopausal range may be used to confirm a postmenopausal state in woman not using hormonal contraception or hormonal replacement therapy, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. - Permanently

sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

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 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 World Health Organization (WHO) Toxicity Grade Scale 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 lowering grade 1 or greater (<=6.5 mmol ; <=109 g/L); - Platelet count below LLN; - Absolute neutrophil count lowering grade 1 or greater (<=1,5 109/); - 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 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 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).

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	25-02-2020
Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Sporanox
Generic name:	Itraconazole
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	04-02-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-02-2020
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	EUCTR2019-005001-49-NL
CCMO	NL72719.056.20

Study results

Date completed: 17-04-2020

Results posted: 12-02-2021

First publication
08-02-2021