A Phase II, double-blind, placebo-controlled, randomized, cross-over, dose-ranging study of oral PHA-022121 for acute treatment of angioedema attacks in patients with hereditary angioedema due to C1-inhibitor deficiency type I and II

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Skin and subcutaneous tissue disorders congenital
Study type	Interventional

Summary

ID

NL-OMON55154

Source
ToetsingOnline

Brief title
RAPIDe-1

Condition

- Skin and subcutaneous tissue disorders congenital
- Angioedema and urticaria

Synonym

C1 esterase inhibitor deficiency; hereditary angioedema

Research involving
Human

Sponsors and support

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

Intervention

Keyword: acute treatment, angioedema, C1-inhibitor deficiency, PHA-022121

Outcome measures

Primary outcome

To evaluate the efficacy of three different single doses of PHA-022121 versus

placebo in achieving angioedema symptom reduction defined as change of VAS-3

score during acute attacks in patients with hereditary angioedema (HAE) type

I/II

Secondary outcome

The key secondary objectives of the study are:

To further evaluate the clinical efficacy of three different single doses of

PHA-022121 versus placebo with regards to

• Onset of symptom relief,

• The proportion of attacks requiring the use of HAE rescue medication

• Time to almost complete and complete symptom relief

• Change in MSCS at 4 h post-treatment,

• Change in TOS at 4 h post-treatment.

Other secondary objectives of the study are:

• To evaluate the safety of three different single doses of PHA-022121 versus placebo

• To evaluate the pharmacokinetics, dose-effect relationship, and concentration-effect relationship of PHA-022121

• To evaluate the frequency and timing of HAE rescue medication use of three different single doses of PHA-022121 versus placebo

• To evaluate the time to onset of primary symptom relief by VAS

• To evaluate the change of the individual VAS scores (skin pain, skin swelling, abdominal pain) from pre-treatment to 4 h post-treatment

• To evaluate the change of MSCS score at 24 h post-treatment

• To evaluate the change of TOS at 24 h post-treatment

• To evaluate the TSQM scores at 48 h post-treatment

Study description

Background summary

HAE is a very rare genetic disease. In most cases, HAE patients have a defect in the gene that controls a blood protein called *C1 Inhibitor". Lack or low level of C1 inhibitor in the blood causes a biochemical imbalance, for example an increased formation of the protein bradykinin. Bradykinin produces the painful symptoms of HAE, such as swelling in various parts of the body, including hands, feet, face and airway (throat). The study drug, PHA-022121, is designed to prevent the effects of bradykinin, thereby preventing the occurrence of swellings (acute attacks). There are already medicines available to treat the swellings of HAE, but they must be injected either into a vein or under the skin. Of all approved drugs currently available to patients with HAE, only one, called icatibant (Firazyr®), prevents the effects of bradykinin. However, icatibant must be injected under the skin, whereas PHA-022121 is a capsule that can be taken by mouth.

Study objective

The purpose of this study is to find out how safe and effective the new drug PHA-022121 is for the treatment of Hereditary Angioedema. The main purpose of this research study is to test the effectiveness of 3 different doses of PHA-022121 in treating HAE attacks. PHA-022121 will be compared to a placebo.

Study design

After signing informed consent, patients will be screened for eligibility.
Eligible patients will be enrolled in the study.
Enrolled patients will be randomized to one of nine treatment sequences comparing three single doses of PHA 022121 (low, medium, high) with placebo treatment. During Part I (at the study site), patients in quiescent state receive the assigned active single dose of PHA-022121 (dose is blinded) to assess pharmacokinetics and safety.
In Part II of the study, patients will self-administer blinded study drug in the assigned treatment sequence at home to treat three qualifying HAE attacks. Immediate study drug treatment should be taken (within 3 h) after at least one attack symptom (skin pain, skin swelling, or abdominal pain) becomes of moderate intensity (VAS score >= 30), and within 6 h after attack onset at any location. The Investigator or designee needs to be consulted and the attack confirmed via remote contact. At 4 h post-treatment, the patient will consult with the Investigator or designee remotely again to assess symptom relief, safety, and any need for rescue medication. Patient-reported outcomes (PROs) are collected from study drug intake until 48 h post-treatment. After each attack a safety follow-up (on-site or remote) will take place within 5 days post-treatment. Meanwhile, pharmacokinetic plasma samples are planned to be collected within 24 h post-treatment (preferably within 12 h) from a subset of patients for at least 50 attacks treated with PHA-022121 or placebo.
The next HAE attack can only be treated with study drug 5 days or more from the previous attack treated with study drug. If patients had an HAE attack that was not eligible for study drug and was treated with the patient*s standard HAE medication, a time window of at least 5 days should be respected before a new attack can be treated with study drug in order to avoid carry-over effects of previous treatments.
The end-of-study visit will take place 10±5 days post-treatment of the last attack.

Intervention

The IMP consists of 10 mg PHA-022121 soft capsules and matching placebo soft capsules for oral use:
• Low dose (10 mg): one capsule of 10 mg PHA-022121 and two placebo capsules
• Medium dose (20 mg): two capsules of 10 mg PHA-022121 and one placebo capsule
• High dose (30 mg): three capsules of 10 mg PHA-022121
• Placebo: three placebo capsules

Study burden and risks

Available preclinical and human data indicate that PHA-022121 is a potent and highly selective B2 receptor antagonist with excellent oral bioavailability. The compound also effectively inhibits the pharmacodynamic effects of exogenously administered bradykinin in humans, which is predictive of efficacy in the treatment of HAE attacks. The efficacy in the bradykinin challenge in humans was obtained with doses that were well tolerated and safe and were within the range of the doses tested in the current study. The dose range tested (10-30 mg) in this study is well covered by the maximum dose of 50 mg tested in SAD and MAD studies, and maximum plasma concentrations of PHA-022121 after single dose administration (10-30 mg) are expected to remain well below the NOAEL in the most sensitive species in the toxicological studies. See also section 1.3 of the protocol.

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. Provision of signed and dated informed consent form
2. Male or female, aged >= 18 and <= 75 years at enrollment
3. Diagnosis of HAE (type I or II) based upon all of the following:
a. Documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling without accompanying urticaria)
b. At least one of the following:
* Age at reported onset of first angioedema symptoms <= 30 years
* Family history consistent with HAE type I or II
* C1q within normal range
c. Diagnostic testing results to confirm HAE type I or II:
* C1-INH functional level < 50% of the normal level
The diagnosis may be established by local laboratory values documented in the medical records or by genotyping of the C1-INH gene (SERPING1). Before entering Part II of the study (home treatment), the diagnosis needs to be confirmed by a central laboratory assessment or by genotyping of the C1-INH gene (SERPING1).
4. Documented history of at least two moderate to severe attacks in the last 4 months, or at least two HAE attacks in the last 2 months prior to screening.
5. Reliable access and experience to use standard of care treatment to effectively manage acute HAE attacks
6. Capable to record PRO data using the ePRO device
7. Female patients of childbearing potential must agree to be abstinent or to use highly effective forms of contraception methods from enrollment until 30 days after the last study drug administration. This includes progestin-only oral contraceptive associated with inhibition of ovulation (oral, injectable, or implantable), intrauterine device (IUD, all types) or intrauterine hormone releasing systems (IUS). A female of childbearing potential whose male partner has had a vasectomy must agree to use one additional form of medically acceptable contraception. Male patients, including males who are surgically sterile (post vasectomy), who have a female partner of childbearing potential must agree to be sexually abstinent or use a medically acceptable form of barrier contraception during the study and for 90 days after the last administration of study drug. In addition, they must agree to not donate sperm during study participation and within 90 days after the last study drug administration.

Exclusion criteria

1. Pregnant or breast-feeding
2. Clinically significant abnormal ECG, most notably a QTcF > 470 ms (for women) or > 450 ms (for men)
3. Any clinically significant history of angina, myocardial infarction,

syncope, stroke, left ventricular hypertrophy or cardiomyopathy, uncontrolled arterial hypertension (systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmhg), bradycardia (<50bpm), or any other cardiovascular abnormality within the previous year
4. Any other systemic disease (e.g., gastrointestinal, renal, respiratory, neurological) or significant disease or disorder that would interfere with the patient*s safety or ability to participate in the study
5. Use of:
a. long-term prophylactic therapy for HAE (C1-INH, oral kallikrein inhibitors, attenuated androgens, or anti-fibrinolytics) within 2 weeks prior to enrollment
b. long-term prophylactic monoclonal therapy for HAE (e.g., lanadelumab) within 12 weeks prior to enrollment
c. acute C1-INH treatment or short-term prophylaxis for HAE within 7 days prior to screening. Short-term prophylaxis is defined as C1-INH, attenuated androgens, or antifibrinolytics to avoid angioedema complications from medically indicated procedures.
Patients who receive long-term prophylactic treatment for HAE are not eligible for the study. Patients who have previously stopped long-term prophylactic HAE treatment because of intolerance or lack of efficacy can enter the study with a sufficiently long wash-out period as defined above for the different drugs.
6. Positive serology for human immunodeficiency virus (HIV) or active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV)
7. Abnormal hepatic function (AST > 2×ULN, ALT > 2×ULN, or total bilirubin > 1.5×ULN)
8. Abnormal renal function (eGFR CKD-EPI < 60 mL/min/1.73 m2)
9. History of alcohol or drug abuse within the previous year, or current evidence of substance dependence or abuse (self-reported alcoholic intake > 3 drinks/day)
10. History of severe hypersensitivity to any medicinal product
11. Participation in any other investigational drug study currently, within the last 30 days or within 5 half-lives of study drug at enrollment (whichever was longer)
12. Regular use of corticosteroids, antihistamines, narcotics, and other pain relief medications for acute HAE attack treatment
13. Use of concomitant medication that are moderate or potent inhibitors/inducers of CYP3A4 or are metabolized by CYP3A4 and have a narrow therapeutic range, such as clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, ritonavir, verapamil, goldenseal and grapefruit as well as phenobarbital, phenytoin, rifampicin, St. John's Wort, and glucocorticoids (not for topical use or inhalation)

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-05-2021
Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	PHA-022121
Generic name:	N/A

Ethics review

Approved WMO Date:	01-12-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-04-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-06-2021
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2020-003445-11-NL
CCMO	NL75072.018.20

Study results