oral PHA-022121 for the acute treatment and prophylaxis Of angioedema attacks in Patients with Acquired C1-Inhibitor Deficiency

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Primary objectives: to evaluate the efficacy of three different single doses of PHA-022121 versus placebo in achieving angioedema symptom relief during acute attacks and the efficacy of prophylactic treatment with PHA-022121 versus placebo in...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Immune disorders NEC
Study type	Interventional

Summary

ID

NL-OMON51973

Source
ToetsingOnline

Brief title
POP-AID

Condition

- Immune disorders NEC

Synonym
Acquired C1-inhibitor deficiency

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Pharvaris

Intervention

Keyword: Acquired C1-inhibitor deficiency, Bradykinin, PHA-022121

Outcome measures

Primary outcome

The main study parameter for part 1 is the change of the 3-symptom composite visual analogue scale (VAS-3) score from pre-treatment to 4 h post-treatment.

The main study parameter for part 2 is the number of investigator-confirmed angioedema attacks recorded during the treatment period expressed as the normalized number of attacks per month of exposure.

Secondary outcome

• Part 1: mean symptom complex severity score (MSCS) score

• Part 1: treatment outcome score (TOS)

• Part 1: treatment satisfaction questionnaire for medication (TSQM) score

• Part 1: number of attacks requiring rescue medication

• Part 1: time to rescue medication use, if applicable

• Part 2: number of investigator-confirmed moderate or severe angioedema attacks during the treatment period

• Part 2: number of investigator-confirmed angioedema attacks requiring acute treatment during the treatment period

• Part 2: number and proportion of days with angioedema symptoms during the treatment period

• Part 2: time to first investigator-confirmed attack (i.e. duration that a patient is attack-free) in the treatment period

• Part 2: angioedema quality of life (AE-QoL) questionnaire

• Part 2: treatment satisfaction questionnaire for medication (TSQM) score

• Part 2: angioedema control test (AECT)

• Part 2: angioedema activity score (AAS)

Study description

Background summary

Effective prophylactic and on demand treatment options for angioedema due to acquired C1-inhibitor deficiency (AAE-C1-INH) are needed, as licensed treatments are currently lacking for this condition.

Study objective

Primary objectives: to evaluate the efficacy of three different single doses of PHA-022121 versus placebo in achieving angioedema symptom relief during acute attacks and the efficacy of prophylactic treatment with PHA-022121 versus placebo in preventing breakthrough angioedema attacks in patients with AAE-C1-INH. Secondary objectives: to further explore the clinical efficacy of PHA-022121 versus placebo with regard to onset of symptom relief, time to complete symptom relief, to evaluate the frequency and timing of rescue medication use, and to evaluate the safety of PHA-022121 versus placebo.

Study design

Double-blind, placebo-controlled, randomized cross-over intervention study

Intervention

In part 1, patients will treat four consecutive angioedema attacks with three single doses of PHA-022121 (10, 20, and 30 mg) and one single dose of placebo, in a randomized and blinded order. In part 2, patients will be randomly allocated to one of two treatment arms: a 20 mg dose of PHA-022121 or placebo twice daily for a total duration of eight weeks, followed by a cross-over to the other treatment arm.

Study burden and risks

Patients will visit the AMC on seven occasions, at each visit safety blood and

urine samples will be collected and physical examinations and ECG*s will be performed. The maximum amount of blood that will be drawn per study visit is 18 ml. In part 1 patients are requested to immediately treat four consecutive attacks (excluding facial and laryngeal swellings) with the study drug after confirmation from the investigator via remote contact and to complete a diary until 48 h post-treatment. In part 2 patients are requested to complete a diary daily for the entire study duration of 16 weeks. The placebo-controlled design is deemed safe, because all patients in the study will have rescue medication (icatibant) available, which they can use for attacks that do not qualify for study treatment or attacks that do not respond within a reasonable time frame to study treatment. All patients have previously responded well to icatibant.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

In order to be eligible to participate in this study, a patient must meet all of the following criteria:
• Provision of signed and dated informed consent form
• Male or female, aged > 35 at enrollment
• Diagnosis of AAE-C1-INH based upon all of the following:
1. Documented clinical history consistent with AAE-C1-INH (subcutaneous or mucosal, nonpruritic swelling without accompanying urticarial and C1-INH activity < 0.63mE/L)
2. At least one of the following:
• Age at reported onset of first angioedema symptoms >= 40 years AND family history negative for angioedema
• C1q below lower limit of normal (88 kU/L) AND absence of SERPING1 mutation
• Serological confirmation of antibodies against C1-INH
• Documented history of at least three angioedema attacks in the last 4 months, or at least two angioedema attacks in the last 2 months.
• Reliable access and experience to use icatibant to effectively manage acute angioedema attacks
• Female patients of childbearing potential must agree to be abstinent or to use highly effective forms of contraception methods from enrollment through the end of the study. 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 for 2 weeks after each administration of study drug. In addition, they must agree to not donate sperm during study participation.

Exclusion criteria

Patients who meet any of the following criteria will be excluded from the study:
• Pregnancy or breast-feeding
• Clinically significant abnormal ECG, most notably a QTcF > 470 ms (for females) or > 450 ms (for males)
• Any clinically significant history of angina, myocardial infarction, syncope, stroke, left ventricular hypertrophy or cardiomyopathy, or any other cardiovascular abnormality within the previous year
• 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
• Active infection with human immunodeficiency virus (HIV) or hepatitis B virus (HBV) or hepatitis C virus (HCV)
• History of abnormal hepatic function (AST > 2×ULN, ALT > 2×ULN, or total bilirubin > 1.5×ULN)
• History of abnormal renal function (eGFR CKD-EPI < 60 mL/min/1.73 m2)
• 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)
• History of documented severe hypersensitivity to any medicinal product
• 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)
• Regular use of corticosteroids, antihistamines, narcotics, and other pain relief medications for acute angioedema attack treatment
• 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)
Patients who meet all in- and exclusion criteria but are unable to adhere to the diary and unforeseen visit requirements of part 1 as determined by the investigator, may participate in part 2 only.

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:	Prevention

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	15-10-2021
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	PHA-022121
Generic name:	PHA-022121

Ethics review

Approved WMO Date:	06-05-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-08-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-11-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-12-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-02-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-03-2022
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	EUCTR2021-000720-36-NL
CCMO	NL76840.018.21