A randomized, double-blind, placebo-controlled, multiple ascending dose study to examine the safety, tolerability and pharmacokinetics of orally administered PHA-022121 in healthy subjects.

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Primary ObjectiveTo assess the tolerability and safety of multiple ascending oral doses of PHA-022121 administered after a standard caloric meal in healthy adult subjects.To assess the PK characteristics of PHA-022121 after administration of...

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

Summary

ID

NL-OMON49075

Source
ToetsingOnline

Brief title
CS0347-200141 Pharvaris MAD

Condition

- Congenital and hereditary disorders NEC

Synonym
Hereditary Angioedema (HAE)

Research involving

Human

Sponsors and support

Primary sponsor: Pharvaris B.V.
Source(s) of monetary or material Support: Pharvaris B.V.

Intervention

Keyword: pharmacokinetics, safety, tolerability

Outcome measures

Primary outcome

Primary endpoint, safety:

- All standard safety assessments including physical examination, vital signs,

adverse events, neurological assessment, hematology, chemistry, urinalysis and

ECG

Primary endpoint, pharmacokinetics:

- After the first and second dose on Day 1:

Plasma PK parameters, Cmax, 1, Cmax, 2, tmax, 1, tmax, 2, AUC0-12h, AUC0-24h,

AUClast, AUCinf, t1/2, CL/F and Vz/F of PHA-022121.

The following urinary PK parameters of PHA-021221 will be derived (x-y

represent the different time intervals): Ae x-y, Ae total, Durine,x-y,

Durine,total and CLR.

After the morning dose on Day 10:

Plasma PK parameters Cmax, tmax, AUC0-12h, AUC0-24h, AUClast, t1/2, CL/F and

Vss/F of PHA-022121.

Urinary PK parameters of PHA-021221 will be derived as on Day 1.

Cmin (pre-dose) every morning.

Secondary outcome

- After the first and second dose on Day 1:

Plasma PK parameters for the major metabolite M2-D: Cmax, 1 , Cmax, 2, tmax, 1,

tmax, 2, AUC0-12h, AUC0-24h, AUClast, AUCinf, and t1/2,.

The following urinary PK parameters of M2-D will be derived (x-y represent the

different time intervals): Ae x-y, Ae total, Durine,x-y, Durine,total and CLR.

- After the morning dose on Day 10:

Plasma PK parameters for the major metabolite M2-D: Cmax, tmax, AUC0-12h,

AUC0-24h, AUClast, and t1/2,.

Urinary PK parameters of M2-D will be derived as on Day 1.

- Cmin (pre-dose) every morning.

- 4-βHC plasma levels and urinary 6-βHC / cortisol ratio as biomarkers for

CYP3A4 activity.

- QT, and the corrected QT interval by Fridericia*s formula (QTcF)

Study description

Background summary

An oral treatment for HAE attacks is currently not available rendering the management of this disease difficult: all of the currently approved drugs for HAE, except for androgens, can only be applied by i.v. or s.c. route, which is often associated with a delay of drug administration, discomforts, local side effects and with a reduction in the QoL for the patients. Therefore, there is a strong unmet medical need for an efficacious orally bioavailable drug for the treatment and/or prevention of acute HAE attacks.
Of all products available to patients or in development, only one other antagonizes the B2 receptor, namely icatibant. Extensive clinical experience has demonstrated the selectivity, safety, and rapid onset of action of this

mechanism to resolve HAE attacks of all causes. PHA-022121 retains these characteristics through the shared mechanism, as demonstrated preclinically in the BK challenge model adapted from human clinical experience to monkey.

Study objective

Primary Objective
To assess the tolerability and safety of multiple ascending oral doses of PHA-022121 administered after a standard caloric meal in healthy adult subjects.
To assess the PK characteristics of PHA-022121 after administration of multiple ascending oral doses, administered after a standard caloric meal.

Secondary Objectives
To assess the PK characteristics of the major active metabolite M2-D after administration of multiple ascending doses of PHA-022121.
To explore the potential of PHA-022121 for CYP3A4 enzyme induction.
To assess the concentration-QTc effect of PHA-022121 after repeated ascending doses.

Study design

This is a randomized, double-blind, placebo-controlled study for PHA-022121 and will be conducted in healthy subjects at a single study center.
This study will consist of four double-blind, randomised, placebo-controlled, multiple ascending dose cohorts, in which the safety, tolerability and PK of PHA-022121 will be assessed when administered B.I.D. for 9 days and a morning dose on Day 10 (with a 12 h time interval). Within each cohort, 10 subjects will be randomized to PHA-022121 (N=8) and to matching placebo (N=2). Accordingly, approximately 40 subjects will be enrolled in this study. Each cohort must comprise of at least 3 female subjects .
Safety and PK data of the corresponding single dose from the SAD extension study and the previous lower multiple dose will be available and submitted to the Safety Monitoring Committee (SMC) and Ethics Committee (EC), which will decide on predefined safety and PK decision criteria whether the next higher multiple dose can be administered.

Intervention

PHA-022121 will be made available as an oral self-micro emulsifying drug delivery system (SMEDDS) solution containing 50 mg/mL PHA-022121.

Study burden and risks

Since the study is being executed in healthy volunteers, there are no anticipated benefits of the IMP. Please see the IB for further

information.

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

Healthy male and female subjects of non-childbearing potential
Between 18 and 65 years of age, inclusive.
Body Mass Index (BMI) between 18.0 and 30 kg/m2 (inclusive).
Healthy on the basis of physical examination, medical history, vital signs, clinical laboratory tests, and 12-lead ECG performed at screening. If any of the results are abnormal, the subject may be included only if the investigator judges that the abnormalities or deviations from normal are not clinically significant. This determination must be recorded in the subject's source documents and initialled by the investigator.

A resting heart/pulse rate (supine position for 5 minutes) between 40 and 100 beats per minute (bpm). If heart/pulse rate is out of range, up to 2 repeated assessments are permitted.
A resting blood pressure (supine position for 5 minutes) between 90 and 140 mmHg systolic, inclusive, and between 40 to 90 mmHg diastolic. If blood pressure requirements are out of range, up to 2 repeated assessments are permitted.

Exclusion criteria

Clinically relevant allergy (except for untreated, asymptomatic, seasonal allergies at time of dosing) or drug hypersensitivity.
Known hypersensitivity to the drug substance, or any inactive ingredient(s) of the investigational product (refer to investigator's Brochure).
History of any medical condition or prior surgery of the GI-tract that could alter the absorption of orally administered drugs (does not apply to history of appendectomy).
History or current evidence of any form of angioedema.
History or current evidence of any form of bronchial asthma.
History of postural disorders, i.e. labile blood pressure or symptomatic orthostatic hypotension, faintings, or blackouts) and/or treatment requiring hypotension

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-06-2020

Enrollment:	40
Type:	Actual

Ethics review

Approved WMO Date:	29-04-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-05-2020
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	EUCTR2020-001533-12-NL
CCMO	NL73626.056.20

Study results

Results posted:	04-03-2021

First publication
01-03-2021