Clinical Study Protocol: PHA022121-C201

Study Title:	A Phase II, double-blind, placebo-controlled, **R**andomized, cross-over, dose-ranging study of oral PHA-022121 for **A**cute treatment of angioedema attacks in **P**atients with hereditary angioedema due to C1-**I**nhibitor **De**ficiency type I and II
Acronym:	RAPIDe-1
Study Number:	PHA022121-C201
Study Phase:	Phase II
Product Name:	PHVS416 (PHA-022121 soft capsules)
Indication:	Hereditary angioedema
EudraCT Number:	2020-003445-11
Investigators:	Multicenter
Sponsor:	Pharvaris Netherlands BV (Leiden, The Netherlands)
Sponsor Contact:	clinical@pharvaris.com
Sponsor Representatives:	[redacted] Chief Medical Officer [redacted] Executive Director Clinical Development

	Date	Protocol version
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SYNOPSIS

Sponsor:

Pharvaris Netherlands BV (Leiden, The Netherlands)

Name of Finished Product:

PHVS416 (PHA-022121 soft capsules)

Name of Active Ingredient:

PHA-022121

Study Title:

A Phase II, double-blind, placebo-controlled, **R**andomized, cross-over, dose-ranging study of oral PHA-022121 for **A**cute treatment of angioedema attacks in **P**atients with hereditary angioedema due to C1-**I**nhibitor **De**ficiency type I and II

Acronym:

RAPIDe-1

Study Number:

PHA022121-C201

Study Phase:

Phase II

Primary Objective:

To evaluate the efficacy of three different single doses of PHA-022121 versus placebo in achieving angioedema symptom reduction, defined as change in the 3-symptom composite visual analogue scale (VAS-3) score during acute attacks in patients with hereditary angioedema (HAE) type I/II

Secondary Objectives:

The key secondary objectives of the study are:

To evaluate the clinical efficacy of three different single doses of PHA-022121 versus placebo with regards to:

- Time to onset of symptom relief by VAS-3,
- Time to almost complete or complete symptom relief by VAS-3,
- Change in mean symptom complex severity (MSCS) score at 4 h post-treatment,
- Treatment outcome score (TOS) at 4 h post-treatment.

Other secondary objectives of the study are:

- To evaluate the clinical efficacy of three different single doses of PHA-022121 versus placebo with regards to:
  - Time to onset of primary symptom relief by visual analog scale (VAS)
  - Proportion of investigational medicinal product (IMP)-treated attacks requiring the use of HAE rescue medication
  - Time to the first use of HAE rescue medication

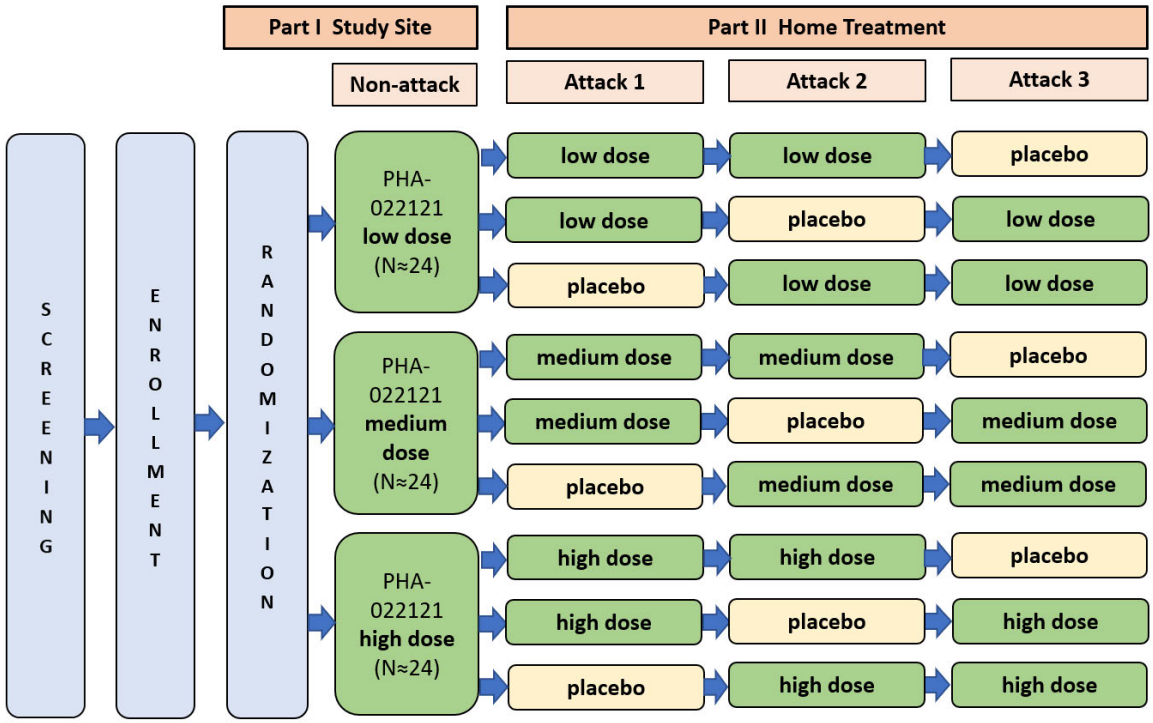
  - Change in the individual VAS scores (skin pain, skin swelling, abdominal pain) from pre-treatment to 4 h post-treatment
  - Change in MSCS score at 24 h post-treatment
  - TOS at 24 h post-treatment
- To evaluate the safety of three different single doses of PHA-022121 versus placebo
- To evaluate the pharmacokinetics, dose-effect relationship, and concentration-effect relationship of PHA-022121
- To evaluate the treatment satisfaction questionnaire for medication (TSQM) scores at 48 h post-treatment

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 the three dose levels (low, medium, high) first, then based on the assigned cohort 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 will 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, which should be consulted and confirmed by the investigator or designee via remote contact. The study drug should be taken when at least one attack symptom (skin pain, skin swelling, or abdominal pain) becomes of moderate intensity (VAS score ≥ 30). When the attack reaches this VAS intensity threshold, study drug should preferably be taken during the remote contact with the investigator or designee. If the patient cannot take the study drug within 3 h after reaching the VAS intensity threshold, the attack does not qualify for study drug treatment and should be treated with the patient's standard HAE medication. In addition, treatment of the attack should happen within 6 h after onset of symptoms at any location. If the study drug cannot be administered within 6 h after onset of symptoms, the attack does not qualify for study drug treatment and should be treated with the patient's standard HAE medication. Any symptoms involving the internal head and neck, regardless of intensity, also render an attack non-qualifying for treatment with study drug and should be treated with the patient's standard HAE medication.
  At 4 h post study drug 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 (including pre-treatment) until 48 h post-treatment. After each attack treated with study drug, a safety follow-up visit 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.
  In order to avoid carry-over effects of previous treatments, HAE attacks that occur

within 5 days of a previously treated attack (regardless of whether study drug or standard HAE medication was used) will not qualify for treatment with study drug.

- The end-of-study visit will take place 10±5 days post-treatment of the last attack. This visit may be waived if patients continue in another clinical study with PHA-022121conducted by the Sponsor.



Study Population:

Approximately 72 male or female, adult patients with HAE due to C1-inhibitor deficiency (HAE type I/II) will be randomized in this study. For eligibility in the study, patients need to have experienced at least three HAE attacks in the last 4 months, or at least two HAE attacks in the last 2 months. The expected study duration per patient amounts to approximately 30 weeks, consisting of the Screening period of up to 4 weeks, the Non-attack visit (Part I), home treatment (Part II) of about 24 weeks (covering 3 qualifying attacks treated with study drug per patient), and up to 2 weeks until the end-of-study visit. In some cases, patients may need longer than 24 weeks to complete the assessments for 3 qualifying attacks; therefore, the individual duration per patient may be longer.

The study is planned to be conducted at approximately 35 study sites across 12-15 countries.

Investigational Medicinal Product (IMP), Dose, and Mode of Administration:

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

Duration of Treatment:

In Part I, patients will receive one single dose of PHA-022121 (10, 20, or 30 mg).

In Part II, patients will receive two single doses of PHA-022121 (10, 20, or 30 mg) and one single dose of placebo.

Efficacy Assessments:

Efficacy will be assessed during Part II with four PROs:

- VAS scores of the three major HAE symptoms, including skin pain, skin swelling, and abdominal pain
- MSCS score
- TOS
- TSQM scores

Safety Assessments:

- Physical examination
- Vital signs
- Digital 12-lead electrocardiogram (ECG)
- Safety laboratory testing (blood chemistry, hematology, coagulation, urinalysis, pregnancy test)
- Adverse events
- HAE diary

Statistical Methods:

All efficacy analyses will be performed on the Modified Intent-To-Treat (mITT) Analysis Set, defined as all randomized patients who had at least one HAE attack treated with study drug (PHA-022121 or placebo) and had non-missing VAS results at both pre-treatment and at least one post-treatment time point of that attack. All statistical tests are carried out 2-sided. The primary endpoint, i.e., the change of the VAS-3 score from pre-treatment to 4-h post-treatment, will be analyzed using a mixed model for repeated measures (MMRM) allowing within-patient and between-patient comparisons. The key secondary efficacy endpoints include time to onset of symptom relief assessed by ≥30% reduction in VAS-3 score from pre-treatment, time to almost complete or complete symptom relief by VAS (all 3 individual VAS scores reduced to ≤ 10 is considered almost complete, all scores reduced to 0 is complete symptom relief), time to ≥50% reduction in VAS-3 score from pre-treatment, change in MSCS score from pre-treatment to 4 h post-treatment, and TOS at 4 h post-treatment. For these endpoints, marginal Cox proportional hazards models (CPHM) will be used for time-to-event endpoints, and MMRM will be used for continuous endpoints. For the analyses of primary and key secondary endpoints, multiplicity control procedure will be applied in testing the medium and high doses with the overall type 1 error rate controlled at a 5% significance level for a 2-sided test.

Date of Original Approved Protocol:

18 August 2020

Date of Most Recent Protocol Amendment:

25 April 2022 (Amendment 7)

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LIST OF ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AP	alkaline phosphatase
AST	aspartate aminotransferase
AUC	area under plasma concentration-time curve
$AUC_{0\text{-}12h}$	AUC from time 0 to 12 h post dosing (non-BQL) concentration, calculated by the linear-linear trapezoidal summation
$AUC_{0\text{-}24h}$	AUC from time 0 to 24 h post dosing (non-BQL]) concentration, calculated by the linear-linear trapezoidal summation
AUC_{inf}	AUC from time 0 to the time of the last measurable (non-BQL) concentration, calculated by the linear-linear trapezoidal summation
AUC_{last}	AUC from time 0 to the time of the last measurable (non-BQL) concentration, calculated by the linear-linear trapezoidal summation
BQL	below quantification limit
BUN	blood urea nitrogen
C1-INH	C1-esterase inhibitor
CFR	Code of Federal Regulations
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	total apparent systemic clearance of drug after extravascular administration, calculated as Dose/AUC_{inf}
C_{max}	maximum observed analyte concentration;
COVID-19	coronavirus disease 2019
CPHM	Cox proportional hazards model
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DNA	deoxyribonucleic acid
EC_{50}	estimated drug concentration for a 50% response

EC_{85}	estimated drug concentration for a 85% response
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form
eGFR	estimated glomerular filtrate rate
EEG	electroencephalogram
EMA	European Medicines Agency
ePRO	electronic patient-reported outcome
EU	European Union
FA	Full Analysis
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GEE	generalized estimating equation
GLP	Good Laboratory Practice
h	hour(s)
HAE	hereditary angioedema
HBsAg	surface antigen of the hepatitis B virus
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCHF	High-calorie high-fat
Hct	hematocrit
HCV	hepatitis C virus
HEENT	head/eyes/ears/nose/throat
Hgb	hemoglobin
HIV	human immunodeficiency virus
HMWK	high molecular weight kininogen
ICF	informed consent form
ICH	International Council for Harmonisation

IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
ISF	investigator site file
iv	intravenous(ly)
KKS	kallikrein-kinin system
LC-MS	liquid chromatography–mass spectrometry
LDH	lactate dehydrogenase
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
min	minute(s)
mITT	Modified Intent-To-Treat
MMRM	mixed model for repeated measures
MS	mass spectrometry
MSCS	mean symptom complex severity
MTD/DRF	Maximum tolerated dose/dose range finding
NCI	National Cancer Institute
NOAEL	no observed adverse effect level
PA	Primary Analysis
PCR	polymerase chain reaction
PK	pharmacokinetic(s)
po	per os, oral
PRO	patient-reported outcome

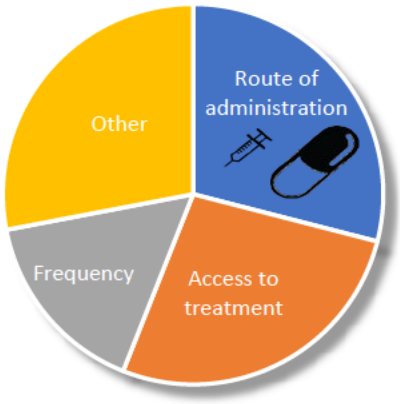
QA	quality assurance
R^2_{adj}	coefficient of determination
RBC	red blood cell
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
sc	subcutaneous
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	apparent terminal elimination half-life, calculated as $0.693/\lambda_z$
TEAE	treatment-related adverse event
TESAE	treatment-emergent serious adverse event
t_{max}	actual sampling time to reach the maximum observed analyte concentration
TMF	trial master file
TOS	treatment outcome score
TSQM	treatment satisfaction questionnaire for medication
US	United States
VAS	visual analogue scale
VAS-3	3-symptom composite visual analogue scale
V_z/F	apparent volume of distribution, based on terminal phase after a single dose
WBC	white blood cell

1 INTRODUCTION

1.1 Study Rationale

An oral treatment for hereditary angioedema (HAE) attacks is currently not available rendering the management of this disease difficult: all of the currently approved drugs for HAE, can only be applied by intravenous (iv) or subcutaneous (sc) route, which is often associated with a delay of drug administration, injection pain, local side effects, and a lower quality of life. In a recent FDA meeting, patients expressed that the route of administration (iv, sc, or po) is the most important consideration for a new HAE therapeutic and that they would prefer oral (po) treatments (FDA 2018). Therefore, there is a strong unmet medical need for an efficacious orally bioavailable drug that could expand patient access to on-demand and prophylactic treatment.

Figure 1 Patient considerations for new HAE therapeutics (FDA)



PHA-022121 is an orally bioavailable, low-molecular weight, competitive bradykinin B2 receptor antagonist. It is being developed to become the first orally effective B2 receptor antagonist with therapeutic potential for acute on-demand and long-term preventive treatment of patients with bradykinin-mediated angioedema.

In this first dose-ranging study, the efficacy and safety of PHA-022121 for on-demand treatment of acute attacks will be explored in patients with HAE due to C1-esterase inhibitor (C1-INH) deficiency (type I/II HAE), which are the most common forms of bradykinin-mediated angioedema.

1.2 Background

1.2.1 Hereditary Angioedema

HAE is an orphan indication estimated to affect between 1 in 10,000 and 1 in 150,000 individuals (Zanichelli et al. 2015; Aygören-Pürsün et al. 2018). The disease manifests as edema attacks most commonly in the limbs, face (lips and tongue), intestinal tract, urogenital region, and airways. Attacks often lead to discomfort, pain and nausea and can become life-threatening in case of airway obstruction and asphyxiation if the attack remains untreated (Zuraw 2008). Although HAE attacks recur with unpredictable frequency, the most severely affected patients can experience attacks every few days.

Three types of HAE have been characterized. Type I and II are defined by mutations in the C1-INH gene and result either in reduced levels of C1-INH (type I) or in reduced activity of C1-INH (type II). In both cases, decreased C1-INH protease activity results in increased activity of Factor XII and plasma kallikrein, resulting in an activated kallikrein-kinin system (KKS), i.e. excessive breakdown of high molecular weight kininogen (HMWK) and increased plasma levels of bradykinin. Type III HAE is characterized by mutations in other genes (e.g., FXII, PLG, and KNG-1) involved in the activation of the KKS and generation of bradykinin, accompanied by normal levels and activity of C1-INH.

Bradykinin is the principal mediator of the signs and symptoms that represent acute attacks in HAE. Two bradykinin receptor types, B1 and B2, have been identified, cloned and characterized. Both are G protein-coupled receptors, seven transmembrane proteins. B1 receptors are inducible, while B2 receptors are constitutively expressed. Bradykinin has a high affinity and high agonist potency at the B2 receptor, but a near 1000-fold lower affinity and potency at the B1 receptor, making it a selective B2 agonist.

In humans, physiological responses to bradykinin include vasodilation through stimulation of endothelial B2 receptors, provoking synthesis and release of vasodilator agents such as endothelium-derived hyperpolarizing factor, prostacyclin, and nitric oxide. Bradykinin also regulates smooth muscle cell contraction.

Excessive bradykinin generation, as in HAE, promotes vascular permeability, leading to plasma extravasation and subcutaneous or submucosal tissue swelling typical of an angioedema attack. Acute episodes of HAE often occur without warning and may be precipitated by triggers such as estrogens, dental procedures, infection, pregnancy, trauma, stress, etc. Disease severity and attack frequency vary significantly in the same patient over time. Angioedema attacks mainly affect gastrointestinal tract, extremities, trunk, face, throat and tongue. Abdominal attacks can be extremely painful, and cause nausea and vomiting. In rare cases it can lead to life-threatening complications including tetany, hemorrhagic stools and intussusception of the colon. Swelling of the throat can lead to dyspnea, loss of consciousness, and in some cases to asphyxiation and death. Frequent angioedema attacks are associated with lower quality of life and psychological burden.

As the B2 receptor is the main target by which bradykinin elicits angioedema in HAE, the selective B2 receptor antagonist, icatibant, has proved to be efficacious, and is currently marketed and recommended as a first-line treatment option for acute attacks of HAE type I/II with C1-INH deficiency (for patients aged 2 years and older). However, this medication requires sc injections, and is associated with injection site pain (SPC 2013).

1.2.2 Current Treatment of HAE

There are currently two treatment approaches to the management of HAE: acute (on-demand) treatment of attacks and prevention of attacks with short or long-term prophylactic therapy.

The currently authorized medicinal products for treatment of acute attacks include C1-INH replacement products such as human plasma-derived C1-INH concentrates (Berinert®, Cinryze®, and Cetor®) or recombinant human C1-INH (Ruconest®), the B2 receptor antagonist icatibant (Firazyr®), and the plasma kallikrein inhibitor ecallantide (Kalbitor®).

Prophylactic therapies include the C1-INH replacement products such as iv Cinryze® and sc Haegarda®/Berinert® 2000/3000, and the monoclonal antibody and plasma kallikrein inhibitor lanadelumab-flyo (sc Takhzyro®).

Subcutaneous icatibant is the only available B2 receptor antagonist indicated for acute attack treatment of HAE type I/II with C1-INH deficiency. In acute attacks icatibant provides a significantly faster onset of relief than placebo (2.0 h versus 19.8 h) (Lumry et al. 2011). Icatibant is recommended as a first-line treatment option for acute attack treatment in patients with HAE (Maurer et al. 2018)

Current treatment guidelines recommend against the use of the traditionally used oral HAE medications, such as antifibrinolytics (tranexamic acid or epsilon aminocaproic acid) for HAE due to limited efficacy (Stoppa-Lyonnet et al. 1987). Attenuated androgens (e.g. danazol, stanozolol, and oxandrolone) are only recommended as second line treatment for prevention of HAE attacks, since there are numerous contraindications, therapeutic class adverse events (AEs) and overall suboptimal control of HAE in many patients. The use of attenuated androgens is limited by numerous safety issues, including seborrhea, altered libido, depression, fatigue, menstrual abnormalities, and masculinization.

Currently, two other angioedema-specific oral medications for acute as well as prophylactic use are in clinical development. Both are kallikrein inhibitors (KVD824 and KVD900). In addition, the kallikrein inhibitor Orladeyo™ (berotralstat), recently approved in the United States, European Union, United Kingdom, and Japan, is a new oral HAE therapy, approved only for prevention of HAE attacks and it should not be used by patients for the treatment of acute attacks (Orladeyo 2020).

1.2.3 PHA-022121

1.2.3.1 Relevant Non-clinical Findings

PHA-022121 has been extensively characterized in primary pharmacological studies as a potent, orally available B2 receptor antagonist. The main findings of results of non-clinical pharmacology and toxicology studies are described briefly below; more details can be found in the PHA-022121 Investigator's Brochure.

Primary Pharmacology

In vitro and *ex vivo* assays demonstrated that PHA-022121 and its metabolite M2-D are competitive antagonists with high binding affinity (similar to icatibant) and high antagonist potency (about 20-fold higher than icatibant) at the human and monkey B2 receptor, without intrinsic agonist activity.

Oral PHA-022121 showed efficacy in two animal models: the bradykinin challenge study in freely moving male Cynomolgus monkeys and the carrageenan-induced paw edema model in male and female humanized B2 Sprague Dawley rats. The duration of action was dose dependent.

Safety Pharmacology

The *in vitro* target profile of PHA-022121 showed a high degree of selectivity for the B2 receptor. Following a single oral administration of up to 50 mg/kg in female and up to

100 mg/kg in male rats, PHA-022121 did not induce any adverse effects on behavioral and physiological parameters, covering the main central and peripheral nervous system functions (Irwin test).

Adverse behavioral signs of PHA-022121 at 200 and 400 mg/kg po observed in maximum tolerated dose and dose range finding studies in Han-Wistar rats, associated with ictal discharges in video-electroencephalogram (EEG), were observed at time of C_{max} of PHA-022121 and M2-D. No EEG signals were detected at 100 mg/kg po, corresponding to a no observed adverse effect level (NOAEL) of PHA-022121 of 100 mg/kg in male rats, the same as in the general toxicology studies.

PHA-022121 and its metabolite M2-D induced a depression of the electrically evoked population spikes responses in a rat hippocampal slice model *in vitro*. The effects were reversible and partially reversible upon washout, respectively.

PHA-022121 did not interact with eight human cardiac ion channels known to contribute to the cardiac action potential including hERG.

In conscious male monkeys, PHA-022121 did not induce any relevant changes in heart rate, arterial blood pressure, body temperature, duration of PR, RR, QT and QTc intervals or QRS complex duration (monitored by telemetry) and did not affect ECG wave form or rhythm at oral doses up to 25 mg/kg, corresponding to a mean total C_{max} of 2020 ng/mL.

Respiratory function was assessed in conscious, freely moving female rats as measured by whole body plethysmography. The administration of PHA-022121 at 50 mg/kg was associated with moderate increases in respiratory rate, tidal volume and minute volume, returning towards vehicle values 4 h post-dose. The NOAEL in the plethysmographic environmental conditions was 15 mg/kg in the female rat.

Toxicology

Dose-limiting toxicity studies with PHA-022121 have been performed in rats and monkeys. In both species, non-tolerated doses were only observed at extremely high PHA-022121 plasma concentrations. The dose limiting toxicity identified in these maximum tolerated dose/dose range finding (MTD/DRF) studies were central nervous system-related clinical signs, that included convulsive episodes and catalepsy (in rat) and imbalance (in monkey). These adverse observations are considered related to C_{max}.

General GLP toxicity studies of up to 6-month and 9-month duration have been completed in rats and monkeys, respectively. No adverse treatment-related effects were observed at any dose level, which included up to 2×100 mg/kg (po) in male rats, 2×50 mg/kg (po) in female rats, and 2×25 mg/kg (po) in male and female monkeys.

PHA-022121 did not show a relevant genotoxic potential *in vitro* or *in vivo*. Neither did it show any potential for phototoxicity in the *in vitro* neutral red uptake phototoxicity assay.

1.2.3.2 Clinical Research

PHA-022121 has been investigated in the Phase I study PHA022121-C001. This was a randomized, double-blind, placebo-controlled, single ascending dose and proof-of-mechanism study to examine the safety, tolerability, pharmacokinetics and pharmacodynamics of orally administered PHA-022121 in healthy subjects.

In total, 52 subjects received single ascending oral doses of PHA-022121 up to 22 mg including bradykinin challenge pharmacodynamic assessments at doses of 12 and 22 mg. Preliminary results show that PHA-022121 at doses up to 22 mg was safe and well tolerated. The total incidence of adverse events was similar between active and placebo groups. For three subjects who received PHA-022121, treatment-related adverse events (AEs) were reported, all within the gastrointestinal disorders system organ class (SOC) and of mild severity: upper abdominal pain, vomiting, and nausea.

A second Phase I single ascending dose study (PHA022121-C002) investigated single oral doses of 22, 33 and 50 mg of PHA-022121 after a standard caloric breakfast and 40 mg in fasting conditions. In this double-blind, placebo-controlled study, a total of 32 subjects received either PHA-022121 (n=24) or placebo (n=8). In general, all doses were well tolerated and no apparent new safety data emerged. There were no SAEs reported. The incidence of treatment-emergent adverse events (TEAEs) was not different between PHA-022121 and placebo. There were no clinically significant changes in laboratory or ECG parameters.

A third Phase I placebo-controlled multiple ascending dose (MAD) study investigated PHA-022121 doses of 12, 22, 33 and 50 mg twice daily for 10 days. The proportion of subjects reporting at least one TEAE was 60.0% (18/30) for PHA-022121 compared with 62.5% (5/8) for placebo. There were no clear differences between the different PHA-022121 dose cohorts versus placebo with respect to the frequency and types of TEAEs reported across the different system organ classes. All reported TEAEs in the study were mild and resolved without treatment.

Pharmacokinetics

Dose proportional PK was observed after single oral administration under fasting condition of PHA-022121 in the dose range of 1 mg to 22 mg for C_{max}, AUC_{last} and AUC_{inf}. Median t_{max} in the dose range of 1 mg to 22 mg was between 0.50 h and 1.00 h, with comparable ranges of individual values (ranging between 0.25 h and 1.02 h). C_{max} ranged from 11.1 ± 4.03 ng/mL at the 1 mg dose to 213 ± 49.5 ng/mL at the 22 mg dose. After the 22 mg dose, C_{12h} was 8.34 ± 4.24 ng/mL and C_{24h} was 1.12 ± 0.786 ng/mL. The apparent $t_{1/2term}$ ranged from 3.49 ± 1.32h for the 1 mg dose to 5.61 ± 0.707 h for the 22 mg dose. However, no clear relationship between the apparent $t_{1/2}$ term and dose was observed. Mean values for apparent CL/F ranged from 31.5 L/h to 42.3 L/h. Mean values of apparent V_z/F ranged from 181 L to 252 L. Less than 1% of the dose was excreted unchanged in urine within 72 h after administration.

M2-D showed dose-proportional PK after single oral administration of PHA-022121 in the dose range 1 mg to 22 mg for C_{max}, AUC_{0-24h}, AUC_{last} and AUC_{inf}. The mean metabolite to parent ratios for C_{max} and AUC_{last} in the dose range from 1 mg to 22 mg were approximately 0.15 and 0.20, respectively.

After a 22 mg dose, mean C_{max} of PHA-022121 was approximately 32% lower while AUC_{inf} was approximately 42% higher when PHA-022121 was administered after a high-calorie-high-fat (HCHF) breakfast compared to administration under fasted conditions. Median t_{max} of PHA-022121 was delayed by approximately 2 h after administration under fed conditions compared to the same dose under fasted conditions with median (range) of 3.00 h (2.00 h – 3.00 h) and 0.75 h (0.25 h – 1.02 h), respectively. Mean (± SD) C_{12h} was 8.34 ± 4.24 h and

19.6 ± 10.7 ng/mL under fasted and fed conditions, respectively. Mean C_{24h} was 1.12 ± 0.786 h to 5.39 ± 5.47 ng/mL under fasted and fed conditions, respectively.

Mean C_{max} of M2-D was approximately 34% lower while AUC_{inf} was approximately 28% higher when PHA-022121 was given under fed conditions compared to administration under fasted conditions. Median t_{max} of M2-D was delayed by 2.5 h after administration under fed conditions compared to under fasted conditions with median (range) of 3.50 h (2.00 h – 4.00 h) and 1.01 h (1.00 h – 2.00 h), respectively.

Repeated bradykinin challenges after oral administration of 12 and 22 mg doses of PHA-022121 under fasting conditions did not lead to changes in PK parameters of PHA-022121 and its major metabolite M2-D.

Pharmacodynamics

PHA-022121 (12 and 22 mg) was administered orally to 16 healthy volunteers. Bradykinin injections were administered before and at 1, 4, 8, 12, and 24 h post PHA-022121 dosing to induce cardiovascular responses. All bradykinin-induced cardiovascular changes were significantly reduced with PHA-022121 treatment. The PK/PD analysis allowed quantitative modeling of these effects and direct comparison with those observed after sc administration of icatibant. Average composite potencies (EC_{50}) were 2.4 ng/mL for PHA-022121 compared to 9.5 ng/mL for icatibant, closely matching respective *in vitro* potencies.

1.3 Risk/Benefit Assessment

1.3.1 Known Potential Risks

Data generated in nonclinical pharmacokinetics, pharmacology, and toxicology studies, as well as the Phase I clinical studies in healthy subjects support the planned clinical study with the B2 receptor antagonist PHA-022121 in HAE patients. Based on the mode of action and on preclinical and clinical data, the following potential risks have been identified.

Potential Risks Based on Toxicology Studies

GLP toxicity studies of up to 6-month and 9-month duration have been completed in rats and monkeys, respectively. No adverse treatment-related effects were observed at any dose level, which included up to 2×100 mg/kg (po) in male rats, 2×50 mg/kg (po) in female rats, and 2×25 mg/kg (po) in male and female monkeys. In dose-range finding toxicology studies in rats and monkeys, the dose-limiting toxicity identified in these studies were central nervous system-related clinical signs, that included convulsive episodes and catalepsy (in rat) and imbalance (in monkey). These adverse observations are considered related to C_{max}. PHA-022121 did not show a relevant genotoxic or phototoxic potential.

Potential Risks to Fetus

Reproductive and development toxicity studies are not available for PHA-022121 so far. For this reason, potential effects of PHA-022121 on the fetus are unknown. Therefore, there may be unknown risks of PHA-022121 which may be serious and unforeseen in case of pregnancy. Women of childbearing potential will only be enrolled if they agree to be abstinent (if that is their usual lifestyle), or use medically acceptable, highly effective forms of contraception during the study. Males with female partners 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. Neither pregnant or breast-feeding women, nor children can be included in this clinical study.

Theoretical Risks Based on the Mechanism of Action

Physiological responses to bradykinin that are modulated by the B2 receptor include vasodilation, natriuresis, nitric oxide and prostaglandin release. B2 receptor blockade could therefore theoretically induce vasoconstriction, increase sodium retention, and reduce nitric oxide and prostaglandin release. Theoretically this could lead to increased blood pressure, reduced heart rate and worsening of ischemia. However, cardiac safety studies in the cynomolgus monkey did not show any of these effects up to the highest PHA-022121 dose tested (25 mg/kg). Preliminary data in healthy volunteers with single ascending doses up to 50 mg did also not show any clinically relevant changes in heart rate, blood pressure or ECG parameters.

Interactions

Based on *in vitro* signals there might be a risk of changes of PHA-022121 exposure with concomitant use of drugs that are strong inhibitors/inducers of CYP3A4. A drug-drug interaction study was conducted to evaluate the effect of itraconazole 200 mg repeated dosing for 5 days on the PK of a single oral dose of 12 mg PHA-022121. The study showed that coadministration of PHA-022121 with the CYP3A4 inhibitor itraconazole to healthy subjects, led to a 2.2-fold increase in C_{max} and an approximate 12-fold increase in AUC_{last}. The clinical data are in line with *in vitro* findings showing that CYP3A4 plays an important role in the metabolism of PHA-022121.

In vitro, PHA-022121 shows a weak inhibitory effect on CYP2C19, a weak to moderate inhibitory effect on CYP3A4 and a moderate inhibition of CYP1A1. *In vitro* induction studies indicate that there is potential of induction for CYP3A4 and to a lesser degree CYP2B6, CYP2C8, and possibly CYP1A2. PHA-022121 is not an inducer of CYP2C9 or CYP2C19. A human drug-drug interaction study indicated that at anticipated therapeutic doses, PHA-022121 does not inhibit or induce CYP1A2, CYP2C19, and CYP3A4. Therefore, medications that are metabolized by CYP1A2, CYP2C19, or CYP3A4 can be used with PHA-022121.

Studies to evaluate whether PHA-022121 is a substrate of transporter(s) mediating drug efflux such as P-glycoprotein or organic anion transporting polypeptides *in vitro* (Caco-2 assay) are currently ongoing.

Potential Risks Based on Icatibant (Firazyr®)

The B2 receptor antagonist icatibant (Firazyr®) has been approved for the symptomatic treatment of acute attacks of HAE in Europe in 2008 and in US in 2011. In contrast to PHA-022121, icatibant is intended for sc administration.

During clinical trials with icatibant (Firazyr®), the most frequently reported AEs which can potentially also occur with PHA-022121 are: dizziness, headache, nausea, rash erythema, pruritus, pyrexia, and increased transaminases (SPC 2013).

A potential risk might be a deterioration of cardiac function and decrease in coronary blood flow under ischaemic conditions (e.g., during an acute myocardial infarction), due to a possible protective effect of bradykinin. Therefore, patients with cardiac risk factors were excluded from the clinical trials, and in the SPC a warning is included for patients with acute ischaemic heart disease and unstable angina pectoris and also stroke.

Potential Risks Due to COVID-19 Pandemic

Neither the HAE disease nor the study drug is expected to pose an extra risk on the patients to develop COVID-19 or to influence the course of the disease in a negative way. The number of planned hospital study visits has been minimized. In case of increased local regulations on social distancing, additional measures such as remote visits or home nursing visits may be implemented to further reduce patient risk.

Potential Risks Based on Phase I Studies

In two Phase I single ascending dose (SAD) studies, single oral doses of PHA-022121 ranging from 1 to 50 mg were well tolerated and safe. The incidence of AEs was not different between active drug and placebo. AEs reported as possibly related to PHA-022121 or placebo were of mild (abdominal pain, nausea, vomiting and headache) or moderate (headache associated with vomiting) severity.

1.3.2 Known Potential Benefits

PHA-022121 is a potent, orally available, highly selective B2 receptor antagonist. The compound was effective in blocking the pharmacodynamic effects of exogenous, iv administered bradykinin in a preclinical animal model and in healthy subjects. The effect in humans was demonstrated with single oral doses of 12 and 22 mg, which were safe and well tolerated. These data suggest that the compound can be expected to have a beneficial effect in the treatment and prevention of HAE attacks.

1.3.3 Assessment of Potential Risks and Benefits

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.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to evaluate the efficacy of three different single doses of PHA-022121 versus placebo in achieving angioedema symptom reduction, defined as change in the 3-symptom composite visual analogue scale (VAS-3) score during acute attacks in patients with HAE type I/II.

2.2 Secondary Objectives

The key secondary objectives of the study are:

To evaluate the clinical efficacy of three different single doses of PHA-022121 versus placebo with regards to:

- Time to onset of symptom relief by VAS-3,
- Time to almost complete or complete symptom relief by VAS-3,
- Change in mean symptom complex severity (MSCS) score at 4 h post-treatment,
- Treatment outcome score (TOS) at 4 h post-treatment.

Other secondary objectives of the study are:

- To evaluate the clinical efficacy of three different single doses of PHA-022121 versus placebo with regards to:
  - Time to onset of primary symptom relief by visual analogue scale (VAS)
  - Proportion of investigational medicinal product (IMP)-treated attacks requiring the use of HAE rescue medication
  - Time to the first use of HAE rescue medication
  - Change in the individual VAS scores (skin pain, skin swelling, abdominal pain) from pre-treatment to 4 h post-treatment
  - Change in MSCS score at 24 h post-treatment
  - TOS at 24 h post-treatment
- 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 treatment satisfaction questionnaire for medication (TSQM) scores at 48 h post-treatment

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

In this study the efficacy of three oral doses (low: 10 mg, medium: 20 mg, and high: 30 mg) of PHA-022121 versus placebo to achieve angioedema symptom reduction will be assessed in adult patients with HAE type I/II.

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 the three dose levels (low, medium, high) first, then based on the assigned cohort, randomized to one of nine treatment sequences comparing three single doses of PHA-022121 (low, medium, high) with placebo treatment. Approximately 72 patients are planned to be randomized.

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, which should be consulted and confirmed by the investigator or designee via remote contact. The study drug should be taken when at least one attack symptom (skin pain, skin swelling, or abdominal pain) becomes of moderate intensity (VAS score ≥ 30). When the attack reaches this VAS intensity threshold, study drug should preferably be taken during the remote contact with the investigator or designee. If the patient cannot take the study drug within 3 h after reaching the VAS intensity threshold, the attack does not qualify for study drug treatment and should be treated with the patient's standard HAE medication. In addition, treatment of the attack should happen within 6 h after onset of symptoms at any location. If the study drug cannot be administered within 6 h after onset of symptoms, the attack does not qualify for study drug treatment and should be treated with the patient's standard HAE medication. Any symptoms involving the internal head and neck, regardless of intensity, also render an attack non-qualifying for treatment with study drug and should be treated with the patient's standard HAE medication.

At 4 h post study drug 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 (including pre-treatment) until 48 h post-treatment. After each attack treated with study drug, a safety follow-up visit 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.

In order to avoid carry-over effects of previous treatments, HAE attacks that occur within 5 days of a previously treated attack (regardless of whether study drug or standard HAE medication was used) will not qualify for treatment with study drug. The end-of-study visit will take place 10±5 days post-treatment of the last attack. This visit may be waived if patients continue in another clinical study with PHA-022121 conducted by the Sponsor.

A schematic flowchart of the study design is shown in Figure 2. For more details see the schedule of events in Appendix 1.

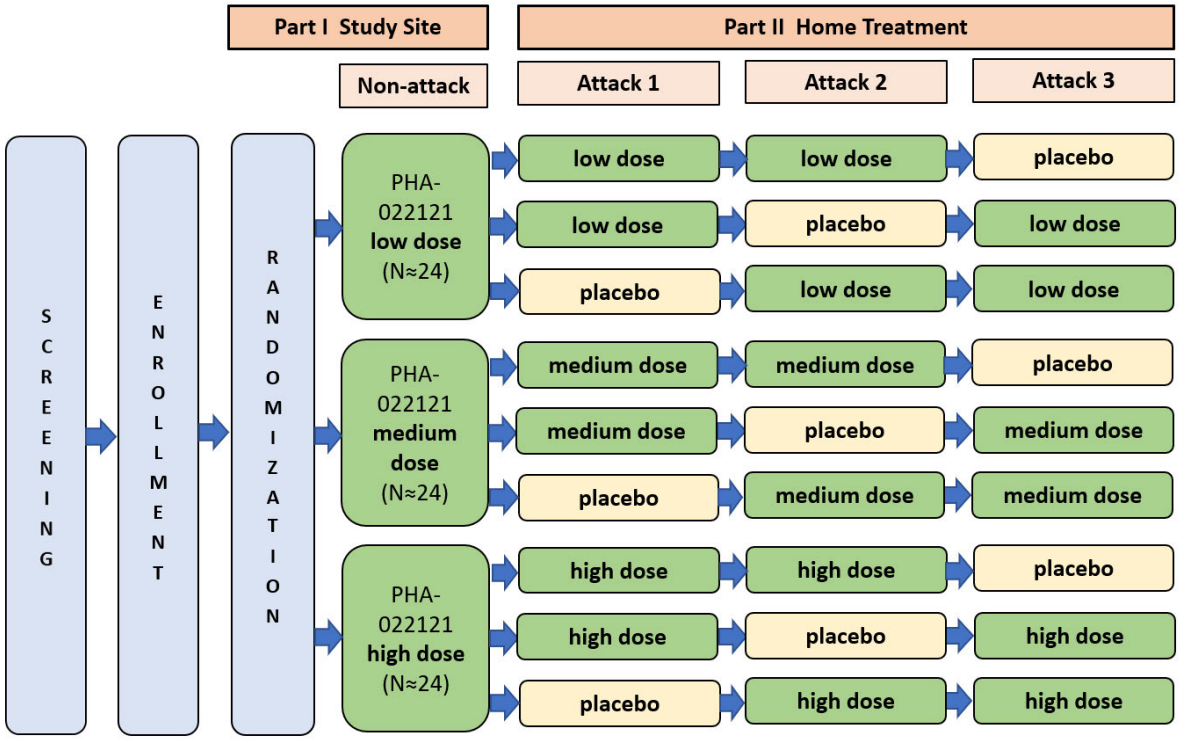


Figure 2 Flowchart of study design

Efficacy will be assessed during Part II with four PROs:

- VAS of the three major HAE symptoms, including skin pain, skin swelling, and abdominal pain
- MSCS score
- TOS
- TSQM scores

The primary endpoint is the change in the VAS-3 score from pre-treatment to 4 h post-treatment.

The key secondary efficacy endpoints of the study are as follows:

- Time to onset of symptom relief, assessed by a ≥30% reduction in VAS-3 score from the pre-treatment score.
- Time to almost complete and complete symptom relief by VAS-3 score
  Almost complete symptom relief is defined as all 3 individual VAS scores of the VAS-3 having a value ≤ 10.
  Complete symptom relief is defined as all 3 individual VAS scores of the VAS-3 having a value of 0.
- Time to a ≥50% reduction in VAS-3 score from the pre-treatment score.

- Change in MSCS score from pre-treatment to 4 h post-treatment
- TOS at 4 h post-treatment

Other secondary efficacy endpoints of the study are as follows:

- Time to onset of primary symptom relief assessed by a 30% reduction in the VAS for the primary symptom, and time to a 50% reduction in the VAS for the primary symptom. The symptom (skin swelling, skin pain, or abdominal pain) with the highest pre-treatment VAS score is considered the primary symptom.
- Proportion of IMP-treated attacks requiring HAE rescue medication within 12 h, within 24 h, and within 48 h post-treatment
- Time to first HAE rescue medication use for IMP-treated attacks, if applicable. An IMP-treated attack refers to an attack treated with blinded IMP (study drug).
- Change in the VAS score for individual symptoms (skin pain, skin swelling, abdominal pain) from pre-treatment to 4 h post-treatment
- Change in MSCS score from pre-treatment to 24 h post-treatment
- TOS at 24 h post-treatment
- TSQM scores at 48 h post-treatment

The safety endpoints of the study are:

- Treatment-emergent adverse events (TEAEs), treatment-related TEAEs, and treatment-emergent serious adverse events (TESAEs), and treatment-related TESAEs
- Clinical laboratory tests (chemistry, hematology, coagulation, and urinalysis)
- Vital signs
- Electrocardiograms (ECGs)

The pharmacokinetic endpoints of the study are:

- Pharmacokinetic parameters based on plasma profiles of PHA-022121 and metabolites: C_{max}, t_{max}, $AUC_{0\text{-}12h}$, $AUC_{0\text{-}24h}$, AUC_{last}, AUC_{inf}, $t_{1/2}$, V_z/F (PHA-022121 only) and CL/F (PHA-022121 only).

3.2 Rationale for Study Design and Control Group

The study adopts a randomized double-blind controlled design in order to objectively quantify the efficacy of PHA-022121 at different doses. A placebo control is considered to be adequate in this study because the key feature of the drug is its potential for oral administration. All currently available on-demand drugs are injectables. An active control group would require a double dummy approach. This would not allow evaluation of an improved acceptance of oral treatment over injectable treatment. In addition, the most frequently used drug for on-demand treatment is icatibant. Injection site reactions are a very common adverse reaction of icatibant, which will lead to unblinding in a high proportion of patients. From a safety point of view, a placebo-controlled design does not put the patient at unnecessary risk because adequate rescue medication is available. All patients in the study will have approved treatment for HAE attacks available, which they can use for attacks that

do not qualify for study drug treatment (see Section 5.3) or attacks that do not respond within a reasonable time frame to study drug treatment.

Patients will treat three qualifying attacks in a double-blind cross-over way. A cross-over design has the advantage that it can assess the within-patient efficacy in addition to the comparison between groups. A major condition is that treatments are sufficiently spaced in time to avoid treatment carry-over effects. In general, a period that covers five times the terminal half-life of the drug is considered sufficient. Given the terminal half-life of approximately 5 h, a period of 5 days after treatment of a single attack before a new attack can be treated is therefore considered sufficient to avoid potential carry-over effects.

Dose Rationale

PHA-022121 is an orally available B2 receptor antagonist. The doses of 10, 20 and 30 mg PHA-022121 selected for this study were supported collectively by the results of PHA-022121 preclinical studies, and safety, PK and PD data from Phase I SAD studies (PHA022121-C001 and PHA022121-C002). Icatibant (Firazyr®), a synthetic decapeptide B2 inhibitor, has been approved for the treatment of acute attacks of HAE, and has been used as a class reference for the dose selection of PHA-022121.

The inhibition of bradykinin challenge model in healthy volunteers has been shown to correlate well with efficacy in the treatment of acute HAE attacks with a B2 receptor antagonist (FDA-CDER 2011). Intravenous administration of icatibant caused dose and time-dependent inhibition of bradykinin-induced hypotension, vasodilation, and reflex tachycardia in healthy subjects. Based on the direct-response PK/PD analysis from the icatibant bradykinin challenge study, an approved sc dose of 30 mg icatibant was predicted to be effective in the treatment of acute attacks for at least 6 h. A single sc dose of 30 mg icatibant gives a 75% probability of having a plasma concentration above the EC_{50} at 6 h and a 50% probability of still being above the EC_{85} at that point in time. This was further demonstrated to correlate well with clinical response in Phase III clinical HAE trials (Cicardi et al. 2010). Recently, a 10-year outcome survey of icatibant clinical effectiveness and safety was published (Maurer et al. 2020). The data collected from 549 patients with a total of 5995 HAE attacks indicated that one single injection of 30 mg icatibant was effective for 93% of attacks and the second injection was able to rescue an additional 6% of attacks. Therefore, approximately 99% of HAE attacks were successfully treated with one or two doses of 30 mg icatibant sc. All clinical and real-world observations match the prediction that was made based on the bradykinin challenge study and suggest that use of a bradykinin challenge for PD assessment is a suitable surrogate endpoint for the development of bradykinin-receptor antagonists such as PHA-022121.

The inhibition of bradykinin challenge was assessed in study PHA022121-C001 with single doses of 12 and 22 mg PHA-022121. A PK/PD analysis using the same approach as in the icatibant evaluation was conducted and
Table 1 lists the EC_{50} and EC_{85} values estimated for each PD response associated with the bradykinin challenge. The composite average shows an EC_{50} of 2.4 ng/mL and an EC_{85} of 13.8 ng/mL for PHA-022121. The free plasma concentration associated with this EC_{50} value of 2.4 ng/mL (plasma protein binding 96.72%), is 170 pM, a potency that is in line with the potency of PHA-022121 for recombinant and endogenous human B2 receptor (150 and 350 pM).

Table 1 Estimated EC_{50} and EC_{85} of PHA-022121 by PD parameter in the bradykinin challenge

	Diastolic blood pressure	Heart rate	Cardiac output	Composite average
EC_{50} (ng/mL)	2.34	3.3	1.68	2.4
EC_{85} (ng/mL)	13.26	18.7	9.52	13.8

Based on the available PK data from the single ascending dose study and these exposure-response relationships it is now possible to project PHA-022121 dosing regimens to reach the two efficacy exposure targets established by icatibant for on-demand HAE treatment:

- EC_{50} should be exceeded with 75% probability (confidence level)
- EC_{85} should be exceeded with 50% probability (confidence level)

Table 2 summarizes the results of the estimated duration of effect of PHA-022121 for each PD response at different dose levels. These calculations and comparison to icatibant show that a single oral dose of 10 mg PHA-022121 can be expected to be at least as efficacious as a sc injection of 30 mg icatibant. A single oral dose of 20 or 30 mg PHA-022121 are expected to have similar efficacy as two sc injections of 30 mg icatibant Q6h, which are shown to be effective for almost all attacks in the 10-year outcome survey of icatibant.

Table 2 Estimated duration of effect of icatibant 30 mg and various doses of PHA-022121

	Icatibant 30 mg sc	PHA-022121 10 mg po	PHA-022121 20 mg po	PHA-022121 30 mg po
75% > EC_{50}				
Diastolic blood pressure	6 h	11 h	13.5 h	16 h
Heart rate	6.5 h	9.5 h	12.5 h	14 h
Cardiac output		12.5 h	16 h	18 h
Composite average	6.5 h	10.5 h	13 h	15.5 h
50% > EC_{85}				
Diastolic blood pressure	5.5 h	7 h	9.5 h	11.5 h
Heart rate	5.5 h	6 h	9 h	10.5 h
Cardiac output		8 h	11 h	13 h
Composite average	5.5 h	7 h	9.5 h	11.5 h

3.3 Study Duration and Dates

The expected study duration per patient amounts to approximately 30 weeks consisting of the Screening period of up to 4 weeks, the Non-attack visit (Part I), home treatment (Part II) of about 24 weeks (covering 3 qualifying attacks treated with study drug per patient), and up to 2 weeks until the end-of-study visit. In some cases, patients may need longer than 24 weeks to complete the assessments for 3 qualifying attacks; therefore, the individual duration per patient may be longer.

Patient recruitment is planned to be started in Q1 2021 and the study is planned to be completed in Q3 2022. Therefore, the expected overall duration of the study is approximately 15-18 months. The overall study duration may be longer if some patients need longer than 24 weeks to complete the assessments for 3 qualifying attacks.

The end of the study is defined as the last visit of the last patient participating in the study.

4 STUDY POPULATION SELECTION

4.1 Study Population

Approximately 72 male or female, adult patients with HAE due to C1-INH deficiency (HAE type I/II) will be randomized in this study. For eligibility in the study, patients need to have experienced at least three HAE attacks in the last 4 months, or at least two HAE attacks in the last 2 months.

The anticipated number of study sites is approximately 35 across 12-15 countries.

4.2 Inclusion Criteria

In order to be eligible to participate in this study, a patient must meet all of the following 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 ≤ 40 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 three HAE attacks in the last 4 months, or at least two HAE attacks in the last 2 months prior to screening
5. Reliable access[1] 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[2] 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).[3] A female of childbearing

[1] Reliable access of a drug is defined as being readily available on the market with guaranteed continuous supply.
[2] Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation) or post-menopausal (defined as no menses for at least 12 months without an alternative medical cause) do not require contraception during the study.
[3] Use of a male condom with or without spermicide or cervical cap, diaphragm or sponge with spermicide or a combination (double-barrier methods) is not considered highly effective

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.

4.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Pregnant or breast-feeding
2. Clinically significant abnormal ECG, most notably a QTcF > 470 ms (for females) or > 450 ms (for males)
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 (< 50 bpm), 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 anti-fibrinolytics 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 C virus (HCV), or active infection with hepatitis B virus (HBV) associated with signs of active liver disease
7. Abnormal hepatic function (AST > 2×ULN, ALT > 2×ULN, or total bilirubin > 1.5×ULN), with the exception of patients with Gilbert's syndrome
8. Abnormal renal function (eGFR CKD-EPI < 60 mL/min/1.73 m^2)
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 documented 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, 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)

5 STUDY TREATMENTS

5.1 Description of Investigational Medicinal Product (IMP)

Note: Blinded PHA-022121 and Placebo are considered as the IMP and may both be referred to as study drug.

5.1.1 PHA-022121

The active study drug consists of 10 mg PHA-022121 soft capsules for oral use with a concentration of the fill of 50 mg/g PHA-022121 in a 40:50:10 (w/w/w) mixture of Kolliphor RH 40, Capryol 90 and propylene glycol.

5.1.2 Placebo

Placebo treatment consists of matching placebo soft capsules for oral use.

5.2 Treatments Administered

The treatments to be administered in the study consist 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

The treatment will consist of three soft capsules (each containing 10 mg PHA-022121 or placebo) that must be ingested at the same time. The capsules are to be swallowed with a cup of water of at least 200 mL.

In Part I of the study, each patient receives a single dose of PHA-022121 (10, 20, or 30 mg).

In Part II, patients will receive two single doses of PHA-022121 (10, 20, or 30 mg) and one single dose of placebo.

In Part II of the study, each patient self-administers two single doses of PHA-022121 (10, 20, or 30 mg) and one single dose of placebo for each of the three qualifying HAE attacks according to one of the following sequences (cross-over design):

1. Low dose - Low dose - Placebo
2. Low dose - Placebo - Low dose
3. Placebo - Low dose - Low dose
4. Medium dose – Medium dose – Placebo
5. Medium dose – Placebo – Medium dose
6. Placebo – Medium dose – Medium dose
7. High dose – High dose – Placebo
8. High dose – Placebo – High dose
9. Placebo – High dose – High dose

5.3 Selection and Timing of Dose for Each Patient

In Part I of the study, patients in quiescent state receive the dose of PHA-022121 under fasting conditions (fasting from midnight or for at least 8 h) according to their randomized treatment assignment.

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, which should be consulted and confirmed by the investigator or designee via remote contact. The study drug should be taken when at least one attack symptom (skin pain, skin swelling, or abdominal pain) becomes of moderate intensity (VAS score ≥ 30). When the attack reaches this VAS intensity threshold, study drug should preferably be taken during the remote contact with the investigator or designee. If the patient cannot take the study drug within 3 h after reaching the VAS intensity threshold, the attack does not qualify for study drug treatment and should be treated with the patient's standard HAE medication. In addition, treatment of the attack should happen within 6 h after onset of symptoms at any location. If the study drug cannot be administered within 6 h after onset of symptoms, the attack does not qualify for study drug treatment and should be treated with the patient's standard HAE medication.

Study drug should not be taken for laryngeal and pharyngeal attacks (because of risk of airway involvement) or attacks associated with vomiting, swallowing difficulty, or intolerable pain. These attacks should be treated with the patient's standard HAE medication (if possible in consultation with the investigator) or the investigator may hospitalize the patient.

At 4 h post study drug treatment, the patient will consult with the investigator or designee remotely again to assess symptom relief, safety, and any need for rescue medication.

In order to avoid carry-over effects of previous treatments, attacks that occur within 5 days of a previously treated attack (regardless of whether study drug or standard HAE medication was used) will not qualify for treatment with study drug.

5.4 Method of Assigning Patients to Treatment Groups

The patients will be randomized to one of the three dose levels (low, medium, high) first, then randomized to one of the nine treatment sequences to be received in Part II of the study (see Section 5.2). The randomization will be stratified by whether the patient is willing to participate in full PK sampling in Part I (Yes, No), which will be done in approximately four patients from each dose cohort (see Section 6.8.2). The stratification factor will not be used for analysis. Then the patients will be further randomized to one of the three treatment sequences with the given dose level. Patients who are initially willing to participate in the full PK sampling but withdraw their consent for this PK sampling before the sampling starts, can continue study participation without full PK sampling. Their full PK sampling slot may be fulfilled by another study patient at the discretion of the Sponsor.

Each treatment sequence is planned to be assigned to eight patients. In Part I of the study, patients in quiescent state will receive the PHA-022121 dose from their randomized treatment assignment.

Randomization will be performed by an interactive response technology (IRT) system. All drug supplies will be handled in a double-blinded manner.

5.5 Blinding

Blinding is achieved because PHA-022121 capsules and placebo capsules have an identical appearance and each single dose consists of a combination of three capsules of 10 mg PHA-022121 and/or placebo as described in Section 5.2.

The labels are blinded and contain a unique code. Assignment of study drug in accordance with their randomized treatment assignment is managed by the IRT system.

Access to study drug assignment will be available if the investigator deems it necessary to break the study blind in the interest of a patient's medical safety, in case of a medical emergency, to meet regulatory reporting obligations, or if warranted during scheduled safety reviews. Where medically appropriate, the investigator will contact the Medical Monitor to discuss the situation which has arisen and resulted in the need for unblinding of the patient. The Medical Monitor will not be involved in the decision to unblind.

5.6 Concomitant Therapy

Concomitant medications will be recorded in the eCRF from the time patients give informed consent until the end of study visit.

5.6.1 Allowed HAE Rescue Medication

If in Part II of the study, patients do not experience symptom relief within 4 h post-study drug, they are allowed to use any approved and prescribed acute HAE rescue medication, such as icatibant, ecallantide, or C1-INH.

The patient's standard HAE medication should be used for the treatment of any laryngeal and pharyngeal attacks (because of risk of airway involvement), or attacks associated with vomiting, swallowing difficulty, or intolerable pain (if possible in consultation with the investigator; see Section 5.3). Use of standard HAE treatment should not be delayed for such attacks.

5.6.2 Prohibited Concomitant Medications

The following medications are not allowed to be used during the study:

- Kallikrein inhibitors for prophylactic use, antifibrinolytics (tranexamic acid or epsilon-aminocaproic acid), attenuated androgens (e.g., danazol, stanozolol, and oxandrolone), or C1-INH for prophylactic use. These medications are prohibited during the study.
- Corticosteroids, antihistamines, narcotics, and other pain relief medications are prohibited for treatment of acute HAE attacks (can be used to treat intercurrent illnesses between HAE attacks if needed). These medications are prohibited during the HAE attack period (Part II). If needed, each patient will have reliable access to use standard of care treatment for acute HAE attacks.

- Moderate or potent inhibitors/inducers of CYP3A4, 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).
  Concomitant use of these medications with the study drug is prohibited throughout the study. If one of these drugs would be prescribed for chronic use (e.g. diltiazem, phenytoin) the subject will be withdrawn from the study. If a patient requires a short-term treatment for an intercurrent illness (e.g. erythromycin for bronchial infection) treatment with study drug should be suspended for the duration of treatment and an appropriate wash out period. The duration of suspension will be defined in agreement with the medical monitor. Any HAE attack during this period will be considered as a non-qualifying attack and should be treated with patient's usual HAE acute attack medication.

5.6.3 COVID-19 Vaccination

The IMP is not known to be an immunomodulator, therefore COVID-19 vaccination for study patients is not prohibited during the study. However, patients who have received the COVID-19 vaccination should not treat an attack with IMP within 48 hours of receiving the vaccine as a precaution (any attack within this timeframe should be treated with their standard HAE medication). If the COVID-19 vaccine is administered while a patient is participating in the study, the details must be documented in the eCRF. The COVID-19 vaccine should be administered in compliance with local guidelines.

5.7 Restrictions

5.7.1 Contraception

In the absence of a completed non-clinical data package on teratogenicity/fetotoxicity, PHA-022121 is considered a study drug with possible human teratogenicity/fetotoxicity in early pregnancy according to the CTFG recommendations(CTFG 2020). Therefore, the inclusion of females of childbearing potential requires the use of medically accepted, highly effective contraceptive measures from enrollment until 30 days after the last study drug administration.

The following birth control methods are considered highly effective:

- Combined (estrogen and progestogen containing) hormonal contraception methods associated with inhibition of ovulation: oral, intravaginal, or transdermal
  Birth control methods containing estrogen such as ethinyl estradiol (EE) can be a trigger for HAE attacks in some females. Although females using EE methods on a stable dose without safety issues may be enrolled on this study, females should not be recommended to use EE methods if they did not use them prior to enrollment in the study.
- Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, or implantable
- Intrauterine device (IUD, all types)
- Intrauterine hormone-releasing system (IUS)
- Sexual abstinence, where it is the anticipated usual lifestyle of the patient

A female patient 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.

5.7.2 Fluid and Food Intake

In Part I of the study, the assigned single dose of PHA-022121 will be given at the study site under fasting conditions (fasting from midnight or for at least 8 h). No other restrictions for fluid and food intake apply during the study.

5.8 Treatment Compliance

Treatment compliance in Part I will be ensured by intake of study drug under supervision of study personnel. Treatment compliance in Part II will be assessed by documenting drug accountability, including review of returned blisters.

The protocol does not allow for dose adjustment. Any deviation from taking the defined number of capsules will be a deviation of treatment compliance. Treatment compliance will be verified by review of patient diaries and returned blisters. The number of capsules taken by the patient will be entered in the clinical database. Non-compliance will be flagged in the clinical database, and taken into account for the analysis of the efficacy and safety profile.

5.9 Packaging and Labeling

The IMPs (study drug or placebo) are packaged and labelled according to current Good Manufacturing Practice.

The IMPs are packaged in aluminium/aluminium (alu/alu) blisters. Each blister will be sealed into a wallet. The wallet will be labelled with a booklet label and rendered tamper evident. Each wallet will contain one single dose, which consists of a combination of three capsules of 10 mg PHA-022121 and/or placebo.

5.10 Storage and Accountability

The IMPs should not be stored above 25 ºC.

Access to the IMPs should be restricted to designated study personnel.

5.11 Investigational Product Retention at Study Site

Not applicable.

6 STUDY PROCEDURES

6.1 Informed Consent

At the Screening visit, a signed informed consent form (ICF) must be obtained from each patient prior to performing any study-related procedures. Each patient should be given both verbal and written information describing the nature and duration of the clinical study. More details on the informed consent are given in Section 10.4.

6.2 Demographics and HAE Characteristics

At Screening, demographic information, including year of birth, gender, race, and ethnicity will be captured in the eCRF for each patient.

In addition, HAE characteristics, including the year of diagnosis, family history, the type of HAE, and the number of attacks in the last 2 and 4 months, and the last year will be collected.

To confirm the HAE diagnosis, results of C1-INH functional level, C1q level, and C4 level must be obtained from a Screening plasma sample by a central laboratory assessment. Only patients with a confirmed HAE Type I/II diagnosis based upon a central laboratory assessment or by genotyping of the C1-INH gene (SERPING1) may continue into Part II of the study.

6.3 Medical History

At Screening, existing general medical history (current or resolved) will be recorded for the following body systems: head/eyes/ears/nose/throat (HEENT), respiratory, cardiovascular, gastrointestinal, genitourinary, musculoskeletal, neurological, endocrine/metabolic, blood/lymphatic, dermatologic, psychiatric, allergy, and other.

6.4 Weight and Height

Height will be measured at the Screening visit. Weight will be measured at Screening and at the Non-attack visit.

6.5 Physical Examination

A physical examination will be conducted at Screening. At minimum, the following body systems will be examined: gastrointestinal system; head/eyes/ears/nose/throat (HEENT); endocrine (including thyroid); respiratory system; cardiovascular system; integumentary system (skin); and nervous system (central and peripheral). Abnormalities will be reported in the eCRF.

6.6 Vital Signs

Vital signs include blood pressure, heart rate, body temperature, and respiratory rate. Blood pressure (systolic and diastolic) and heart rate will be taken after the patient has rested in

supine position for at least 5 min, at Screening, at the Non-attack visit (pre-dose, and 1 and 4 h post-dose), and at the Post-attack visits. Blood pressure measurements must be obtained with an appropriate cuff size and with the patient's arm supported at the level of the heart. It is acceptable to obtain a pulse rate from the blood pressure or ECG machine.

6.7 Digital 12-Lead Electrocardiogram (ECG)

A 12-lead ECG (digital triplicate) will be recorded after the patient has rested in supine position for at least 10 min at Screening and at the Non-attack visit (pre-dose, and 1 and 4 h post-dose). ECGs will be evaluated by the investigator and any abnormalities will be reported in the eCRF. Central reading of all recorded ECGs will be performed by the ECG vendor.

6.8 Clinical Laboratory Tests

6.8.1 Safety Laboratory Parameters

Patients will be in a seated or supine position during blood collection. Safety laboratory tests are listed in Table 3. Blood and/or urine sampling for blood chemistry, hematology, urinalysis, and pregnancy test will be done at the Screening visit, the Non-attack visit (pre-dose), and the Post-attack visits. Blood sampling for viral testing will be done at Screening only.

Blood and urine samples will be processed by a central laboratory. The investigator will classify all laboratory values outside the normal range of the central laboratory as "Clinically significant" or "Not clinically significant".

The estimated glomerular filtration rate (eGFR) at Screening will be calculated with the CKD-EPI creatinine equation based on serum creatinine and patient characteristics (Levey et al. 2009).

Table 3 List of safety laboratory tests

Hematology:

- Hematocrit (Hct)
- Hemoglobin (Hgb)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Mean corpuscular volume (MCV)
- Platelet count
- Red blood cell (RBC) count
- White blood cell (WBC) count with percent and absolute differential counts (neutrophils, bands, lymphocytes, eosinophils, monocytes, and basophils)

Coagulation:

- Prothrombin time (PT)
- International normalized ratio (INR)

Urinalysis:

- Macroscopic analysis:
  - Bilirubin
  - Blood
  - Glucose
  - Ketones
  - Leukocyte esterase
  - Nitrite
  - pH
  - Protein
  - Specific gravity
  - Urobilinogen
- Microscopic analysis:
  - Bacteria
  - Casts
  - Crystals
  - Epithelial cells
  - RBCs
  - WBCs
  - Yeast
- Urine drug test *

Blood chemistry:

- Albumin
- Alkaline phosphatase (AP)
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Blood urea nitrogen (BUN)
- Bicarbonate
- Calcium
- Chloride
- Creatinine
- Glucose
- Lactate dehydrogenase (LDH)
- Magnesium
- Phosphate
- Potassium
- Sodium
- Total bilirubin
- Direct bilirubin
- Total protein
- Uric acid
- eGFR CKD-EPI (calculated)

Pregnancy test (for women of childbearing potential and surgically sterile women):

- Serum human chorionic gonadotropin (hCG)

Testing to confirm post-menopausal status of women**:

- Serum follicle-stimulating hormone (FSH)

Viral testing **:

- HBV (HBsAg)
- HCV (antibodies, if positive followed by HCV-RNA)
- HIV1/2 (antibodies)

* Non-attack visit only

** At Screening only

6.8.2 Pharmacokinetic Plasma Sampling, Storage, and Shipping

In Part I of the study, in approximately four patients from each dose cohort (~12 patients in total), plasma samples will be collected at pre-dose, 15±5 and 30±5 min post-dose, and 1h±10min, 2h±10min, 4h±15min, 8h±15min, and 10h±15min post-dose (full PK profile). From all other patients in Part I, plasma samples will only be collected pre-dose, and at 1h±10min and 4h±15min post-dose.

In Part II of the study, sparse blood sampling within 24 h post-dose (preferably within 12 h post-dose) will be applied for PK purposes. The goal is to collect blood samples from a subset of patients for at least 50 attacks treated with PHA-022121 or placebo.

Collected plasma samples will be stored at -80±16°C. Plasma samples will be transferred frozen to the bioanalytical laboratory contracted by the sponsor.

To allow selection of samples, the bioanalytical laboratory will receive randomization lists per treatment sequence. Unblinding of the treatment code will be performed at the bioanalytical laboratory only, and will be subjected to a procedure that will ensure that codes will not be revealed to anyone involved in the execution of the study.

Plasma will be analyzed to determine concentrations of PHA-022121 and metabolites using validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) methods under the supervision of the sponsor.

6.9 Dispensing Study Drug

The study drug must be dispensed under the supervision of the investigator using the IRT system for assigning treatments, allocating drug supplies, minimizing drug wastage, and assisting with reordering supplies. The investigator or designee pharmacist will maintain complete and current accountability records recording receipt, dispensing, return and destruction of all clinical study supplies. Local regulations should be adhered to.

Any damaged or unusable study drug in a given shipment will be documented in the study files and recorded in IRT. The investigator must notify study sponsor of any damaged or unusable study drugs that were supplied to the investigator's site.

All used and unused study drug will either be returned to Pharvaris (or nominated facility) or following written agreement with Pharvaris can be destroyed on site (according to local regulations) or by an authorized destruction unit. All correspondence related to study drug destruction must be filed with the study accountability records.

Any medication errors, including incorrect dosage, using expired drug, storage requirement excursions, administration errors etc., should be recorded as protocol deviation and Pharvaris should be immediately informed.

6.10 Efficacy Assessments

Patients will complete electronic diaries at home in real-time to collect information on attack locations and attack severity as assessed by four patient-reported outcomes (PROs): a visual analogue scale (VAS), the mean symptom complex severity (MSCS) score, the treatment outcome score (TOS), the treatment outcome score (TOS), and the satisfaction questionnaire for medication (TSQM) scores. For this purpose an ePRO device will be applied, which throughout Part II of the study needs to be checked daily by the patient and also contains an HAE diary in which the patient will record on a daily basis potentially relevant HAE events not treated with IMP.

Patients will be trained in the use of the ePRO device at Screening and at the Non-attack visit according to the ePRO device training instructions.

6.10.1 VAS

The VAS scores of the three major HAE symptoms (skin swelling, skin pain, and abdominal pain) range between 0 (No swelling/No pain) and 100 (Extreme swelling/Excruciating pain) (Lumry et al. 2011; Kusuma et al. 2012). They must be reported pre-treatment at the time the investigator is consulted to confirm eligibility of the attack for study drug treatment. Thereafter the VAS scores have to be reported every 30±10 min from 0 to 4 h post-treatment, and at 5±0.5, 6±0.5, 8±1, 24±4 and 48±6 h post-treatment. If the 5 h and/or 6 h timepoints fall during the overnight/sleeping hours, these timepoints are optional to report. All other time points are required.

A symptom is considered to be severe when the patient has scored the severity as ≥ 50 on the VAS, moderate when the score is between 30 and 50, and mild when a patient has scored the symptom as < 30 on the VAS.

The primary endpoint of the study is the change of the 3-symptom composite visual analogue scale (VAS-3) score from pre-treatment to 4 h post-treatment. This endpoint is the mean of the VAS scores of the three major HAE symptoms: skin swelling, skin pain, and abdominal pain.

The VAS is a validated tool for assessing a patient's perception of symptom severity, which has been widely used in clinical studies in diseases other than hereditary angioedema but with similar symptoms, to assess abdominal pain, cutaneous pain, and swelling (Cicardi et al. 2010).

6.10.2 MSCS Score

The MSCS score evaluates global symptom severity at a point in time. The MSCS score is made up of two components: (1) symptom complex identification (patients identify where on the body symptoms are occurring); and (2) severity assessment of each symptom complex (Vernon et al. 2009).

Patients are asked to identify where on the body they are experiencing symptoms. Symptoms that may be occurring within a symptom complex site include pain, swelling, rash, etc. Patients do not identify specific symptoms (i.e., rash), but rather identify symptom complexes (body areas) where symptoms are occurring. There are five symptom complexes in total: internal head/neck, stomach/gastrointestinal, genital/buttocks, external head/neck, and cutaneous. After affected body sites are identified, the patient is asked to rate the severity of symptoms within each symptom complex. For example, if patients indicate that they are experiencing symptoms in the stomach/gastrointestinal (abdominal) area, they are asked to rate the severity of the symptoms within that area. Severity options include normal=0, mild=1, moderate=2, severe=3.

Pre-treatment and at 1±0.25, 2±0.25, 4±0.25, 6±1, 8±1, 24±4, and 48±6 h post-treatment (Attack 1, 2, and 3), patients will report the symptom complexes within which they are experiencing symptoms and the severity of symptoms within each affected symptom complex (called the severity assessment). If the 6h timepoint falls during the overnight/sleeping hours, this timepoint is optional to report. All other time points are required.

The MSCS score is calculated by taking the arithmetic mean of the individual symptom complex severity assessments. Please note that no zeros are included in the pre-treatment scoring, but zeros can be included in the post-treatment scoring if they refer to symptom complexes experienced pre-treatment.

6.10.3 TOS

The TOS is a composite measure that evaluates patient's recollection of symptom change in response to treatment, taking into account symptom severity. The TOS is made up of three components: (1) symptom complex identification pre-treatment (patients identify where on the body symptoms are occurring); (2) severity assessment of each symptom complex pre-treatment; and (3) response assessment post-treatment (Vernon et al. 2009).

Pre-treatment (Attack 1, 2, and 3), patients are asked to identify where on the body they are experiencing symptoms. Symptoms that may be occurring within a symptom complex site include pain, swelling, rash, etc. Patients do not identify specific symptoms (i.e., rash), but rather identify symptom complexes (body areas) where symptoms are occurring. There are five symptom complexes in total: internal head/neck, stomach/gastrointestinal, genital/buttocks, external head/neck, and cutaneous. After affected body sites are identified, the patient is asked to rate the severity of symptoms within each symptom complex. For example, if patients indicate that they are experiencing symptoms in the stomach/gastrointestinal (abdominal) area, they are asked to rate the severity of the symptoms within that area. Severity options include severe=3, moderate=2, or mild=1.

At 1±0.25, 2±0.25, 4±0.25, 6±1, 8±1, 24±4, and 48±6 h post-treatment (Attack 1, 2, and 3), patients are asked to rate change in the affected symptom complexes they identified pre-treatment (called the response assessment). The response assessment includes the following options: significant improvement=100, improvement=50, the same=0, worsening=-50, or significant worsening = -100. If the 6h timepoint falls during the overnight/sleeping hours, this timepoint is optional to report. All other time points are required.

The TOS is calculated as the sum of individual symptom complex response assessments multiplied by the symptom complex severity assessment at pre-treatment, divided by the sum of all individual symptom complex severity assessments at pre-treatment.

6.10.4 TSQM Scores

The 11-item treatment satisfaction questionnaire for medication (TSQM version II) evaluates patient treatment satisfaction with the medication for the following scales: effectiveness, side effects, convenience, and overall satisfaction (Atkinson et al. 2005). Scale scores are transformed into scores ranging from 0 to 100 and can be used to calculate a total composite score.

Patients are requested to rate the 11 items of the TSQM at 48±6 h post-treatment (Attack 1, 2, and 3).

6.11 Adverse Events and Serious Adverse Events

6.11.1 Definitions

An adverse event (AE) as is as any untoward medical occurrence in a clinical investigation patient administered study drug (i.e., IMP) and which does not necessarily have a causal relationship with this study drug. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study drug, whether or not related to the study drug.

Pre-existing diseases, symptoms, or abnormal diagnostic/laboratory values are not considered as an AE, and should be recorded in the eCRF as medical history. However, worsening in severity or increase in frequency of a pre-existing medical condition or value is considered to be an AE.

An adverse drug reaction (ADR) is defined as a noxious and unintended response to a study drug related to any dose. This means that a causal relationship between the study drug and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out (ICH E2A).

A serious adverse event (SAE) is any untoward medical occurrence (AE) that at any dose:

- results in death;
- is life-threatening (at the time of the event);
- requires inpatient hospitalization or prolongation of an existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- is an important medical event that may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above.

For the purpose of this protocol, HAE attacks and their associated symptoms will not be defined as AEs, unless they meet the criteria for an SAE. HAE attacks and associated symptoms will be recorded in the patient's diary (ePRO). The events that may trigger a HAE attack such as an infection or trauma are considered AEs and should be reported per the usual AE reporting process.

6.11.2 Adverse Event Assessments

The investigator or qualified designee will be responsible for assessing AEs. Reporting of AEs may result from spontaneous reports by the patient, general questioning by the investigator or designee, clinically significant abnormalities found during physical examination, or clinically significant findings from vital signs ECGs, or diagnostic test results, including laboratory tests. Clinically significant abnormalities are defined as abnormalities that require investigation and/or treatment. Simply repeating an abnormal test is not considered sufficient for clinical significance.

The investigator is responsible for monitoring the safety of patients who participate in the study and for providing appropriate medical care. In addition, the investigator is responsible for alerting the sponsor or its designee to any AE or finding that seems unusual, whether or

not that finding is considered related to study drug, and even if it may be considered to be an unanticipated beneficial effect.

All AEs (including SAEs) are to be recorded on the eCRF from the time of signing informed consent until the end-of-study visit. AEs should be described in acceptable medical terminology using a single reached diagnosis (versus signs and symptoms of the reached diagnosis). Abnormal diagnostic test results that support the reached diagnosis should not be recorded. However, if the diagnosis is initially unknown or uncertain, signs and symptoms must be recorded. As soon as the diagnosis causing the signs and symptoms is known, the event terms must be adjusted to the final reached diagnosis.

Other event information to be collected includes (but is not limited to): onset date, assessment of severity (CTCAE grading), relationship to the IMP (i.e., causality assessment), action taken, outcome, and date of resolution/stabilization of the event.

AEs are to be followed up until the event resolves (or resolves with sequelae/stabilizes) or the patient is lost to follow-up. If a Grade 1 or 2 event (see Section 6.11.3.1 for AE grading) is ongoing at the end-of-study visit, it does not need to be followed if it has been assessed as unrelated to the IMP. If possible, for all Grade 3-5 events and events assessed as related to the IMP, the event should be followed until the AE is resolved, the patient is in a clinically stable condition in regard to the AE, the patient withdraws from the study, the patient is lost to follow-up, or the patient has died.

The sponsor/designee retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

If a patient dies during participation in the study or during a recognized follow-up period (and only if allowed by local legislation), the investigator should attempt to provide the sponsor/designee with relevant information regarding the death (e.g., a redacted copy of relevant post-mortem findings, autopsy report, death certificate, pathology findings, etc.).

6.11.3 Classification of an Adverse Event

6.11.3.1 Severity and Grade

The severity of an AE provides a qualitative assessment of the extent or intensity of an AE, as determined by the investigator. The severity does not always reflect the clinical seriousness of the event, only the degree or extent of the affliction or occurrence (e.g. severe nausea, mild seizure).

The severity grade should be evaluated and recorded on the eCRF according to the grading described in the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (NCI 2017). The severity grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on the following general guideline:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
  Grade 5: Death related to AE

6.11.3.2 Relationship to IMP

All AEs will be examined to determine their relationship to the IMP (causality). The investigator will assess the causality as "Related" or "Unrelated". AEs should be considered "Related" only if there is a reasonable possibility of a causal relationship to the IMP.

Rationales for an Unrelated assessment may include:

- Event attributed to concomitant medication or disease
- Event not reasonably temporally associated with IMP administration
- Negative dechallenge and/or negative rechallenge

Rationales for a Related assessment may include:

- Temporal relationship of event to IMP exposure
- Event is known to be associated with the IMP or drug class
- Event improved on discontinuation or dose reduction of IMP
- Event reoccurred on rechallenge with study drug
- Biological plausibility

6.11.4 Reporting Serious Adverse Events

All SAEs after signing of the informed consent through the end-of-study visit must be reported by the investigator, within 24 h of knowledge of their occurrence to the sponsor or its designee, independent of the circumstances or suspected cause.

The report must be completed via Electronic Data Capture (EDC) in English and must include a causality assessment (relationship to IMP). Simultaneously, information about every SAE should be recorded on the applicable eCRF pages, including information on AEs and concomitant medications. If the electronic data capture (EDC) system is unable to be accessed, a back-up paper SAE Report Form should be completed in the interim. The paper SAE report form should be sent by e-mail or fax to:

Medpace Clinical Safety

SAE Reporting Phone Line:	+1-800-730-5779, dial 3 or +1-513-579-9911, dial 3 (US) +49 89 89 55 718 44 (EU)
Safety Fax:	+1-866-336-5320 or +1-513-570-5196 (US) +49 89 89 55 718 104 (EU)
E-mail:	medpace-safetynotification@medpace.com

If a paper SAE Report Form was utilized, the original SAE report form, together with the fax confirmation sheet (if applicable), must be kept at the study site. If the initial report is made verbally or by telephone, a written confirmation via e-mail or fax must follow within 24 h. The investigator will be requested to supply detailed information regarding the event at the time of the initial report.

Each SAE should be recorded as a single reached diagnosis on the SAE report form. Accompanying signs (including abnormal diagnostics tests, laboratory values and ECG findings) or symptoms should not be reported as additional SAEs. However, if initially the diagnosis is unknown, the signs and symptoms should be reported. As soon as the reached diagnosis causing the signs and symptoms is known, the event terms will be adjusted to the final reached diagnosis.

For all SAEs occurring during the study, the investigator must submit follow-up reports to the sponsor or its designee regarding the patient's subsequent course until the SAE has resolved, or until the condition stabilizes (in the case of persistent impairment), or the patient dies.

The Medical Monitor will be responsible for determining whether an SAE is expected or unexpected. An SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the list of expected adverse reactions (Reference Safety Information) included in the Investigator's Brochure version in place at the time of the assessment.

All suspected unexpected serious adverse reactions (SUSARs) will be subject to expedited reporting to the regulatory authorities by the sponsor or designee, per recognized regulatory timelines. The timelines and procedure for follow-up reports are the same as those for the initial report (unless the initial SAE report meets 7-day reporting rules).

6.11.5 Events of Special Interest

Not applicable. At the time of this protocol version, no events of special interest have been identified for PHA-022121.

6.11.6 Reporting of Pregnancy

Any female patient who becomes pregnant during the course of the study should have study drug discontinued immediately and must be followed to the end of the pregnancy (i.e. pregnancy outcome). While pregnancy is not considered an SAE per se, pregnancies must be reported immediately to the sponsor or designee using the pregnancy report form and following SAE reporting timelines.

A pregnancy in a patient exposed to the study drug should be followed to term to assess for any potential occurrence of congenital anomalies or birth defects. All pregnancies must be followed to outcome, which will be reported on the pregnancy outcome report form. Pregnancy outcomes include: live birth (full term or pre-term); stillbirth; spontaneous abortion; and induced abortion (therapeutic or by choice).

If a spontaneous abortion occurs or a congenital abnormality/birth defect is observed, such events will be reported immediately to the sponsor or designee.

6.12 Concomitant Medication Assessments

The investigator or designee is responsible for assessing and reviewing the use of concomitant medication from the Screening visit. Details of concomitant medication use (generic name, dose, administration route, indication) are recorded on the eCRF.

All patients in the study must refrain from taking prohibited concomitant medications as outlined in Section 5.6.2.

The use of rescue medication for HAE attacks will be recorded separately.

6.13 Removal of Patients from the Study or Study Drug

Patients are free to withdraw from participation in the study at any time upon their request.

An investigator should discontinue or withdraw a patient from the study for the following reasons:

- Pregnancy
- Significant study drug non-compliance
- If any clinical (S)AE, laboratory abnormality, or other medical condition or situation occurs that negatively impacts the benefit-risk assessment in such way that continued participation in the study would not be in the best interest of the patient, e.g., worsening of HAE or disease progression requiring initiation of standard of care treatment prohibited in Section 5.6.2, based on the patient's treating physician criteria and as per local guidelines.
  The following stopping criteria for individual patients will be applied for Part I and Part II of the study:

- Any patient that develops an SAE within 48 h after study drug administration that is considered to have a reasonable possibility of a causal relationship with the study drug, will be discontinued from the study and provided treatment and follow up as appropriate.
- Any patient that develops an AE with a CTCAE grading of 3 and above within 48 h after drug administration that is considered to have a reasonable possibility of a causal relationship with the study drug, will be discontinued from the study and provided treatment and follow-up as appropriate.
- Any other AE that, in the opinion of the investigator, would substantially increase the risk for the patient during the treatment of an acute attack at home will be discontinued from the study.

- If the patient meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- Patients without a confirmed HAE Type I/II diagnosis based upon a central laboratory assessment or by genotyping of the C1-INH gene (SERPING1) should not enter Part II of the study and must be withdrawn.
- If the patient is unable to complete the assessments for three qualified attacks within a reasonable treatment period.

A patient will be considered lost to follow-up if he or she fails to return for a scheduled visit and is unable to be contacted by the study site staff.

The reason for patient discontinuation or withdrawal from the study will be recorded on the electronic case report form (eCRF).

Withdrawn patients will be requested to be available for the end-of-study visit. Patients withdrawn during Part II of the study will be requested to attend the post-attack visit after their last HAE attack that was treated with IMP (if applicable).

Randomized patients who subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

6.14 Premature Study Termination

This study will be prematurely terminated or suspended if there is sufficient reasonable cause. Patients in the study will be contacted, as applicable, and be informed of changes to the study visit schedule. Circumstances that warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients, e.g. new and unjustifiable risk and/or toxicity in risk-benefit analysis, such as occurrence of new severe or serious adverse events that have a reasonable possibility of a causal relationship with the IMP and were previously unknown in respect of their nature, severity, duration or frequency in relation to the current established safety profile; new preclinical or clinical scientific evidence becoming available during the study that could affect the patient's safety.
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements

- Data that are not sufficiently complete and/or evaluable
- Determination of futility

6.15 Appropriateness of Measurements

All efficacy, safety, and pharmacokinetic measurements in the study are widely used and generally recognized as reliable, accurate, and relevant.

7 STUDY ACTIVITIES

In the following sections all study procedures to be performed are listed by visit/period.
A concise schedule of study events is provided in Appendix 1.

Since the study will be conducted during the COVID-19 pandemic it is foreseen that some of the planned visits and assessments will be done remotely or by a visiting home nurse where feasible. However, the Screening visit and the Non-attack visit (Part I) have to be performed at the study sites.

7.1 Screening

The Screening period may take up to 28 days. It consists of an on-site visit and a remote visit. At the latter visit the investigator may confirm that the patient is eligible for the study after the results of all safety laboratory tests have become available.

The following assessments will take place at the on-site visit:

- Informed consent: the informed consent form must be signed by the patient before any study-specific procedures are performed.
- Demographics and HAE characteristics including plasma sampling for laboratory assessment of C1-INH functional level, C1q level, and C4 level
- Medical history
- Weight and height
- Physical examination
- Vital signs: blood pressure, heart rate, body temperature, and respiratory rate
- Digital 12-lead ECG
- Blood chemistry: sampling
- Pregnancy test: for women of childbearing potential and surgically sterile women, sampling for a serum pregnancy test must be performed.
- Menopause test: for post-menopausal women, serum sampling for FSH test
- Hematology: sampling
- Coagulation: sampling
- Urinalysis: sampling
- Concomitant medications: all concomitant medications used during the study are to be recorded.
- Initial ePRO device training: patient is introduced in the use of the ePRO device and capability to complete ePROs as requested is confirmed.
- Enrollment (within 28 days of informed consent):
  After written informed consent has been obtained and preliminary eligibility according to the inclusion and exclusion criteria has been established, the study site will submit documentation supporting eligibility to the sponsor or designee and obtain the sponsor's approval to enroll the patient into Part I of the study.

7.2 Part I: Non-Attack

If a patient experiences HAE attack symptoms after enrollment, but before the non-attack visit, the non-attack visit should be postponed until symptoms have resolved.

If a patient is treated with acute C1-INH treatment after screening but prior to non-attack visit, the patient can continue with the non-attack visit as long as symptoms of the HAE attack have resolved at the time of the visit.

The Non-attack visit takes place at the study site.

- Randomization: the investigator requests randomization of the patient by the IRT system. Randomization may be done at the day of the onsite visit or one day before.
- Study drug administration: the patient (in quiescent state) receives a single dose of the study drug (PHA-022121) under fasting conditions, according to their randomized treatment assignment.
- Weight: at pre-dose
- Vital signs (blood pressure, heart rate, body temperature, and respiratory rate): at pre-dose, and 1 and 4 h post-dose
- Digital 12-lead ECG (digital triplicate): at pre-dose, and 1 and 4 h post-dose
- Blood chemistry: sampling at pre-dose
- Pregnancy test: for women of childbearing potential, sampling for a serum pregnancy test must be performed at pre-dose.
- Hematology: sampling at pre-dose
- Coagulation: sampling at pre-dose
- Urinalysis: sampling at pre-dose
- Urine drug test: pre-dose
- PK plasma sampling: In approximately four patients from each dose cohort (~12 patients in total), plasma samples will be collected at pre-dose, 15 and 30 min post-dose, and 1, 2, 4, 8, and 10 h post-dose.
  From all other patients, plasma samples will only be collected pre-dose, and at 1 and 4 h post-dose.
- Continued ePRO device training: patient is fully trained in the use of the ePRO device and how to consult with the investigator or designee remotely.
- Adverse events: all AEs with onset after signing informed consent (including SAEs) are to be recorded.
- Concomitant medications: all concomitant medications used during the study are to be recorded.

7.3 Part II Home Treatment: Attack 1, Attack 2, Attack 3

Only patients with a confirmed HAE Type I/II diagnosis based upon a central laboratory assessment or by genotyping of the C1-INH gene (SERPING1) may continue into Part II of the study.

In Part II of the study, the patient self-administers blinded study drug according to the randomly assigned treatment sequence at home to treat three qualifying HAE attacks,

remotely guided by the investigator. Part II is expected to take approximately 24 weeks, but may take longer.

- 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 via remote contact in order to confirm the attack and exclude any contraindications for administering study drug (e.g. prohibited medication, prior HAE attack treated within the past 5 days).
  Study drug should not be taken for laryngeal and pharyngeal attacks (because of risk of airway involvement) or attacks associated with vomiting, swallowing difficulty, or intolerable pain. These attacks should be treated with the patient's standard medication (if possible in consultation with the investigator) or the investigator may hospitalize the patient.
- At 4 h post-treatment, the patient consults the investigator or designee remotely to assess symptom relief, safety, and any need for rescue medication. If no symptom relief within 4 h has been experienced, the patient is allowed to use any approved and prescribed acute HAE medication.
- Adverse events: all AEs with onset after signing informed consent (including SAEs) are to be recorded.
- Concomitant medications: all concomitant medications used during the study are to be recorded.
- ePRO device - daily device check and recording of HAE attacks
- ePRO device - VAS scores: pre-treatment, every 30±10 min from 0 to 4 h post-treatment, and at 5±0.5, 6±0.5, 8±1, 24±4 and 48±6 h post-treatment
- ePRO device - MSCS scores: pre-treatment, at 1±0.25, 2±0.25, 4±0.25, 6±1, 8±1, 24±4, and 48±6 h post-treatment
- ePRO device - TOS: pre-treatment, at 1±0.25, 2±0.25, 4±0.25, 6±1, 8±1, 24±4, and 48±6 h post-treatment
- ePRO device – TSQM scores: at 48±6 h post-treatment

7.4 Part II Home Treatment: Post-Attack 1, Post-Attack 2, Post-Attack 3

After each HAE attack treated with study drug, an on-site Post-attack visit will take place within 5 days post-treatment. Visits may be performed remotely if required, and only if in compliance with the protocol and local regulations.

- Vital signs: blood pressure, heart rate, body temperature, and respiratory rate
- Blood chemistry: sampling
- Pregnancy test: for women of childbearing potential, sampling for a serum pregnancy test must be performed.
- Hematology: sampling
- Coagulation: sampling
- Urinalysis: sampling

- PK plasma sampling: 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.
- Adverse events: all AEs with onset after signing informed consent (including SAEs) are to be recorded.
- Concomitant medications: all concomitant medications used during the study are to be recorded.
- HAE diary: daily device check and recording of potentially relevant HAE events not treated with IMP (throughout Part II of the study; starting after the Non-attack visit)

7.5 End of Study

The end-of-study visit will take place remotely 10±5 days post-treatment of the last attack and if possible in case of withdrawal from the study.

- Adverse events: all AEs with onset after signing informed consent (including SAEs) are to be recorded.
- Concomitant medications: all concomitant medications used during the study are to be recorded.

This visit may be waived if patients continue in another clinical study with PHA-022121 conducted by the Sponsor.

8 QUALITY CONTROL AND ASSURANCE

Procedures relevant to the clinical management of this study are either described in the applicable standard operating procedures (SOPs) of Pharvaris or their representatives. In accordance with Pharvaris SOPs, this study may be subject to independent QA GCP audits at the study sites.

Pharvaris will not allow any waivers to the applicable protocol throughout the conduct of the study. An unplanned excursion from the protocol not implemented or intended as a systematic change, which could not be justified as necessary to protect the safety, rights, or welfare of the patients, will be reported and followed up according to the local IEC/IRB requirements.

Investigators and other study personnel will be appropriately trained by the sponsor or its designee. The study will be monitored by sponsor-independent clinical monitors (see also Section 10.6).

To ensure the collection of accurate, consistent, and reliable data, laboratory tests will be done at central laboratories, and ECG-reading will be centralized.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

The planned analyses are summarized below. Any deviations from these analyses will be justified in the clinical study report (CSR). Details of the planned analyses will be described in the statistical analysis plan (SAP). All analyses will be carried out using SAS® software version 9.4 or higher.

Unless otherwise specified, all analyses for efficacy endpoints will be based on assessment results of HAE attacks that are treated with IMP. For efficacy analyses described in this section, post-treatment results refer to the assessment results collected from HAE attacks after they are treated with IMP.

For the analyses of primary and key secondary endpoints for the medium and high doses, multiplicity control procedure will be applied to control the overall type 1 error rate at a 5% significance level for a 2-sided test. The low dose will be included in the analysis for evaluating dose response but will not spend α in the multiplicity control procedure; the nominal p values for testing the 10-mg dose will be provided. A graphical multiple testing procedure (Bretz et al. 2011) will be used to control the overall type 1 error rate in testing in the primary and key secondary endpoints for the medium and high doses. Details on the multiplicity control procedure, including the ordering of the key secondary endpoints and the selection of weight that determines the fraction of local α from a rejected hypothesis to subsequent hypotheses will be specified in the SAP.

9.2 Determination of Sample Size

The study is powered for the expected treatment effect on the VAS-3 score at 4 h post-treatment, assuming a treatment difference between PHA-022121 and placebo of 10 in VAS-3 score change from pre-treatment at 4 h post-treatment with a standard deviation of 11, based on the previous HAE studies with oral on-demand (Longhurst et al. 2019) and with icatibant treatment (Lumry et al. 2011). With the cross-over design, there are nine different treatment sequences comparing twice the same active dose and placebo within the same patient. Assuming a very low correlation of 0.2 between the within-patient measurements on the different attacks, a total of 72 randomized patients, i.e. 8 patients per sequence randomized to the nine sequences, will provide approximately 90% power to detect a difference of 10 in VAS-3 score change from pre-treatment at 4 h post-treatment between a PHA-022121 treatment group (medium dose or high dose) and the placebo group at a conservative significance level of 2.5% for a 2-sided test, and the power will reach 94% for a significance level of 5% for a 2-sided test. This sample size is adjusted to take into account a 20% attrition rate for evaluable attacks and 5% of attacks that will be treated with rescue medication within 4 h post-treatment.

The study is planned to be conducted at approximately 35 study sites across 12-15 countries. On average, two patients per study site are projected to be enrolled.

9.3 Analysis Sets

The following analysis sets will be analyzed in the study:

- Full Analysis Set, defined as all patients enrolled and randomized in the study
- Modified Intent-To-Treat (mITT) Analysis Set, defined as all randomized patients who had at least one IMP-treated (blinded PHA-022121 or placebo) HAE attack and who had non-missing VAS results at both pre-treatment and at least one post-treatment time point of that attack.
- Safety Analysis Set, defined as all randomized patients who received any dose of study drug
- Pharmacokinetic Analysis Set, defined as all patients for whom PK parameters can be estimated

9.4 Demographics and Baseline Characteristics

The three doses will be compared on demographics and baseline characteristics, using descriptive statistics.

Descriptive statistics will be tabulated as follows:

- Categorical data will be summarized in frequencies and percentages.
- Continuous data will be summarized using number of non-missing values (n), mean, standard deviation, median (25th, 75th), minimum, and maximum values.

9.5 Primary Endpoint

The primary endpoint of the study is the change in the 3-symptom composite visual analogue scale (VAS-3) score from pre-treatment to 4 h post-treatment. The VAS-3 score is the mean of the patient-reported VAS scores of the three major HAE symptoms: skin swelling, skin pain, and abdominal pain. It was applied earlier in a large Phase III study investigating the efficacy of icatibant in patients with acute HAE attacks (Lumry et al. 2011).

All efficacy analyses will be performed on the mITT Analysis Set. All statistical tests are carried out 2-sided. The primary endpoint will be analyzed using a mixed model for repeated measures (MMRM) allowing within-patient and between-patient comparisons. All available composite VAS-3 score data measured on the different time points before intake of rescue medication (if applicable), will be used to estimate the least squares mean difference for VAS-3 change at 4 h between PHA-022121 and placebo. The MMRM includes the fixed effects of treatment, time, treatment-by-time interaction, period, and pre-treatment VAS-3 score. No carry-over effect is assumed. The MMRM assumes Missing at Random. This hypothetical strategy for handling the intercurrent event “rescue medication intake” would estimate the treatment effect of PHA-022121 in change in VAS-3 score at 4 h post-treatment, as if all patients had remained on planned treatment regimen throughout each period and had not taken rescue medication before 4 h post-treatment. Other sensitivity analyses, including an alternative imputation method and another intercurrent event handling strategy, may be employed. Details will be included in the SAP.

The testing procedure for the primary endpoint and key secondary endpoints with multiplicity control is described in Section 9.1.

In addition, summary statistics of the changes from pre-treatment at the different post-treatment time points will be provided, for the different periods and for the different doses of PHA-022121.

9.6 Secondary Endpoints

9.6.1 Secondary Efficacy Endpoints

The key secondary efficacy endpoints of the study are as follows:

- Time to onset of symptom relief assessed by a ≥30% reduction in VAS-3 score from the pre-treatment score.
- Time to almost complete or complete symptom relief by VAS-3 score.
  Almost complete symptom relief is defined as all 3 individual VAS scores of the VAS-3 having a value ≤ 10.
  Complete symptom relief is defined as all 3 individual VAS scores of the VAS-3 having a value of 0.
- Time to a ≥50% reduction in VAS-3 score from the pre-treatment score.
- Change in MSCS score from pre-treatment to 4 h post-treatment
- TOS at 4 h post-treatment

Other secondary efficacy endpoints of the study are as follows:

- Time to onset of primary symptom relief assessed by a 30% reduction in the VAS for the primary symptom, and time to 50% reduction in the VAS for the primary symptom.
  The primary symptom is determined as follows. The symptom with the highest pre-treatment VAS score is considered the primary symptom. If skin pain and abdominal pain tie at pre-treatment, abdominal pain is taken forward as primary. If skin pain and skin swelling tie, then skin pain is taken forward as primary. If all are tied, abdominal pain would be taken forward as primary.
- Proportion of IMP-treated attacks requiring HAE rescue medication within 12 h, within 24 h, and within 48 h post-treatment
- Time to first HAE rescue medication use for IMP-treated attacks, if applicable.
  An IMP-treated attack refers to an attack treated with blinded IMP (study drug).
- Change in the VAS score for individual symptoms (skin pain, skin swelling, abdominal pain) from pre-treatment to 4 h post-treatment
- Change in MSCS score from pre-treatment to 24 h post-treatment
- TOS at 24 h post-treatment
- TSQM scores at 48 h post-treatment

All secondary efficacy endpoints will be analyzed on the mITT Analysis Set. Only IMP-treated HAE attacks are considered for these endpoints. For key secondary efficacy endpoints, multiplicity control procedure will be applied as described in Section 9.1. For other secondary efficacy endpoints, analyses are descriptive in nature and nominal p-values will be provided as applicable.

Each of the time-to-event endpoints will be modeled using a marginal Cox proportional hazards model (CPHM) with a robust variance-covariance estimator to account for the

within-patient correlation. Patients who have not had the event of interest at the time of the analysis (i.e. 48 h time period) will be censored. Patients will also be censored at the time of intake of rescue medication (except for the endpoint Time to first HAE rescue medication). Estimated hazard ratio of each PHA-022121 dose versus placebo with 95% CI and p-value will be provided from the CPHM.

For the endpoint of proportion of study drug treated attacks requiring HAE rescue medication, which is based on binary outcome data, the generalized estimating equation (GEE) with a logit link (Jones and Kenward 2014) will be used to analyze the proportion of IMP treated attacks requiring HAE rescue mediation. The model will include treatment, period, and pre-treatment VAS-3 score as fixed effects. The estimated odds ratio of each PHA-022121 dose versus placebo will be provided with 95% CI and p-value.

For continuous endpoints including change in MSCS score, TOS, change of individual VAS score at 4 h, and TSQM score, analyses based on MMRM will be carried out similarly to the analysis for the primary endpoint.

In addition, descriptive summary statistics of the secondary endpoints will also be provided.

9.6.2 Safety Endpoints

The safety endpoints of the study are:

- Treatment-emergent adverse events (TEAEs), treatment-related TEAEs, and treatment-emergent serious adverse events (TESAEs), and treatment-related TESAEs
- Clinical laboratory tests
- Vital signs
- ECGs

AEs will be coded with MedDRA.

Safety endpoints will be summarized by actual treatment received using the Safety Analysis Set. Frequencies and percentages will be provided.

If applicable, descriptive statistics of safety related baseline assessments will be tabulated combined with those of their repeat assessments during the study (e.g., safety laboratory, vital signs, ECG), by visit/time point.

9.6.3 Pharmacokinetic Endpoints

The pharmacokinetic endpoints of the study are:

- Pharmacokinetic parameters based on plasma profiles of PHA-022121 and metabolites

Based on the individual concentration-time data, using the actual sampling times, the following PK parameters will be derived for PHA-022121 and its metabolites (only for those patients from whom a complete PK profile is obtained in Part I) using non-compartmental analysis:

C_{max}, t_{max}, AUC_{0-12h}, AUC_{0-24h}, AUC_{last}, AUC_{inf}, $t_{1/2}$, V_z/F (PHA-022121 only) and CL/F (PHA-022121 only). Other PK parameters may be estimated as appropriate for exploration of the data.

For the PK parameters, definitions and methods of calculations are:

C_{max}	The maximum observed analyte concentration;
t_{max}	The actual sampling time to reach the maximum observed analyte concentration;
AUC_{0-12h}	AUC from time 0 to 12 h post dosing (non-below quantification limit [BQL]) concentration, calculated by the linear-linear trapezoidal summation;
AUC_{0-24h}	AUC from time 0 to 24 h post dosing (non-below quantification limit [BQL]) concentration, calculated by the linear-linear trapezoidal summation;
AUC_{last}	AUC from time 0 to the time of the last measurable (non-below quantification limit [BQL]) concentration, calculated by the linear-linear trapezoidal summation;
AUC_{inf}	AUC from time 0 to infinite time, calculated as $AUC_{last} + C_{last}/\lambda_z$, where Clast is the last observed measurable (non-BQL) concentration; extrapolations of more than 20 % of the total AUC are reported as approximations;
$t_{1/2}$	Apparent terminal elimination half-life, calculated as $0.693/\lambda_z$;
V_z/F	Apparent volume of distribution, based on terminal phase after a single dose;
CL/F	Total apparent systemic clearance of drug after extravascular administration, calculated as $Dose/AUC_{inf}$;

The following requirements should be met for an acceptable calculation of $t_{1/2}$, λ_z and AUC_{inf} (and related parameters):

a. At least 3 data points used in the calculation (not including t_{max}), otherwise $t_{1/2}$ and AUC_{inf} (and related parameters) will be reported as not assessable.
b. Coefficient of determination (R^2_{adj}) is at least 0.90.

If requirement b. is not met, $t_{1/2}$, λ_z and AUC_{inf} (and related parameters) will be reported as approximations.

Dose normalization will be done by dividing the relevant PK parameters by the dose.

Actual sampling times will be checked for major aberrations. In case a major aberration occurs for an actual sampling time of > 20% deviation from scheduled time, this plasma concentration will be excluded from descriptive statistics in the plasma concentration-time table.

Other PK parameters may be estimated as appropriate for exploration of the data.

For those patients from whom only sparse samples have been obtained, the PK parameters will be determined using the existing population PK model for PHA-022121.

9.7 Interim Analysis

No interim analyses are planned.

9.8 Study Analyses

A Primary Analysis (PA) may be performed before all enrolled patients have experienced 3 qualified attacks, because some patients may be unable to complete the assessments for 3 qualified attacks within a reasonable treatment period.

If a PA is conducted, all the formal statistical tests for the efficacy endpoints as specified in Section3.1 9.5 and Section 9.6 will be performed for the PA. Following the PA, a Final Analysis (FA) will be conducted at the very end of the study once most patients have completed the assessments for 3 qualified attacks or have been discontinued from the study. The FA will include all data accumulated from the beginning of the study through the end of the entire study. All statistical analyses at the FA will be regarded as descriptive in nature.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

Coordinating Investigator:	[redacted] (Berlin, Germany)
Investigators:	Names and contact details of participating investigators are available in the trial master file.
Sponsor:	Pharvaris Netherlands BV J.H. Oortweg 21 2333 CH Leiden The Netherlands
Medical Monitor:	Medpace Inc (Cincinatti, US)
Study Monitoring:	Medpace Inc (Cincinatti, US)
Randomization and IMP Allocation:	Medpace Inc (Cincinatti, US)
Drug supplies:	Catalent
Central Laboratory (Safety):	Medpace Inc (Cincinatti, US)
Central Laboratory (Pharmacokinetics):	Ardena Bioanalysis (The Netherlands)
Data Management:	Medpace Inc (Cincinatti, US)
Statistician (protocol):	[redacted] (Sponsor)
Statistician (analysis):	Medpace Inc (Cincinatti, US)
Safety Management:	Medpace Inc (Cincinatti, US)
IDMC:	Names and contact details of IDMC members are available in the trial master file.

10.2 Independent Ethics Committee (IEC) or Institutional Review Board (IRB) Approval

In accordance with Good Clinical Practice (GCP), the protocol, informed consent form(s), recruitment materials, and all patient materials will be submitted to appropriate IECs/IRBs for review and approval. Approval of both the protocol and the ICF must be obtained before a patient is enrolled at any site. Any substantial amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. Non-

substantial amendments, e.g., containing administrative changes, will only be submitted to the IEC/IRB for notification. All changes to the consent form must be IEC/IRB approved.

10.3 Ethical Conduct of the Study

The study will be conducted in accordance with this study protocol, the International Council for Harmonisation GCP (ICH GCP E6[R2]), and applicable local laws and regulations. Compliance with ICH-GCP provides public assurance that the rights, safety and well-being of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the IEC/IRB, except where necessary to eliminate an immediate hazard to the patients. All relevant personnel involved in the conduct of this study have completed ICH GCP training.

10.4 Patient Information and Consent

At the Screening visit, a signed informed consent form (ICF) must be obtained from each patient prior to performing any study-related procedures. Each patient should be given both verbal and written information describing the nature and duration of the clinical study.

The ICF must describe in detail the study drug treatment, study procedures, and risks of study participation. The ICF and any other written study material provided to the patient has to be approved by an IEC/IRB before patient enrollment.

The investigator or designee is responsible for explaining the nature and purpose of the study as well as other study-related matters to patients, using the written information, and for obtaining their full understanding and written consent to participate in the study at their own free will. No patient may be subjected to undue influence, such as compulsory enrollment into a study. The investigator or designee who provided explanations to the patient should sign and date the ICF as well as the patient. The patient should receive a copy of the signed ICF and the original must be filed by the investigator. The process and communication of the consent should be documented on medical records of the patient. The signed ICFs will be retained by the investigator and made available upon request (for review only) to the study monitor and auditor.

The language and expressions used in the written information should be as plain and understandable as possible. Patients should be given the opportunity to ask questions and receive satisfactory answers to the inquiry and should have adequate time to decide whether or not to participate in the study. Written information should not contain any language or content that causes the patient to waive or appears to waive any legal rights, or that releases/mitigates or appears to release/mitigate the study site, the investigator, other study personnel, collaborators, or the sponsor from liability for negligence.

If an ICF is updated as a result of a substantial protocol amendment, the new IEC/IRB-approved version will be used to re-consent currently enrolled patients and must be provided to newly enrolled patients prior to their entry into the study.

10.5 Patient Confidentiality

The information to be obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is strictly prohibited. Upon the patient's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her medical welfare.

Pharvaris will use the information obtained during the conduct of this study for the development of PHA-022121. The investigator is obliged to provide Pharvaris or its designees with complete test results and all data collected in this study, as described in this protocol.

Access to stored samples will be limited. Samples and data will be stored using codes assigned by the sponsor. The code key linking the patient name to the research records will be kept by the investigator and may not be released outside the study site. The coded data does not include any identifying information of the patient, such as name or address. Data will be kept in password-protected computers. Only investigators, the sponsor and affiliates or contracted parties will have access to the coded samples and data.

Data generated by this study must be available for inspection by representatives of the European Medicines Agency (EMA), the Food and Drug Administration (FDA), Health Canada, and any other competent authority. Even though individuals involved in the study, such as study monitors and auditors, may get to know matters related to patients' privacy due to direct access to source documents, or from other sources, they may not disclose these contents to third parties.

10.6 Study Monitoring

Pharvaris is responsible for monitoring the clinical study to ensure that patients' human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and any study-specific documents (e.g., CRF completion guidelines), to GCP ICH E6(R2), and to applicable regulatory requirements, and that study data reported by the investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The sponsor or designee will determine the extent and nature of the monitoring and assign sponsor-independent clinical monitors who are GCP-trained. The sponsor will provide the monitors with adequate training on the study protocol. The study will be monitored in accordance with the clinical study monitoring plan, which specifies the monitoring tasks.

Monitoring visits or remote monitoring will be conducted to confirm that e.g.:

- The investigational team is adhering to the study protocol.
- Informed consent has been obtained from all patients.
- AEs/SAEs are being reported as required.
- Data are being accurately recorded in the CRFs.
- Study drug is being stored correctly and drug accountability is being performed on an on-going basis.
- Facilities are, and remain, acceptable throughout the study.

- The investigator and site are receiving sufficient information and support throughout the study.

10.7 Case Report Forms and Study Records

A validated EDC system will be used for entry of the data by the investigator into study-specific eCRFs designed by the Sponsor or its designee. All information recorded on eCRFs for this study must be consistent with the patient's source documentation. The investigator will attempt to obtain specific source documents for all data recorded in the eCRF (e.g. eligibility criteria, medical history). Where there is no specific source available in the medical records, the investigator will attempt to obtain specific, written source documents from previous treating physicians. Only when no written source is available, may the investigator obtain responses from the patient him/herself during the intake interview(s), record these into the source documents and enter the data into the eCRF.

Initial data entry and any changes to the data will be made only by authorized users, and data entries and changes will be captured in an electronic audit trail. An explanation of any data change should be recorded.

A validated ePRO system including ePRO device will be used for entry of the patient reported outcome data by the patient into a study-specific patient diary designed by the Sponsor or its designee. ePRO data will be considered source data.

10.8 Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be assembled prior to the study to review accumulating safety data on a regular basis (and ad-hoc in case of unexpected safety issues) throughout the study. The review of safety data will be performed according to an IDMC charter, which will be prepared before data collection starts. All relevant data available from this study will be provided for these reviews. The IDMC will consist of independent experts external to the study.

The responsibilities of the IDMC include:

- to minimize the exposure of patients to an unsafe therapy or dose
- to make recommendations for changes in study processes where appropriate
- to advise on the need for dose adjustments because of safety issues
- to endorse continuation of the study if warranted

Further details on the membership, responsibilities and working procedures of the IDMC are described in the IDMC charter, provided as a separate document in the study file.

10.9 Protocol Violations/Deviations

The following deviations from the protocol will be considered protocol violations:

- Deviations from the inclusion and exclusion criteria
- Deviations from concomitant medication restrictions

- Deviations from any other protocol requirements that result in a significant added risk to the patient or their rights, or have an impact on the quality of the data collected or the outcome of the study.

Protocol violations will be reported in the final clinical study report.

10.10 Access to Source Documentation

The investigator and the study site must accept monitoring and auditing by Pharvaris or their representatives as well as inspections from the IEC/IRB and relevant regulatory authorities. Source documents may be reviewed remotely during monitoring, using regulatory-compliant and documented computerized systems, when agreed upon with the investigator study site (and study patients), as applicable by local regulations. In these instances, the site must provide all study-related records, such as source documents when they are requested by the monitors and auditors, the IEC/IRB, or regulatory authorities. The confidentiality of the patients' identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access. In accordance with Pharvaris procedures, this study may be subject to an independent QA GCP audit at the study sites.

For France only:

If remote source data verification is needed in France, the study site will provide the Clinical Research Associate, under the responsibility of the Principal Investigator, with access to the source documentation through a secure video conference platform. The remote source data verification will be conducted using a validated and encrypted videoconference system (including, but not limited to, WebEx, Zoom, Microsoft Teams, etc.), as well as a Webcam that will allow for the Clinical Research Associate to view the source documents in real-time only (i.e., no file sharing will take place). To ensure the privacy and rights of the study subject are maintained, the Clinical Research Associate will ensure that no other individuals have a view of their screen or access to their laptop while the remote source data verification is ongoing and will only be provided with source data from subjects participating in the clinical study.

10.11 Data Generation and Analysis

The investigator or designee must enter all protocol-required data in the available electronic case report form (eCRF), which is a validated system. In the interest of collecting data in the most efficient manner, the investigator or designee should enter data into the eCRF as soon as possible after the patient's visit. Laboratory results from the central laboratory will be electronically integrated with the EDC data. The eCRFs and any supporting documents should be available for retrieval at any given time. The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them. If any inconsistency is detected on the eCRFs, the monitor must query the investigator and the investigator should make corrections/additions in the eCRF or provide an explanation within the eCRF system. The monitor should verify the corrected data with source documents to confirm that there are no inconsistencies between them, and also check that appropriate records on the corrections/additions of data are maintained.

Patients will be provided with electronic diaries (ePRO) to carry with them at all times in order to collect information on attack locations and severity in real time. The ePRO device is a validated "21 CFR Part 11 compliant" electronic data capture tool.

For screening failures, defined as patients who signed informed consent but were not eligible for study participation, relevant data will be collected in the eCRF.

The investigator is responsible to ensure that all data in the eCRFs are accurate and complete, and that all entries are verifiable with source documents. Source data must be available at the site to document the existence of the study patients, and to substantiate the integrity of study data collected (see also Section 10.7). In case a patient is prematurely discontinued, the reason for discontinuation must be documented in the source documents. Study data collected from a patient before study discontinuation will still be used in the overall data analysis.

Data management will be coordinated by a delegated CRO, in accordance with their SOPs for data management. All study specific processes and definitions will be described in the data management plan. Coding of medical terms will be performed using the Medical Dictionary for Regulatory Activities (MedDRA) and medications will be coded with the WHO Drug Dictionary (WHO-DD).

10.12 Retention of Data

All records (data and documents) relating to the study that are generated by or collected by the CRO will be filed in a trial master file (TMF) according to ICH-GCP. The TMF will be transferred to Pharvaris after the study and will be archived for at least 25 years. Also, all records relating to the study that are generated by or collected by the investigators will be filed in an investigator site file (ISF) according to ICH GCP. Investigators will retain the ISF for at least 25 years. The investigators will also retain source documents that are under their control for at least 25 years. All medical records will be retained by the medical center according to their own internal procedures.

10.13 Publication and Disclosure Policy

All data generated from this study are the property of Pharvaris and shall be held in strict confidence along with all information provided by Pharvaris. Except as provided through written agreement between Pharvaris, independent analysis and/or publication of these data by the investigator or any member of his/her staff is not permitted without prior written consent of Pharvaris. Such consent will not be withheld unreasonably. Pharvaris is in agreement with the principle of full disclosure of clinical trial results.

11 REFERENCE LIST

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Appendix 1 Schedule of Events

	Screening[1]		Part I	Part II Home Treatment		
			Non-Attack	Attack 1 Attack 2 Attack 3	Post-Attack 1 Post-Attack 2 Post-Attack 3	End of Study
	On-site	Remote	On-site	Remote	On-site[2]	Remote [3]
Informed consent [4]	X					
Enrollment [5]		X				
Randomization			X			
Demographics and HAE characteristics [6]	X					
Medical history	X					
Weight and height [7]	X		X [7]			
Physical examination	X					
Vital signs [8]	X		X [9]		X	
12-lead ECG (digital triplicate)	X		X[9]			
Blood chemistry [10]	X		X [11]		X	
Pregnancy test [10] [12]	X		X [11]		X	
Menopause test [10] [13]	X					
Hematology [10]	X		X [11]		X	
Coagulation [10]	X		X [11]		X	
Viral testing [10]	X					
Urinalysis [10]	X		X [11]		X	
PK plasma sampling			X [14]		X [15]	
Study drug administration			X [16]	X [17]		
ePRO device training	X		X			
Adverse events [18]	◄			———		►
Concomitant medications	◄			———		►
ePRO: HAE diary [19]			◄	———	►	
ePRO: VAS scores [20]				X		
ePRO: MSCS scores [21]				X		
ePRO: TOS [22]				X		
ePRO: TSQM scores [23]				X		

For table footnotes see next page.

[1] Screening period may take up to 28 days from ICF signature until enrolment.
[2] Within 5 days post treatment. Visits may be performed remotely if required, and only if in compliance with the protocol and local regulations.
[3] 10±5 days post-treatment of the last attack
[4] Informed consent form must be signed by the patient before any study-specific procedures are performed.
[5] After preliminary eligibility according to the inclusion and exclusion criteria has been established, the study site will submit documentation supporting eligibility to the sponsor or designee and obtain the sponsor's approval to enroll the patient. The patient will be informed that he/she is eligible for participation and an appointment for the Non-attack visit will be made.
[6] Including plasma sampling for laboratory assessment of C1-INH functional level, C1q level, and C4 level
[7] Height is only measured at Screening.
[8] Blood pressure, heart rate, body temperature, and respiratory rate
[9] Pre-dose, and 1 and 4 h post-dose
[10] For details see Table 3 in section 6.8.1.
[11] Pre-dose; urinalysis including urine drug test
[12] For women of childbearing potential and surgically sterile women, a serum pregnancy test must be performed.
[13] For postmenopausal women, serum sampling for a FSH test must be performed.
[14] In approximately four patients from each dose cohort, plasma samples will be collected at pre-dose, 15±5 and 30±5 min post-dose, and 1h±10min, 2h±10min, 4h±15min, 8h±15min, and 10h±15min post-dose (full PK profile). From all other patients, plasma samples will only be collected pre-dose, and at 1h±10min and 4h±15min post-dose.
[15] PK 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.
[16] The patient (in quiescent state) receives a single dose of the randomized study drug (PHA-022121) at the study site under fasting conditions.
[17] Attack treatment: Before administration of study drug the investigator or designee must confirm eligibility of the attack for study drug treatment via a remote consultation. The study drug should be taken when at least one attack symptom (skin pain, skin swelling, or abdominal pain) becomes of moderate intensity (VAS score ≥ 30). When the attack reaches this VAS intensity threshold, study drug should preferably be taken during the remote contact with the investigator or designee. If the patient cannot take the study drug within 3 h after reaching the VAS intensity threshold, the attack does not qualify for study drug treatment and should be treated with the patient's standard HAE medication. In addition, treatment of the attack should happen within 6 h after onset of symptoms at any location. If the study drug cannot be administered within 6 h after onset of symptoms, the attack does not qualify for study drug treatment and should be treated with the patient's standard HAE medication. Any symptoms involving the internal head and neck, regardless of intensity, also render an attack non-qualifying for treatment with study drug and should be treated with the patient's standard HAE medication. At 4 h post study drug treatment, the patient will consult with the investigator or designee remotely again to assess symptom relief, safety, and any need for rescue medication.
[18] All AEs with onset after signing informed consent (including SAEs) are to be recorded. Last follow-up for AEs will occur 10±5 days after the last attack treatment.
[19] Daily device check and recording of potentially relevant HAE events not treated with IMP (throughout Part II of the study; starting after the Non-attack visit)
[20] VAS score: pre-treatment, every 30±10 min from 0 to 4 h post-treatment, and at 5±0.5, 6±0.5, 8±1, 24±4 and 48±6 h post-treatment
[21] MSCS score: pre-treatment, and at 1±0.25, 2±0.25, 4±0.25, 6±1, 8±1, 24±4, and 48±6 h post-treatment
[22] TOS: pre-treatment, and at 1±0.25, 2±0.25, 4±0.25, 6±1, 8±1, 24±4, and 48±6 h post-treatment
[23] TSQM scores: at 48±6 h post-treatment

Appendix 2 Sponsor Signature

Study Title:	A Phase II, double-blind, placebo-controlled, **R**andomized, cross-over, dose-ranging study of oral PHA-022121 for **A**cute treatment of angioedema attacks in **P**atients with hereditary angioedema due to C1-**I**nhibitor **De**ficiency type I and II
Acronym:	RAPIDe-1
Study Number:	PHA022121-C201
Original Protocol:	Version 1.0 (18 August 2020)
Amendment 7:	Version 3.0 (25 April 2022)

This clinical study protocol was subject to critical review and has been approved by the sponsor.

Signed: _____ Date: _____

[redacted]
Executive Director
Clinical Development
Pharvaris Netherlands BV

Appendix 3 Principal Investigator Signature

Study Title:	A Phase II, double-blind, placebo-controlled, **R**andomized, cross-over, dose-ranging study of oral PHA-022121 for **A**cute treatment of angioedema attacks in **P**atients with hereditary angioedema due to C1-**I**nhibitor **De**ficiency type I and II
Acronym:	RAPIDe-1
Study Number:	PHA022121-C201
Original Protocol:	Version 1.0 (18 August 2020)
Amendment 7:	Version 3.0 (25 April 2022)

I have read all pages of this clinical study protocol for which Pharvaris Netherlands BV is the sponsor. I agree that it contains all the information required to conduct this study. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with the ICH GCP guidelines (ICH E6[R2]) and the provisions of the Helsinki Declaration. I will also ensure that all relevant members of my staff have access to copies of this protocol, the ICH GCP guidelines and the Helsinki Declaration to enable them to work in accordance with the provisions of these documents."

Signed:_____ Date:_____

Printed name: …….

Affiliation: …….

……

……

Protocol Amendment 7: PHA022121-C201

Study Title:	A Phase II, double-blind, placebo-controlled, **R**andomized, cross-over, dose-ranging study of oral PHA-022121 for **A**cute treatment of angioedema attacks in **P**atients with hereditary angioedema due to C1-**I**nhibitor **De**ficiency type I and II
Acronym:	RAPIDe-1
Study Number:	PHA022121-C201
Study Phase:	Phase II
Product Name:	PHA-022121 soft capsules (PHVS416)
Indication:	Hereditary Angioedema
EudraCT Number:	2020-003445-11
Investigators:	Multicenter
Sponsor:	Pharvaris Netherlands B.V. J.H. Oortweg 21 2333 CH Leiden The Netherlands
Sponsor Contact:	clinical@pharvaris.com
Sponsor Representative(s):	[redacted] Chief Medical Officer [redacted] Executive Director Clinical Development

	Date	Protocol version
Original Protocol:	18 August 2020	1.0
Amendment 1 (UK only):	22 December 2020	1.1
Amendment 2 (Germany only):	27 January 2021	1.2
Amendment 3 (France only):	08 March 2021	1.3
Amendment 4 (Czech Republic only):	12 March 2021	1.4
Amendment 5 (global):	08 April 2021	2.0
Amendment 6 (France only):	28 June 2021	2.1
Amendment 7 (global):	25 April 2022	3.0

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1 SUMMARY AND JUSTIFICATION OF CHANGES

The protocol was amended to include brief results from the most recent non-clinical and clinical studies, to modify the secondary efficacy endpoints, to update the statistical methods, to make a change to the AE causality text per a request by a regulatory authority, and to incorporate changes from a previous amendment prepared for sites in France (Amendment 6, version 2.1).

Other changes made pertain to:

- Waiving the end-of-study visit if patients continue in another clinical study with PHA-022121 conducted by the Sponsor
- Extending the duration of participation and overall study if some patients need longer than 24 weeks to complete assessments for 3 qualifying HAE attacks
- Allowing inclusion of patients with positive hepatitis B serology if they have normal liver function tests and no signs of active liver disease
- Allowing bilirubin elevation at screening if elevation is due to Gilbert's syndrome
- Removing the prohibition on concomitant medications that are metabolized by CYP3A4
- Defining clinically significant as it pertains to abnormal findings from safety assessments
- Indicating that Part II is subject to the same stopping rules as Part I
- Clarified the use of the ePRO device for recording HAE attacks
- Adding a new section for "Study Analyses" to describe the circumstance under which the Sponsor may elect to perform a Primary Analysis and a Final Analysis

Material changes are summarized in the table below. Administrative changes, editorial changes, and those made to correct formatting, grammatical, or typographical errors are not itemized.

None of the revisions are judged to have a clinically significant impact on the safety of patients or the integrity of the study.

Protocol Amendment		
Summary of Changes from Protocol Version 2.0 (08 April 2021)		
Amendment Number: **7**	**Amendment Date:** **25 April 2022**	**Scope:** **Global**
Change	**Rationale**	**Location(s) Affected**
Removed the following from the key secondary efficacy objectives/endpoints: • The proportion of attacks requiring the use of HAE rescue medication.	To focus the key secondary objectives/endpoints on the assessment of symptom improvement for HAE attacks; however, the proportion of attacks requiring rescue medication use is being retained as a secondary efficacy endpoint	Synopsis, Section 2.2, Section 3.1, Section 9.6.1

Protocol Amendment		
Summary of Changes from Protocol Version 2.0 (08 April 2021)		
Amendment Number: 7	**Amendment Date: 25 April 2022**	**Scope: Global**
Change	**Rationale**	**Location(s) Affected**
Added a statement that the end-of-study visit may be waived if patients continue in another clinical study with PHA-022121 conducted by the Sponsor.	To avoid an unnecessary delay in treatment should the patient qualify for another PHA-022121 study	Synopsis, Section 3.1, Section 7.5
Added text to indicate that individual patient participation and overall study duration may be longer than previously specified	To allow for some patients who need longer than 24 weeks to complete assessments for 3 qualifying HAE attacks	Synopsis, Section 3.3, Section 7.3
To specify that for inclusion in the Modified Intent-to-Treat Analysis Set, the patient must have a pre-treatment VAS assessment and at least one post-treatment assessment for the qualifying HAE attack.	Changes in VAS scores cannot be analyzed if the pre-treatment assessment and/or all post-treatment assessments are missing.	Synopsis, Section 9.3
Added the following as a key secondary efficacy endpoint: • Time to onset of symptom relief assessed by a ≥30% reduction in VAS-3 score from the pre-treatment score Added/further defined the following as other secondary efficacy endpoints: • Time to onset of primary symptom relief assessed by a 30% reduction in the VAS for the primary symptom, and time to a 50% reduction in the VAS for the primary symptom • Proportion of IMP-treated attacks requiring HAE rescue medication within 12 h, within 24 h, and within 48 h post-treatment	Since patients treat HAE attacks early and in the home setting, baseline HAE attack severity is relatively moderate; thus, for some attacks a 50% reduction in VAS-3 would achieve almost complete symptom resolution. Therefore, based on the feedback from a recent advisory board meeting, the key opinion leaders believe that the onset of symptom relief should be defined as a reduction of at least 30% in VAS-3. The definition for onset of symptom relief is being updated to a reduction of ≥30% in VAS-3, and time to 50% reduction in VAS-3 is being retained as one of the key secondary efficacy endpoints.	Synopsis, Section 3.1, Section 9.6.1 Section 3.1, Section 9.6.1

Protocol Amendment		
Summary of Changes from Protocol Version 2.0 (08 April 2021)		
Amendment Number: 7	**Amendment Date: 25 April 2022**	**Scope: Global**
Change	**Rationale**	**Location(s) Affected**
Multiplicity control procedure will be applied only to the medium and high dose groups	The three dose levels used in this study were chosen based on the data from the bradykinin challenge in healthy individuals performed in the Phase 1 study PHA022121-C001 (see Section 3.2 Rationale for Study Design and Control Group of the protocol for details). All three dose levels used in this study are expected to be as effective as one or two 30-mg doses of icatibant, which is the approved dose of icatibant. The 20- and 30-mg dose levels of PHA-022121 were projected to provide a duration of efficacy comparable to that of two injections of icatibant. At this point in the study with 57 patients having received at least one dose of PHA-022121 and ~110 attacks having been treated with blinded study treatment (PHA-022121 or placebo), PHA-022121 appears to be well tolerated and no significant safety issue has been observed. Therefore, the Sponsor proposes not to spend α in the multiplicity control procedure for the 10-mg dose to maximize the chance of meeting the primary endpoint and all the key secondary endpoints with the 20- and 30-mg doses. The nominal p-values for testing the 10-mg dose will be provided.	Synopsis, Section 9.1
Updated the text pertaining to the approval status of berotralstat with recent marketing authorization approvals in the European Union and the United Kingdom	Incorporated this change from a prior protocol amendment prepared for sites in France (Amendment 6, version 2.1).	Section 1.2.2
Updated the nonclinical toxicology and potential risk sections with information from the completed 6- and 9-month GLP studies	To provide the most recently available nonclinical safety data to the investigators	Section 1.2.3.1, Section 1.3.1

Protocol Amendment		
Summary of Changes from Protocol Version 2.0 (08 April 2021)		
Amendment Number: 7	**Amendment Date: 25 April 2022**	**Scope: Global**
Change	**Rationale**	**Location(s) Affected**
Updated the clinical research section with the most recent information from completed Phase 1 studies	To provide the most recently available nonclinical and clinical safety data to the investigators	Section 1.2.3.2
Updated the potential risk section with brief results from the drug-drug-interaction study in humans	To provide the most recently available clinical safety data to the investigators	Section 1.3.1
Modified exclusion criterion #6 to indicate that patients who test positive for HBsAg and who have normal liver function tests with no clinical sign of liver disease are not excluded from the study.	Patients who test positive for HBsAg and who have normal liver function tests with no clinical sign of liver disease should undergo testing to quantify HBsAg or HBV DNA, and detection of HBeAg. Patients who test negative for HBeAg and have low or intermediate level of HBV DNA and normal ALT, formerly called “inactive carriers” are considered at low risk of progression to cirrhosis and liver carcinoma, according to the European Association for the Study of the Liver (EASL) 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection, as published in Journal of Hepatology, 2017, vol. 67, pp 370–398. Therefore, such patients are not excluded from the study.	Section 4.3, Section 6.8.1 (Table 3)
Modified exclusion criterion #7 such that a bilirubin level >1.5 × the upper limit of normal is not exclusionary if consistent with a diagnosis of Gilbert’s syndrome	In such patients, the increased bilirubin is not indicative of liver injury, thus there is no increased risk for these patients to participate in the study.	Section 4.3
Medications metabolized by CYP3A4 are no longer prohibited concomitant medications and are no longer exclusionary.	The recently completed human drug-drug interaction study (PHA022121-C004) indicates that at anticipated therapeutics doses, PHA-022121 does not inhibit or induce CYP3A4; therefore, medications that are metabolized by CYP3A4 are no longer prohibited or exclusionary.	Section 4.3, Section 5.6.2

Protocol Amendment		
Summary of Changes from Protocol Version 2.0 (08 April 2021)		
Amendment Number: 7	**Amendment Date: 25 April 2022**	**Scope: Global**
Change	**Rationale**	**Location(s) Affected**
Added a standard definition of clinically significant as it pertains to abnormal findings from safety assessments.	To guide assessments made by the investigator	Section 6.11.2
Deleted "Event is expected in the targeted disease and/or population" from the list of rationales for the investigator to assess an event as unrelated to study treatment	Per feedback from regulatory authority on the AE causality text and for compliance with International Council for Harmonisation E2A section 2A2	Section 6.11.3.2
Clarified that the stopping criteria for individual patients applies to both Part I and Part II	To avoid misunderstanding	Section 6.13
Modified the procedural text pertaining to use of the ePRO device	All HAE attacks are to be recorded in the HAE diary, whether treated with IMP or not	Section 7.3
Revised the significance level, power, and attrition rate in the sample size calculation	To reflect testing for the medium and high dose levels, without the low dose level	Section 9.2
Added a new section entitled "Study Analyses" to describe the circumstance under which the Sponsor may elect to perform a Primary Analysis and a Final Analysis	A Primary Analysis may be performed before all enrolled patients have experienced all 3 qualified attacks, because some patients may take longer than 24 weeks to complete assessments for all 3 attacks	Section 9.8
For France only: Added text to describe the process and method of remote source data verification for study sites located in France, for situations where on-site monitoring would not be possible	Incorporated this change from a prior protocol amendment prepared for sites in France (Amendment 6, version 2.1)	Section 10.10

SPONSOR SIGNATURE

Study Title:	A Phase II, double-blind, placebo-controlled, **R**andomized, cross-over, dose-ranging study of oral PHA-022121 for **A**cute treatment of angioedema attacks in **P**atients with hereditary angioedema due to C1-**I**nhibitor **De**ficiency type I and II
Acronym:	RAPIDe-1
Study Number:	PHA022121-C201
Original Protocol:	18 August 2020, Version 1.0
Amendment 7:	25 April 2022, Version 3.0

This protocol amendment was subject to critical review and has been approved by the sponsor.

Signed: _____ Date: _____

[redacted]
Executive Director
Clinical Development
Pharvaris Netherlands BV

PRINCIPAL INVESTIGATOR SIGNATURE

Study Title:	A Phase II, double-blind, placebo-controlled, **R**andomized, cross-over, dose-ranging study of oral PHA-022121 for **A**cute treatment of angioedema attacks in **P**atients with hereditary angioedema due to C1-**I**nhibitor **De**ficiency type I and II
Acronym:	RAPIDe-1
Study Number:	PHA022121-C201
Original Protocol:	18 August 2020, Version 1.0
Amendment 7:	25 April 2022, Version 3.0

I have read all pages of this protocol amendment for which Pharvaris Netherlands BV is the sponsor. I agree that it contains all the information required to conduct this study. I agree to conduct the study as outlined in the protocol and amendments and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with the ICH GCP guidelines (ICH E6[R2]) and the provisions of the Helsinki Declaration. I will also ensure that all relevant members of my staff have access to copies of this protocol amendment, the ICH GCP guidelines and the Helsinki Declaration to enable them to work in accordance with the provisions of these documents."

Signed:_____ Date:_____

Printed name: …….

Affiliation: …….

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