



Clinical Study Protocol: PHA022121-C301

Study Title: A Phase II, Double-blind, Placebo-controlled, Randomized, Dose-ranging, Parallel Group Study to Evaluate the Safety and Efficacy of PHA-022121 Administered Orally for Prophylaxis Against Angioedema Attacks in Patients with Hereditary Angioedema due to C1-Inhibitor Deficiency (Type I or Type II)

Acronym: CHAPTER-1

Study Number: PHA022121-C301

Study Phase: Phase II

Product Name: PHA-022121 soft capsules (PHVS416)

Indication: Hereditary Angioedema

EudraCT Number: 2021-000227-13

EU Trial Number: 2023-505549-18-00

IND Number: 153097

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] MD PhD [REDACTED], MD
Chief Medical Officer Sponsor Medical Expert

Medical Monitor: IQVIA Biotech Ltd

Protocol Version: See following page:

Confidential

The information contained in this document is the property of Pharvaris Netherlands BV and may not be reproduced, published or disclosed to others without written authorization from Pharvaris Netherlands BV.

	Date	Protocol version
Original Protocol:	09 February 2021	1.0
Amendment 1	05 April 2021	2.0
Amendment 2	21 April 2021	3.0
Amendment 3	27 August 2021	4.0
Amendment 4:	07 December 2021	4.1 (Germany only; finalized but not submitted)
	01 February 2022	4.2 (Germany only)
	15 April 2022	4.3 (Germany only)
Amendment 5:	28 April 2022	5.0
Amendment 6:	25 May 2022	5.1 (Germany only)
Amendment 7:	20 July 2022	5.2 (United Kingdom only)
Amendment 8:	19 October 2022	6.0
Amendment 9	02 November 2022	6.1 (United Kingdom only)
Amendment 10	18 November 2022	6.2 (Germany Only)
Amendment 11:	03 May 2023	7.0

SYNOPSIS

Sponsor:

Pharvaris Netherlands B.V. (Leiden, The Netherlands)

Name of Finished Product:

PHA-022121 soft capsules (PHVS416)

Name of Active Ingredient:

PHA-022121

Study Title:

A Phase II, Double-blind, Placebo-controlled, Randomized, Dose-ranging, Parallel Group Study to Evaluate the Safety and Efficacy of PHA-022121 Administered Orally for Prophylaxis Against Angioedema Attacks in Patients with Hereditary Angioedema due to C1-Inhibitor Deficiency (Type I or Type II)

Acronym:

CHAPTER-1

Study Number:

PHA022121-C301

Study Phase:

Phase II

Primary Objectives:Part 1

- To evaluate the safety and tolerability of two dose regimens of PHA-022121 administered as prophylaxis against hereditary angioedema (HAE) attacks.
- To evaluate the efficacy of two dose regimens of PHA-022121 administered as prophylaxis against HAE attacks.

Part 2

- To evaluate the safety of PHA-022121 administered as long-term prophylactic HAE treatment.

Secondary Objective:Part 1

- To characterize the pharmacokinetics/pharmacodynamics (PK/PD) of two dose regimens of PHA-022121 administered as prophylaxis against HAE attacks.
- To evaluate the impact on quality of life (QoL) of two dose regimens of PHA-022121 administered as prophylaxis against HAE attacks.

Part 2

- To evaluate the efficacy of PHA-022121 administered as long-term prophylactic HAE treatment.

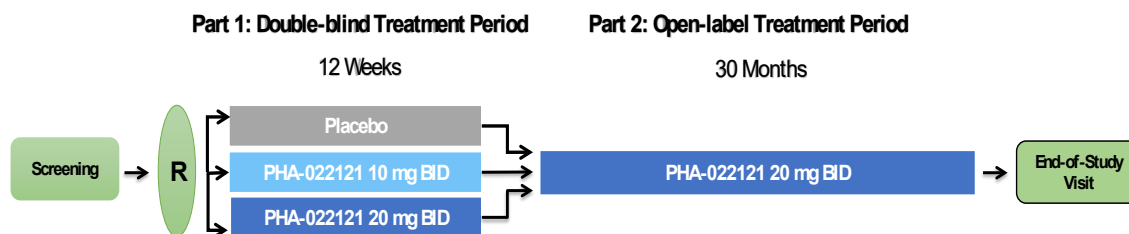
- To evaluate the PK/PD of PHA-022121 administered as long-term prophylactic HAE treatment.
- To evaluate the impact on QoL of PHA-022121 administered as long-term prophylactic HAE treatment.

Study Design:

- This is a Phase II, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, parallel group, 2-part study to evaluate the safety and efficacy of PHA-022121 administered orally for prophylaxis against angioedema attacks in HAE patients due to C1-inhibitor (C1-INH) deficiency (type I or type II) (see study design schematic below).
- The study consists of 2 parts, with patients completing participation in Part 1 prior to initiation of treatment in Part 2. Part 1 is a double-blind, placebo-controlled, 12-week evaluation of the efficacy and safety of 2 dose regimens of PHA-022121. Part 2 is an open-label evaluation of the long-term safety and efficacy of a single dose regimen of PHA-022121. The duration of the treatment period in Part 2 is 30 months and may be extended until another clinical study is available for patients to continue open-label treatment with PHA-022121, provided that the safety and efficacy data from the ongoing studies support continuing the use of PHA-022121. If the treatment period is extended, revisions will be addressed via a protocol amendment. Any patient who withdraws consent or is discontinued from the study at any time will complete an end-of-study visit 4 weeks after the last treatment administration.
- Following signing of informed consent, patients will undergo screening assessments. The screening period may last up to 8 weeks.
- For Part 1, eligible patients will be randomized in a 1:1:1 ratio to receive placebo or one of two dose regimens of PHA-022121 (10 mg or 20 mg twice daily [BID]). Each patient will receive blinded investigational medicinal product (IMP) (i.e., PHA-022121 or placebo) to be administered orally BID after breakfast and dinner for a duration of 12 weeks of treatment.
- For Part 2, patients will administer open-label PHA-022121 20 mg BID after breakfast and dinner for a duration of 30 months. To be eligible for continued treatment in Part 2, the patient must have completed Part 1, unless discontinued from Part 1 due to regulatory actions. If there is a gap in treatment between Parts 1 and 2, Visit 7 safety assessments are to be performed, with results reviewed by the Investigator, and patient eligibility reconfirmed before the patient may restart treatment in Part 2.
- Throughout the study (both Part 1 and Part 2), an electronic patient-reported outcomes (ePRO) HAE diary (i.e., ePRO HAE diary) will be used daily to record any symptoms and details of HAE attacks, including relevant treatments. Patients will have access and be able to treat any HAE attack that may occur using standard of care on-demand acute therapies, in accordance with World Allergy Organization (WAO) guidelines and local regulations. In addition to the collection information on HAE attacks, the ePRO HAE diary will be used as a dosing diary to record each administration of IMP.
- Patients will complete an end-of-study visit 4 weeks after the last treatment administration. This visit may be waived if patients continue in another clinical study of open-label

treatment with PHA-022121.

Study Design Schematic



Abbreviations: BID=twice daily; R=randomization.

Study Population:

Approximately 30 male or female, adult patients with HAE type I/II will be randomized.

HAE diagnosis will be confirmed through documented clinical history consistent with HAE and diagnostic testing conducted during the screening visit.

The study will be conducted at approximately 30 study sites globally (North America, and Europe).

Test Product, Dose, and Mode of Administration:

PHVS416 is a soft capsule formulation containing PHA-022121. Patients will record daily in the ePRO HAE diary each administration of IMP.

Part 1

The IMP consists of 10 mg PHA-022121 soft capsules and matching placebo capsules for oral intake. The capsules are to be swallowed with at least 200 mL of water after breakfast and dinner, with 12 ± 2 hours between each dose.

Patients will randomly be assigned to one of three treatment groups and will receive blinded IMP as indicated:

- 10 mg BID: one capsule of 10 mg PHA-022121 and one placebo capsule after breakfast and dinner
- 20 mg BID: two capsules of 10 mg PHA-022121 after breakfast and dinner
- Placebo: two placebo capsules after breakfast and dinner

Part 2

All patients will receive open-label PHA-022121 20 mg BID, which consists of two capsules of 10 mg PHA-022121 to be administered orally after breakfast and dinner.

The capsules are to be swallowed with at least 200 mL of water after breakfast and dinner, with 12 ± 2 hours between each dose.

Duration of Treatment:

In Part 1, patients will administer blinded IMP (PHA-022121 10 mg BID, or PHA-022121 20 mg BID, or placebo BID) for a duration of 12 weeks.

In Part 2, patients will administer open-label PHA-022121 20 mg BID for a duration of 30 months, which may be extended until another clinical study is available for patients to continue open-label treatment with PHA-022121, provided that the safety and efficacy data

from the ongoing studies support continuing the use of PHA-022121. If the treatment period is extended, revisions will be addressed via a protocol amendment.

Safety Assessments:

Safety will be assessed based on the following:

- Adverse events
- Safety laboratory testing (hematology, biochemistry, coagulation, urinalysis and pregnancy)
- Vital signs (heart rate, blood pressure, body temperature and, in Part 1 only, respiratory rate)
- Physical examination
- 12-lead electrocardiogram (ECG) (digital triplicate)

Efficacy Assessments:

Efficacy will be assessed based upon investigator-confirmation of patient-reported details of occurrences of HAE attacks. During screening, site personnel will discuss with patients the requirements for reporting attacks, including the information that is to be captured for each HAE attack.

Information on HAE attacks will be collected daily in an ePRO HAE diary. Patients will receive training on how to use the ePRO device at the screening visit and throughout the study, as needed. Patients will be instructed to report details of any HAE attack to the study site within 72 hours of onset of symptoms of an attack.

The investigator will complete a separate electronic case report form (eCRF) for each confirmed attack based on their review of the data in the patient's ePRO HAE diary and in follow-up with the patient. Additional queries by the investigator or site personnel during patient follow-up will include questions such as: whether the patient only experienced prodromal symptoms, whether the symptoms experienced were typical or different from prior attacks, or whether there were possible alternative etiologies for the symptoms. Any patient-reported HAE attack that is not confirmed by the investigator as an HAE attack, must have an alternate adverse event (AE) diagnosis recorded.

Information recorded in the eCRF will include, but is not limited to, the following:

- Date and time of onset of symptoms of an HAE attack
- Location (site) of the swelling or pain (e.g., upper airways [laryngeal, pharyngeal], gastrointestinal/abdominal, facial, truncal, genitourinary; multiple sites may be involved)
- Severity (mild, moderate, or severe) based on impact of symptoms on patient's daily activity
- Investigator assessment of symptom(s)
- Acute treatments administered for the HAE attack (date, time, and medication(s) including the number of doses administered)
- Date and time of resolution of HAE symptoms
- If hospitalization or a visit to emergency department occurred

Pharmacokinetic Assessments:

Blood samples will be collected at specified time points to determine plasma concentrations of PHA-022121 and metabolites.

Quality of Life Assessments:

The angioedema quality of life questionnaire (AE-QoL), the angioedema control test 4-week version (AECT-4wk), patient global assessment of quality of life (PGA-QoL) and patient global assessment of change (PGA-change) questions, and the treatment satisfaction questionnaire for medication (TSQM) will be used to assess health-related quality of life.

Statistical Methods:

Safety Analysis

Part 1 and Part 2

The analysis of safety will be performed on the Safety Analysis Set (i.e., all randomized patients who have received at least 1 dose of PHA-022121 or placebo). Treatment-emergent AEs (TEAEs) are defined as AEs that start or pre-existing AEs that have worsened after the initiation of IMP treatment. For patients with no gap between Part 1 and Part 2, Part 1 TEAEs are AEs that start or pre-existing AEs that have worsened during the time period between the first dose of IMP in Part 1 and the first dose in Part 2; Part 2 TEAEs are AEs that start or pre-existing AEs that have worsened during the time period between the first dose of IMP in Part 2 and 4 weeks after the last dose of IMP in Part 2 or the End of Study visit, whichever is later. For patients with a gap between Part 1 and Part 2, Part 1 TEAEs are AEs that start or pre-existing AEs that have worsened during the time period between the first dose of IMP in Part 1 and 4 weeks after the last dose of IMP in Part 1. Part 2 TEAEs are AEs that start or pre-existing AEs that have worsened during the time period between the first dose of IMP in Part 2 and 4 weeks after the last dose of IMP in Part 2 or the End of Study visit, whichever is later.

The number and percentage of patients with TEAEs in Part 1 will be displayed for each treatment group by body system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries in terms of Common Terminology Criteria for Adverse Events (CTCAE) grade/severity and relationship to IMP will also be provided. Serious AEs (SAEs) will be summarized separately in a similar fashion. Patient listings of TEAEs leading to discontinuation of IMP, AEs/SAEs leading to death, patient withdrawals, pregnancies, and SAEs will also be produced.

Usage of concomitant medications (other than rescue medications) in Part 1 will be summarized descriptively for each of the treatment groups and the combined active treatment group.

Clinical laboratory data, vital signs, physical examination, and ECG data will be presented in summary tables and/or individual listings.

The safety data will be analyzed separately for Part 1. Safety data from Parts 1 and 2 will be combined for a long-term safety assessment.

Efficacy Analysis

Part 1

The primary efficacy endpoint will be the number of investigator-confirmed HAE attacks during the treatment period in Part 1 (Day 0 through Day 84) and will be expressed as the normalized number of attacks per month (4 weeks) of exposure. The monthly attack rate is calculated for each patient as number of HAE attacks occurring during the treatment period divided by the number of days the patient contributed to the treatment period multiplied by 28 days.

The analysis of the primary efficacy endpoint will be performed based on the intent-to-treat (ITT) Analysis Set, and will compare each PHA-022121 dose group with the placebo group using a generalized linear model (GLM) assuming a Poisson distribution with a log link function and Pearson chi-square scaling of standard errors to account for potential dispersion. The model will include fixed effects for treatment group (categorical), the normalized baseline attack rate (continuous), the stratification factor of baseline attack rate (categorical), and an offset term of the logarithm of patient's follow-up time (in months) during the efficacy evaluation period. The estimated least squares (LS) mean rate for each PHA-022121 dose group and the mean rate ratios relative to the placebo group will be provided with 95% confidence intervals. These estimates will be reported as monthly attack rates (mean numbers of events per 4 weeks) by transforming the estimates using the exponential function and scaling by the unit of time. The treatment effect in the primary efficacy endpoint will be tested using a Wald-based chi-square test. Analysis using a negative binomial GLM will be performed as sensitivity analysis. In addition, Wilcoxon two-sample test will also be conducted comparing each PHA-022121 dose group with the placebo group.

The primary efficacy analysis will be conducted after all patients have completed Part 1 of the study.

Part 2

The analysis of the efficacy endpoints in Part 2 will be performed based on the ITT analysis set. The number of investigator-confirmed HAE attacks during the treatment period in Part 2 will be expressed as the normalized number of attacks per month (4 weeks) of exposure. The normalized number of investigator-confirmed HAE attacks during the treatment period in Part 2 will be descriptively summarized. Similarly, normalized number of investigator-confirmed moderate or severe HAE attacks during the treatment period in Part 2, normalized number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period in Part 2, and proportion of days with HAE symptoms during the treatment period in Part 2 will be summarized.

All efficacy analyses in Part 2 will be descriptive.

Pharmacokinetic/Pharmacodynamic Evaluation

The plasma concentrations of PHA-022121 will be summarized.

The pharmacokinetic evaluation will consist of a population pharmacokinetic analysis of the sparse samples taken in this study. The relationship between plasma exposure and efficacy/safety parameters will also be evaluated (pharmacodynamics).

Date of Original Approved Protocol:

09 February 2021

Date of Most Recent Protocol Amendment:

03 May 2023 (Amendment 11)

TABLE OF CONTENTS

SYNOPSIS.....	3
LIST OF APPENDICES.....	13
LIST OF TABLES.....	13
LIST OF FIGURES.....	13
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS.....	14
1 INTRODUCTION.....	17
1.1 Hereditary Angioedema.....	17
1.2 Current Treatment of HAE.....	18
1.3 PHA-022121 for the Treatment of HAE.....	19
2 STUDY OBJECTIVES.....	21
2.1 Primary Objectives.....	21
2.2 Secondary Objective.....	21
3 INVESTIGATIONAL PLAN.....	22
3.1 Overall Study Design and Plan.....	22
3.2 Rationale for Study Design and Control Group.....	23
3.3 Study Duration and Dates.....	28
4 STUDY POPULATION SELECTION.....	29
4.1 Study Population.....	29
4.2 Inclusion Criteria.....	29
4.3 Exclusion Criteria.....	30
5 STUDY TREATMENTS.....	32
5.1 Description of Treatments.....	32
5.1.1 PHA-022121.....	32
5.1.2 Placebo.....	32
5.2 Treatments Administered.....	32
5.3 Selection and Timing of Dose for Each Patient.....	32
5.4 Method of Assigning Patients to Treatment Groups.....	33
5.5 Blinding.....	33
5.6 Prior and Concomitant Therapy.....	34
5.6.1 Management of HAE Attacks.....	34
5.6.2 Prohibited Concomitant Medications.....	35
5.6.3 Nonpharmacologic Treatments and Procedures.....	35
5.7 Restrictions.....	35
5.7.1 Contraception.....	35
5.7.2 Fluid and Food Intake.....	35
5.7.3 Patient Activity Restrictions.....	36
5.8 Treatment Compliance.....	36

5.9	Packaging and Labeling.....	36
5.10	Storage and Accountability.....	36
5.11	Investigational Product Retention at Study Site	36
6	STUDY PROCEDURES	37
6.1	Informed Consent.....	37
6.2	Demographics and HAE Characteristics	37
6.3	Medical History	37
6.4	Weight and Height	37
6.5	Physical Examination.....	38
6.6	Vital Signs.....	38
6.7	Digital 12-Lead Electrocardiogram	38
6.8	Clinical Laboratory Tests.....	38
6.8.1	Safety Laboratory Parameters.....	38
6.8.2	Pharmacokinetic Plasma Sample Collection, Storage, and Shipping	39
6.9	Dispensing IMP	40
6.10	Efficacy Assessments.....	40
6.10.1	Definition of an HAE Attack	40
6.10.2	Reporting of HAE Attacks.....	41
6.11	Health-related Quality of Life Assessments	42
6.11.1	Angioedema Quality of Life Questionnaire.....	42
6.11.2	Angioedema Quality of Life Anchor Questions	42
6.11.3	Angioedema Control Test.....	42
6.11.4	Treatment Satisfaction Questionnaire for Medication Scores	43
6.12	Adverse Events and Serious Adverse Events	43
6.12.1	Definitions.....	43
6.12.2	Adverse Event and Serious Adverse Event Assessments	44
6.12.3	Classification of an Adverse Event.....	45
6.12.3.1	CTCAE Grade and Severity.....	45
6.12.3.2	Relationship to IMP	46
6.12.4	Reporting Serious Adverse Events	46
6.12.5	Events of Special Interest.....	47
6.12.6	Reporting of Pregnancy	48
6.13	Concomitant Medication Assessments	48
6.14	Removal of Patients from the Study or IMP.....	48
6.15	Premature Study Termination.....	49
6.16	Appropriateness of Measurements.....	49
7	STUDY ACTIVITIES	50
7.1	Screening.....	50

7.2	Part 1: Double-blind Treatment Period (Day 0 to Day 84).....	51
7.2.1	Visit 1 (Day 0) Procedures.....	51
7.2.2	Visit 2 (Day 14) Procedures.....	52
7.2.3	Visit 3 (Day 28) Procedures.....	52
7.2.4	Visit 4 (Day 42) Procedures.....	52
7.2.5	Visit 5 (Day 56) Procedures.....	53
7.2.6	Visit 6 (Day 84, End of Part 1) Procedures	53
7.3	Part 2: Open-label Treatment Period	54
7.3.1	Visit 7 (Day 91) Procedures.....	54
7.3.2	Visits 8 and 10 (Days 126 and 210) Procedures.....	55
7.3.3	Visit 9, 12, 14, and 16 (Days 168, 343, 525, and 777) Procedures.....	55
7.3.4	Visit 11, 13, 15, and 17 (Day 252, 434, 686, and 938) Procedures	55
7.4	Early Discontinuation Procedures.....	56
7.5	End-of-Study Procedures (Visit 18; Day 966).....	56
8	QUALITY CONTROL AND ASSURANCE	57
9	PLANNED STATISTICAL METHODS	58
9.1	General Considerations.....	58
9.2	Determination of Sample Size	58
9.3	Analysis Sets.....	58
9.4	Demographics and Baseline Characteristics.....	58
9.5	Safety Endpoints	59
9.6	Efficacy Endpoints.....	60
9.7	Pharmacokinetic and Quality of Life Endpoints.....	61
9.8	Planned Analyses	62
10	ADMINISTRATIVE CONSIDERATIONS.....	63
10.1	Investigators and Study Administrative Structure	63
10.2	Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval	63
10.3	Ethical Conduct of the Study	64
10.4	Patient Information and Consent	64
10.5	Patient Confidentiality	65
10.6	Study Monitoring.....	65
10.7	Case Report Forms and Study Records	66
10.8	Independent Data Monitoring Committee	66
10.9	Protocol Violations/Deviations.....	66
10.10	Access to Source Documentation	67
10.11	Data Generation and Analysis	67
10.12	Retention of Data	68

10.13	Financial Disclosure.....	68
10.14	Publication and Disclosure Policy	68
11	REFERENCE LIST	69

LIST OF APPENDICES

Appendix 1	Schedule of Events.....	73
Appendix 2	Sponsor Signature	79
Appendix 3	Principal Investigator Signature.....	80

LIST OF TABLES

Table 1	Estimated EC ₅₀ and EC ₈₅ of PHA-022121 by PK/PD Analysis in the Bradykinin Challenge in Study PHA022121-C001	25
Table 2	Extrapolated Average C _{max} and C _{min} of PHA-022121 on Day 1 and at Steady-State for Proposed Dose Regimens Administered After Standard Meals.....	28
Table 3	List of Safety Laboratory Tests.....	39
Table 4	Part 1: Double-blind Treatment Period.....	73
Table 5	Part 2: Open-label Treatment Period	76

LIST OF FIGURES

Figure 3-1:	Study Design Schematic	23
Figure 3-2:	Simulated Profiles of 10 mg BID and 20 mg BID PHA-022121 Dose Regimens Under Fed Conditions	27

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AECT-4wk	angioedema control test 4-week
ADL	activities of daily living
AE	adverse event
AE-QoL	angioedema quality of life (questionnaire)
ALT	alanine aminotransferase
ANGPT1	angiopoietin-1
AST	aspartate aminotransferase
AUC	area under plasma concentration-time curve
AUC _{0-12h}	AUC from time 0 to 12 h post-dosing concentration
AUC _{0-24h}	AUC from time 0 to 24 h post-dosing concentration
AUC _{inf}	AUC from time 0 to infinity post-dosing concentration
AUC _{last}	AUC from time 0 to the time of the last measurable concentration
BID	twice daily
C1-INH	C1-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 drug concentration
C _{min}	minimum observed drug concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
CRO	contract resource organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
EC ₅₀	estimated drug concentration for a 50% response
EC ₈₅	estimated drug concentration for a 85% response
ECG	electrocardiogram
eCRF	electronic case report form
eTMF	electronic trial master file
EDC	electronic data capture
EEG	electroencephalogram
EFD	embryofetal development
EMA	European Medicines Agency
ePRO	electronic patient-reported outcome

FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FXII	Factor XII
GCP	Good Clinical Practice
GLM	general linear model
GLP	Good Laboratory Practice
HAE	hereditary angioedema
HAEA	Hereditary Angioedema Association
hCG	human chorionic gonadotropin
hERG	human Ether-à-go-go-related gene
IC ₅₀	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	investigational medicinal product; IMP in Part 1 is PHA-022121 or placebo, IMP in Part 2 IMP is PHA-022121
IRB	Institutional Review Board
IRT	interactive response technology
ISF	investigator site file
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone releasing system
iv	intravenous(ly)
K _b	equilibrium dissociation constant of a ligand determined by means of a functional assay
KKS	kallikrein-kinin system
KNG1	kininogen-1
LC-MS/MS	liquid chromatography–mass spectrometry/mass spectrometry
LS	least squares (mean)
LTP	long-term prophylaxis
MAD	multiple ascending dose
MSCS	mean symptom complex severity
MedDRA	Medical Dictionary for Regulatory Activities
MYOF	myoferlin
NCI	National Cancer Institute
NOAEL	no observed adverse effect level
OLE	open-label extension

PA	Primary analysis
PD	pharmacodynamic(s)
PGA-change	patient global assessment of change (question)
PGA-QoL	patient global assessment of quality of life (question)
PK	pharmacokinetic(s)
PLG	plasminogen
po	per os, oral
QA	quality assurance
QD	once daily
QoL	quality of life
RBC	red blood cell (count)
RNA	ribonucleic acid
RSI	reference safety information
SAD	single ascending dose
SADext	single ascending dose extension
SAE	serious adverse event
SAP	statistical analysis plan
sc	subcutaneous(ly)
SMP	safety management plan
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TOS	treatment outcome score
TSQM	treatment satisfaction questionnaire for medication
US	United States
VAS	visual analogue scale
WAO	World Allergy Organization
WBC	white blood cell (count)
WHO-DD	World Health Organization-Drug Dictionary

1 INTRODUCTION

1.1 Hereditary Angioedema

Hereditary angioedema (HAE) is a rare disease. It is estimated that HAE affects 1 in 50,000 individuals, though reports vary between 1 in 10,000 and 1 in 150,000 individuals (Zuraw 2008; Bygum 2009; Zanichelli et al. 2015; Aygören-Pürsün et al. 2018).

The disease manifests as edematous 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; Bork et al., 2012). Asphyxiation can occur rapidly in patients of any age, and it has occurred in patients with no previous history of respiratory symptoms (Bork et al., 2012). The number and severity of attacks vary highly between patients and throughout a patients' lifetime. If untreated, attacks last 2 to 5 days (Zuraw, 2008; Nordenfelt et al., 2016; Cicardi and Zuraw, 2018). The most severely affected patients can experience multiple attacks a month.

Acute episodes of HAE often occur without warning and may be precipitated by triggers such as estrogens, dental procedures, pregnancy, and stress (Busse and Christiansen, 2020). The unexpected nature of HAE attacks result in the disruption of normal life with the need of frequent healthcare visits, many days of absence from work or school, and impaired quality of life (Lumry et al., 2010; Nordenfelt et al., 2014; Caballero et al., 2014; Nordenfelt et al., 2016). Despite advances in treatment options, patients with HAE continue to have a high burden of illness (Banerji et al., 2020).

Three types of HAE have been characterized. Type I and II are defined by mutations in the SERPING1 gene which encodes the C1-inhibitor (C1-INH) protein 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), with associated excessive breakdown of high molecular weight kininogen and increased plasma levels of bradykinin (Kaplan and Joseph, 2010). A new form of HAE was first described in 2000 where affected individuals (mainly women) had normal levels and activity of C1-INH (Binkley and Davis, 2000; Bork et al., 2000). Initially classified as type III HAE, the disease is currently defined as HAE with normal C1-INH (HAE-nC1-INH). The disease is characterized by mutations in other genes (e.g., FXII, PLG, ANGPT1, KNG1, MYOF) involved in the activation of the KKS and generation of bradykinin or in the stabilization of the vasculature (Dewald and Bork, 2006; Bork et al., 2018; Bafunno et al., 2018; Bork et al., 2019a; Ariano et al., 2020).

Bradykinin is the principal mediator of the signs and symptoms that represent acute HAE attacks. Excessive bradykinin generation, as in HAE, promotes vascular permeability, leading to plasma extravasation and subcutaneous or submucosal tissue swelling typical of an angioedema attack. Two bradykinin receptor types, B1 and B2, have been identified, cloned and characterized. Both are G protein-coupled receptors, seven transmembrane proteins. Bradykinin 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 bradykinin a selective B2 receptor agonist.

1.2 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. Patients and their physicians have several choices for on-demand or prophylactic treatment, but because there are differences in the route of administration, side effect profiles, and efficacy between these medications, patient preference and experience need to be considered in selecting the most appropriate therapy.

Various guidelines for treatment of HAE have evolved over the years, in part in response to the increasing availability of treatment options. According to the United States Hereditary Angioedema Association (US HAEA) Medical Advisory Board 2020 Guidelines (Busse et al., 2021), all patients must have ready access to effective on-demand and self-administered (or administered by a caregiver) treatment, and all attacks should be treated regardless of their location or severity. According to these same guidelines, the decision on when to use long-term prophylactic treatment cannot be made on rigid criteria but should reflect the needs of the individual patient. Early on, guidelines proposed that the overall goal of treatment in HAE was to “restore normal quality of life to the patient” (Zuraw et al., 2013). The most recent guidelines (Bork et al., 2019b; Maurer et al., 2022) and the ones developed with a state-of-the-art methodology (Delphi process), which is the international consensus on treatment goals in HAE (Maurer et al., 2021), define the goal of HAE treatment as achieving an absence of attack, thus implying that most patients should be on a prophylactic treatment. The 2022 World Allergy Organization/European Academy of Allergy and Clinical Immunology (WAO/EAACI) guideline (Maurer et al., 2022) recommends that patients are evaluated for long-term prophylaxis at every visit, taking disease activity, burden, and control as well as patient preference into consideration.

On-demand treatments

The bradykinin B2 receptor antagonist icatibant (Firazyr®) is the mainstay of acute treatment due to its quick onset of action and easy subcutaneous (sc) self-administration by a prefilled syringe. The kallikrein inhibitor ecallantide (Kalbitor®) requires hospital or health professional sc administration due to potential anaphylaxis. Ecallantide has approval in the United States only. Plasma-derived or recombinant C1-INH concentrates (Berinert®, Cinryze® and Ruconest®) require intravenous (iv) administration.

Prophylactic treatments

The plasma-derived C1-INH concentrates (Cinryze and Haegarda®/Berinert® 2000/3000) are administered by iv and sc route, respectively. These products are administered twice weekly (every 3 or 4 days). Plasma kallikrein inhibitors include lanadelumab (Takhzyro®), a fully human recombinant monoclonal antibody which is administered sc once or twice a month and berotralstat administered orally, once daily. Attenuated androgens (including danazol, stanozolol, oxandrolone, oxymetholone, tibolone, methyltestosterone) and antifibrinolytics, such as ε-aminocaproic acid and tranexamic acid are used for the prevention of acute attacks and are licensed in some countries. However, current treatment guidelines recommend against the use of attenuated androgens and antifibrinolytics as first-line therapy due to limited efficacy and/or safety issues with associated contraindications (Maurer et al., 2022; Busse et al., 2021).

Investigational treatments

Currently there are two other oral medications in clinical development for on-demand or prophylactic therapy in patients with HAE; these products are plasma kallikrein inhibitors

(KVD824 and KVD900). In addition to these oral medications, other therapies in development for HAE patients include a monoclonal antibody antagonist of Factor XIIa (garadacimab), an antisense oligonucleotide against plasma prekallikrein (IONIS-PKK-LRx), and a plasma-derived C1-INH concentrate (OCTA-C1-INH).

All but one of the medications approved in the last decade for the management of HAE type I/II are administered parenterally via iv or sc routes, which are often associated with a delay of drug administration, injection pain, local side effects, and a lower quality of life. Orladeyo is a new oral HAE therapy available to patients, but the efficacy profile is relatively modest. The product is indicated for prevention of HAE attacks and should not be used by patients for the treatment of acute attacks (Orladeyo USPI, 2020).

In a Food Drug Administration (FDA) Patient-Focused Drug Development meeting, patients expressed that the route of administration (iv, sc, or oral) is the most important consideration for a new HAE therapeutic, with a preference for oral (po) treatments (FDA, 2018a). Therefore, there is a high unmet medical need for an efficacious oral medicine that can be administered to either treat or prevent attacks due to HAE and other various forms of bradykinin-mediated angioedema and thereby improve compliance, outcomes, and the overall care and quality of life for patients.

1.3 PHA-022121 for the Treatment of HAE

PHA-022121 is an orally bioavailable, low-molecular weight, competitive antagonist of the human bradykinin B2 receptor with high affinity, high antagonist potency, and high selectivity (more than 5,000-fold compared with B1 receptor and other molecular targets).

Nonclinical support for the potential efficacy of PHA-022121 derives from nonclinical studies in which orally administered PHA-022121 demonstrated dose-dependent inhibition of bradykinin-induced hemodynamic changes in cynomolgus monkeys and carrageenan-induced paw edema in humanized bradykinin B2 receptor Sprague Dawley rats. Support for the safety of PHA-022121 derives from completed respiratory, central nervous system (CNS), and cardiovascular safety pharmacology studies, which did not reveal any safety concerns at the exposure levels anticipated to be achieved at clinically planned doses, as well as results of 4- and 13-week Good Laboratory Practice (GLP) repeat-dose toxicology studies in rat and GLP studies in monkey of up to 39 weeks duration. In a 6-month general toxicity rat study and 10-week humanized bradykinin B2-receptor transgenic male rat fertility study, a low incidence of handling-induced convulsions was observed. The overall incidence of convulsions in the studies was 4.2% in the 26-week rat toxicity study and 5% in the male fertility study. These incidences were within the upper range of historical incidences at the conducting sites and in the literature. Moreover, the onset, frequency, and severity were not dose- or exposure-related, had no histopathologic correlate, and occurred in animals at 22 weeks of age or older when spontaneous convulsions can be observed in rats. Furthermore, the incidence of handling-induced convulsions in an ongoing 2-year carcinogenicity study is of 0.57%, is well below the incidence observed in the 26-week rat study and male fertility study despite higher systemic exposure, longer duration of treatment (up to 17 months duration), and greater number of animals treated (≥ 500).

Results of the primary analysis from double-blind, placebo-controlled Study PHA022121-C201, showed that PHA-022121 10, 20, and 30 mg significantly ($p < 0.0001$, nominal for 10 mg) reduced attack symptoms from pre-treatment to 4 hours post treatment versus placebo.

Furthermore, all key secondary endpoints were met, demonstrating that, versus placebo, PHA-022121 had a significantly shorter time to onset of symptom relief by a $\geq 30\%$ reduction in 3-symptom composite visual analogue scale (VAS-3) score from the pre-treatment score, shorter time to a $\geq 50\%$ reduction in VAS-3 score from the pre-treatment score, shorter time to almost complete or complete symptom relief by VAS-3, greater decrease in mean symptom complex severity (MSCS) score from pre-treatment to 4 hours post-treatment, and improved treatment outcome score (TOS) at 4 hours post-treatment.

Safety results from ongoing study PHA022121-C201 have revealed no clear dose relationship with regard to the incidence of TEAEs, either in Part I (non-attack) or Part II (Attack 1, 2, 3). The only TEAE that occurred in >1 participant in Part I was headache (2 participants). In Part II, of the 103 attacks treated with PHA-022121 in 59 participants, the only individual TEAE that was associated with >1 attack was fatigue, which was reported twice.

Overall, PHA-022121 has been shown to be generally well tolerated in completed and ongoing clinical studies to date. The TEAEs reported to date in completed clinical trials have been mild to moderate in severity, and all have resolved. To date, there have been no reports of SARs, deaths, or clinically significant shifts in safety parameters (e.g., lab or ECG). Moreover, the incidence and type of TEAEs were similar between active drug and placebo groups in Phase I SAD or MAD studies.

Given the potential benefit to treat the HAE population, especially with the validated mechanism of action and positive PD effects demonstrated by the BK challenge in monkey, the benefit--risk assessment of PHA-022121 is considered acceptable if used according to the clinical study protocols, and in accordance with the recommendations and guidance provided in the IB.

Please see the Investigator's Brochure (IB) for additional information regarding PHA-022121.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are:

Part 1

- To evaluate the safety and tolerability of two dose regimens of PHA-022121 administered as prophylaxis against HAE attacks.
- To evaluate the efficacy of two dose regimens PHA-022121 administered as prophylaxis against HAE attacks.

Part 2

- To evaluate the safety of PHA-022121 administered as long-term prophylactic HAE treatment.

2.2 Secondary Objective

The secondary objectives of this study are:

Part 1

- To characterize the PK/PD of two dose regimens of PHA-022121 administered as prophylaxis against HAE attacks.
- To evaluate the impact on quality of life (QoL) of two dose regimens of PHA-022121 administered as prophylaxis against HAE attacks.

Part 2

- To evaluate the efficacy of PHA-022121 administered as long-term prophylactic HAE treatment.
- To evaluate the PK/PD of PHA-022121 administered as long-term prophylactic HAE treatment.
- To evaluate the impact on QoL of PHA-022121 administered as long-term prophylactic HAE treatment.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase II, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, parallel group, 2-part study to evaluate the safety and efficacy of PHA-022121 administered orally for prophylaxis against angioedema attacks in HAE patients due to C1-INH deficiency (type I or type II).

The study will be conducted at approximately 30 sites globally (North America and Europe).

The study consists of 2 parts with patients completing participation in Part 1 prior to initiation of treatment in Part 2. Part 1 is a double-blind, placebo-controlled, 12-week evaluation of the efficacy and safety of 2 dose regimens of PHA-022121. Part 2 is an open-label evaluation of the long-term safety and efficacy of a single dose regimen of PHA-022121. The duration of the treatment period in Part 2 is 30 months and may be extended until another clinical study is available for patients to continue open-label treatment with PHA-022121, provided that the safety and efficacy data from the ongoing studies support continuing the use of PHA-022121. If the treatment period is extended, revisions will be addressed via a protocol amendment. Any patient who withdraws consent or is discontinued from the study at any time will complete an end-of-study visit 4 weeks after the last treatment administration.

Following signing of informed consent, patients will undergo screening assessments. The screening period may last up to 8 weeks. All patients receiving HAE medications for long-term prophylaxis (LTP) will be required to discontinue these medications prior to screening. The duration of the washout period for prophylactic treatments is dependent upon pharmacokinetic profile of the prophylactic medication and should be equivalent to at least 5 half-lives of the drug. For patients who receive any form of C1-INH replacement, there is the additional restriction that the last dose before the confirmatory C1-INH testing should be given at least 5 half-lives before the date of sampling.

For Part 1, eligible patients will be randomized in a 1:1:1 ratio to receive placebo or one of two dose regimens of PHA-022121 (10 mg or 20 mg BID). Each patient will receive blinded IMP to be administered orally BID after breakfast and dinner for a duration of 12 weeks of treatment.

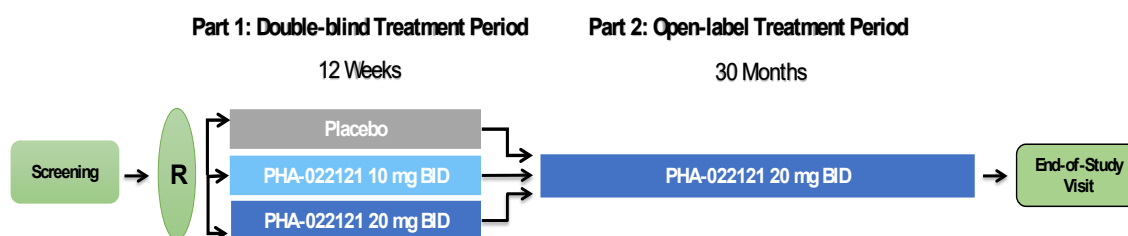
For Part 2, patients will administer open-label PHA-022121 20 mg BID after breakfast and dinner for a duration of 30 months. patients must have completed Part 1. To be eligible for continued treatment in Part 2, the patient must have completed Part 1, unless discontinued from Part 1 due to regulatory actions. If there is a gap in treatment between Parts 1 and 2, Visit 7 safety assessments are to be performed, with results reviewed by the Investigator, and patient eligibility reconfirmed before the patient may restart treatment in Part 2.

Throughout the study (both Part 1 and Part 2), an electronic patient-reported outcomes (ePRO) HAE diary (i.e., ePRO HAE diary) will be used daily to record any symptoms and details of HAE attacks, including relevant treatments. Patients will have access and be able to treat any HAE attack that may occur using standard of care on-demand acute therapies, in accordance with WAO guidelines and local regulations. In addition to the collection of information on HAE attacks, the ePRO HAE diary will be used as a dosing diary to record each administration of IMP.

Patients will complete an end-of-study visit 4 weeks after the last treatment administration. This visit may be waived if patients continue in another clinical study of open-label treatment with PHA-022121.

A schematic of the study design is shown in [Figure 3-1](#). A detailed schedule of events for Part 1 ([Table 4](#)) and Part 2 ([Table 5](#)) is provided in [Appendix 1](#).

Figure 3-1: Study Design Schematic



BID=twice daily; R=randomization

3.2 Rationale for Study Design and Control Group

This Phase II, double-blind, placebo-controlled, randomized, dose-ranging, parallel group, 2-part study aims to evaluate the safety and efficacy of 2 dosing regimens of PHA-022121 for the prophylaxis of angioedema attacks in patients with HAE type I/II.

Part 1

Part 1 of the study employs a placebo comparator to evaluate and interpret the efficacy of PHA-022121 for preventing attacks of HAE. The use of a placebo-controlled design is justified as (i) patients are required to have adequate access and are able to treat any HAE attack using standard of care on-demand acute therapies in accordance with WAO guidelines and local regulations; therefore patients are not placed at any unnecessary risk, and (ii) all therapies currently approved and recommended for prophylaxis of HAE attacks (Maurer et al., 2022; Busse et al., 2021), are administered either by iv or sc routes, which are not feasible for blinding the study.

The duration of treatment is reflective of Part 1 study objectives. The primary objectives are the evaluation of safety, with number of investigator-confirmed attacks during the treatment period being the main endpoint for the assessment of efficacy. A treatment duration of 12 weeks will allow an appropriate initial evaluation of safety of the prophylactic PHA-022121 dose regimens compared with placebo, while also providing reasonable power (approximately 85%) to demonstrate whether the BID administration of PHA-022121 is able to reduce attack rates versus placebo.

The study will employ endpoints that are standard in HAE trials for evaluating the efficacy of prophylactic treatment (Zuraw and Kalfus, 2012; Longhurst et al., 2017; Banerji et al., 2018; Zuraw et al., 2021). Efficacy endpoints detailing HAE attacks are medically appropriate, as attacks represent the fundamental event underlying the morbidity and mortality of HAE.

Part 2

This study includes an open-label treatment period to allow patients to continue in the study until another means of treatment with PHA-022121 can be provided (if the safety and efficacy data from the ongoing studies support continuing the use of PHA-022121).

The primary objective of the open-label period is evaluate the safety of PHA-022121 (20 mg BID) administered as long-term prophylactic treatment. Secondary objectives include the evaluation of the long-term efficacy of PHA-022121, evaluation of PK/PD, and impact on QoL with 20 mg BID PHA-022121 administered as long-term prophylactic HAE treatment.

As in Part 1, patients will be able treat to any HAE attack that may occur in Part 2 using standard of care on-demand acute therapies, in accordance with WAO guidelines and local regulations.

Dose Rationale

The dose regimens for this study were selected based on the following approach:

- i. A Bradykinin Challenge model was conducted in a similar manner as had been done for icatibant. The data from the bradykinin challenge were analyzed in a PK/PD model to obtain the EC₅₀ and EC₈₅ of PHA-022121.
- ii. In parallel, a population PK model was developed to estimate plasma concentrations over time for different doses of PHA-022121.
- iii. Population PK and PD models were combined to simulate the therapeutic effect over time of different dosing regimens for PHA-022121. These simulations facilitated the selection of PHA-022121 dosing regimens that are most likely to show continued target engagement and efficacy over the chosen dosing interval during long-term daily treatment.

PHA-022121 Inhibitory Activity in a Bradykinin Challenge Model

During the clinical development of icatibant, the inhibition of a bradykinin challenge in healthy volunteers has been shown to correlate well with efficacy in the treatment of acute HAE attacks (EMA-CHMP, 2008; FDA-CDER, 2011). Intravenous administration of icatibant caused dose- and time-dependent inhibition of bradykinin-induced vasodilation in healthy subjects. Based on the direct-response PK/PD analysis from the icatibant bradykinin challenge study, EC₅₀ and EC₈₅ were determined, and an sc dose of 30 mg icatibant was predicted to be effective in the treatment of acute attacks for at least 6 hours (h).

The inhibition of bradykinin challenge was assessed in Study PHA022121-C001 with single doses of 12 and 22 mg PHA-022121. PHA-022121 was demonstrated to show dose- and time-dependent inhibition of bradykinin-induced vasodilatation, e.g., protection against bradykinin-mediated diastolic blood pressure (DBP), systolic blood pressure (SBP), mean arterial pressure (MAP), cardiac output (CO), and heart rate (HR) alterations (Bonner; Cockcroft et al., 1994; Honing et al., 2000; Prasad et al., 2000). A PK/PD analysis using the same approach as in the icatibant evaluation was conducted. The PD outcomes for DBP, SBP, mean blood pressure (MBP), CO, and HR were converted to percent inhibition of vasodilatation, via the following transformation:

$$Pinh = 100 - \left(\frac{PD}{PD_{base}} \right) \cdot 100$$

Where PD corresponds to the endpoints, and PD_{base} is the baseline value calculated as the average of PD assessments pre-bradykinin dose. NONMEM® datastreams were built for PK/PD

analysis, containing the absolute bradykinin challenge-induced vasodilatation effects and percent test-item-mediated inhibition thereof next to the corresponding observed plasma concentrations.

Percent inhibition (of bradykinin challenge), $Pinh$, for the final modelled endpoints, was characterized by an “ E_{max} ” function whose general form was described by the following model:

$$Pinh_{ij} = \frac{Emax_j \cdot Cp_{ij}^n}{Cp_{ij}^n + EC_{50j}^n}$$

Where $Pinh_{ij}$ and Cp_{ij} are the percent inhibition of either DBP, CO, or HR and the timewise corresponding plasma concentration of PHA-022121, respectively, recorded at the i^{th} time-point for the j^{th} trial subject; $Emax_j$ is the maximum attainable (model predicted) effect; and EC_{50j} is the concentration level where 50% of the maximum (model predicted) effect is attained for the j^{th} individual. The exponent “n” is a Hill exponent parameter, which was also preliminarily tested. The observed and modelled outcomes were plotted both as effect (bradykinin-induced vasodilatation reduction) vs. PHA-022121 concentration as well as effect vs. time.

Table 1 summarizes the EC_{50} and EC_{85} for the separate endpoints (DBP, HR, and CO). The PK/PD parameters from the three endpoints were simply averaged to obtain the composite average of EC_{50} and EC_{85} for PHA-022121. The composite average shows an EC_{50} of 2.4 ng/mL and an EC_{85} of 13.8 ng/mL for PHA-022121, which are approximately 4-fold more potent than icatibant with an EC_{50} of 9.5 ng/mL and an EC_{85} of 53.8 ng/mL (EMACHMP, 2008; FDA-CDER, 2011).

Table 1 Estimated EC_{50} and EC_{85} of PHA-022121 by PK/PD Analysis in the Bradykinin Challenge in Study PHA022121-C001

	Diastolic blood pressure	Heart rate	Cardiac output	Composite average
EC_{50} (ng/mL)	2.3	3.3	1.7	2.4
EC_{85} (ng/mL)	13.3	18.7	9.5	13.8

EC_{50} =estimated drug concentration for 50% response; EC_{85} =estimated drug concentration for 85% response

Population Pharmacokinetic Modelling

The PK of PHA-022121 in healthy subjects was investigated in SAD studies from 1 to 40 mg under fasted status and from 12 to 50 mg under fed status (Studies PHA022121-C001 and PHA022121-C002). Furthermore, the PK of PHA-022121 was investigated in a multiple ascending dose study in healthy subjects for doses ranging from 12 to 50 mg BID under fed conditions (Study PHA022121-C006). The results revealed approximately dose-proportional PK for PHA-022121 and a half-life of approximately 4 h. Food evaluation indicated that mean C_{max} for PHA-022121 was lower, while mean AUC_{0-24h} was comparable under fed status with standard meals compared to fasted conditions.

The PK model was a two-compartment model with first order absorption with a fixed effect separating the fasted from the fed parameter for absorption in the follow-up model. The models were implemented in NONMEM® version 7.3 using subroutine ADVAN 4, and parameter estimation was performed using the first order conditional estimation method (FOCE) with interaction.

The two-compartment model was parameterized as apparent clearance: CL/F (L/h); apparent volume for the central compartment: V_2/F (L); apparent inter-compartmental clearance: Q/F (L/h); apparent deep-tissue volume of distribution: V_3/F (L); a first order absorption: K_a (h^{-1}) as $K_{a_{fed}}$ and $K_{a_{fasted}}$; and a lag time: $ALAG$ (h). Random effects were tested on all parameters including separate effects for fed and fasted subgroups in the follow-up model.

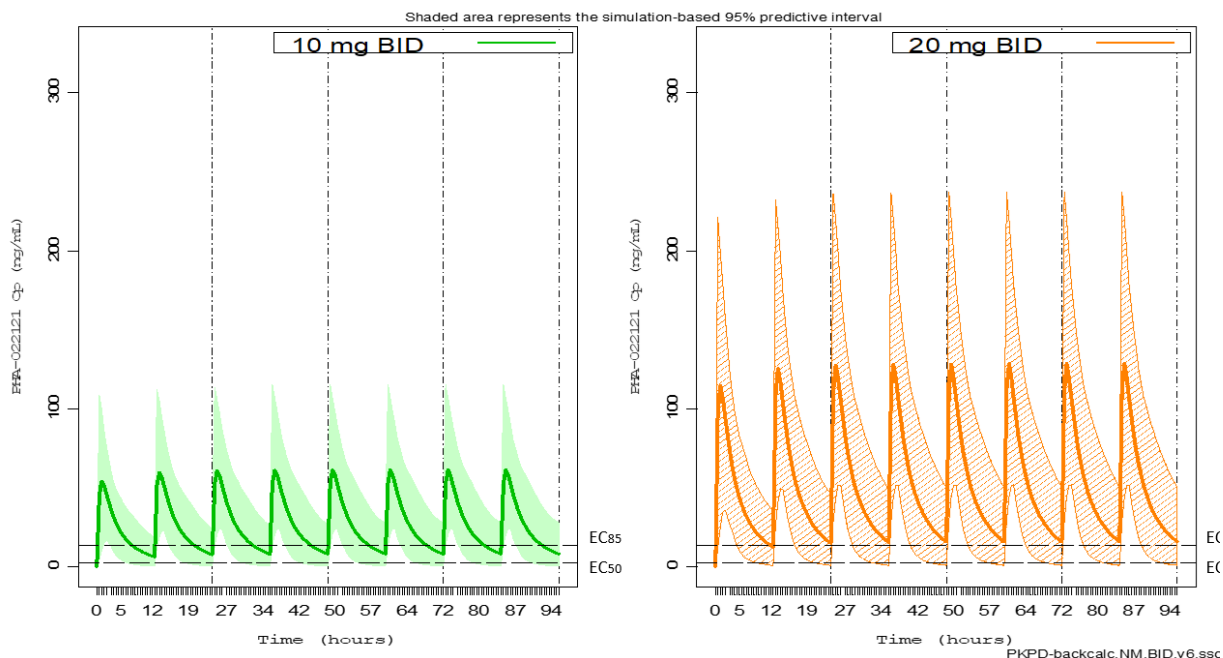
Two-compartment population PK models were developed both for test-item treated subjects in the PD (bradykinin challenge) cohorts (12 mg and 22 mg PHA-022121, fasted, N=16 subjects) and for all other cohorts (that were not subjected to a bradykinin challenge) with dual absorption rates for fed (high fat high calorie breakfast) and fasted situations (N=52 subjects).

Simulations of Anticipated Pharmacological/Therapeutic Effect as a Function of Time at Different Dose Levels

The final PK/PD model was used to calculate probability of durations of effect as well as to visualize effect-time evolution across dose levels in order to assist in dose selection for this prophylactic study. In simulation focus was first placed on the single dose, and then the repeat dose up to steady-state PK/PD was simulated.

The safety and PK of PHA-022121 have been investigated in a multiple ascending dose study in healthy subjects for doses ranging from 12 to 50 mg BID under fed conditions (Study PHA022121-C006). The results revealed that all dose regimens up to 50 mg BID are safe and dose-proportional PK for PHA-022121 with a population average half-life of approximately 4 to 5 h. Therefore, based on the availability of PK and PD data, the simulated profiles of proposed dose regimens for prophylactic treatment, 10 mg BID and 20 mg BID administered after standard meals, are presented in [Figure 3-2](#); and plasma C_{max} and minimum observed drug concentration (C_{min}) of PHA-022121 on Day 1 and steady-state are summarized in [Table 2](#).

Figure 3-2: Simulated Profiles of 10 mg BID and 20 mg BID PHA-022121 Dose Regimens Under Fed Conditions



Left Panel: Mean pharmacokinetic (ng/mL vs. time) profiles after multiple dosing of PHA-022121 10 mg/kg BID dose regimen under fed conditions

Right Panel: Mean pharmacokinetic (ng/mL vs. time) profiles after multiple dosing of PHA-022121 20 mg/kg BID dose regimen under fed conditions

BID=twice daily

Steady-state trough concentrations following PHA-022121 10 mg BID and 20 mg BID administration would be approximately 10 ng/mL and 20 ng/mL, which are approximately 4-fold and 8-fold above the EC₅₀ value derived from the bradykinin challenge study. For the 10 mg BID regimen, approximately 92% and 35% of the patients are expected to remain above the EC₅₀ and EC₈₅ values, respectively, at all times. For the 20 mg BID regimen, approximately 98% and 68% of the patients are expected to remain above the EC₅₀ and EC₈₅ values, respectively, at all times. Both repeated dose regimens are expected to provide adequate blockage of B2 receptors at all times to effectively prevent HAE attacks, and therefore these two dose regimens are proposed for safety and prophylactic efficacy evaluation of PHA-022121 in Part 1 of the study.

Table 2 Extrapolated Average $C_{\max}$ and $C_{\min}$ of PHA-022121 on Day 1 and at Steady-State for Proposed Dose Regimens Administered After Standard Meals

Dose (mg)	$C_{\max}$ (Day 1) (ng/mL)	$C_{\min}$ (Day 1) (ng/mL)	$C_{\max}$ (ss) (ng/mL)	$C_{\min}$ (ss) (ng/mL)
10 mg BID	75	5	100	10
20 mg BID	150	10	200	20

BID=twice daily; $C_{\max}$ =maximum observed drug concentration; $C_{\min}$ =minimum observed drug concentration; ss=steady-state
Note: Based on extrapolation using PK data from Studies PHA022121-C001, PHA022121-C002, and PHA022121-C006.

In Part 2, the 20 mg BID regimen of PHA-022121 is to be administered during the open-label treatment period (up to 30 months). As noted above, the majority of patients (~70%) are expected to have plasma levels of PHA-022121 above the EC_{85} at all times with the 20 mg BID dose regimen (compared with 35% of patients with the 10 mg BID regimen). Provided that the IDMC evaluation of data from ongoing clinical studies in HAE patients remains positive with no safety concerns identified (including the BID regimens in Part 1 and Part 2 of this study), as it has been so far, then the benefit/risk assessment favors 20 mg BID dosing in Part 2 to allow patients to continue prophylactic therapy with PHA-022121.

3.3 Study Duration and Dates

The overall expected study duration for each patient who participates is to be approximately 36 months. This estimation is based on a screening period of up to 8 weeks, a double-blind treatment period of 12 weeks, an open-label treatment period of 30 months, and a follow-up period of 4 weeks. The duration of the treatment period in Part 2 may be extended until another clinical study is available for patients to continue open-label treatment with PHA-022121, provided that the safety and efficacy data from the ongoing studies support continuing the use of PHA-022121. If the treatment period is extended, revisions will be addressed via a protocol amendment.

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 30 male or female, adult patients with HAE type I/II will be randomized.

HAE diagnosis will be confirmed through documented clinical history consistent with HAE and diagnostic testing conducted during the screening visit.

4.2 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study.

1. Male or female patients aged ≥ 18 to ≤ 75 years at screening.
2. Diagnosis of HAE (type I or II) based upon all of the following:
 - a. Documented clinical history consistent with HAE (subcutaneous and/or mucosal swelling without accompanying wheals)
 - b. At least one of the following:
 - Age at reported onset of first angioedema symptoms ≤ 30 years
 - Family history consistent with HAE type I or II
 - C1q within normal range
 - c. Diagnostic testing results to confirm HAE type I or II:
 - C1-INH functional level $< 50\%$ of the normal level

The diagnosis should be documented prior to randomization by a local or central laboratory value documented in the medical records.

Note: For patients who receive any form of C1-INH replacement, the last dose before the confirmatory C1-INH testing should be given at least 5 half-lives before the date of sampling.

3. Documented history of at least 3 HAE attacks within the last 3 consecutive months prior to screening. If the patient has no documentation or has less than 3 attacks in the 3 months before the screening visit, or was on prophylactic treatment, patient must experience a minimum of 2 HAE attacks during the screening period (up to 8 weeks).
4. Is assessed by the investigator to have reliable access and ability to use standard of care treatments alone to effectively manage acute HAE attacks.
5. Body weight of ≥ 40 kg at screening.
6. Investigator considers that the patient is willing and able to adhere to all protocol requirements, including being capable of and compliant with data recording into an electronic Patient Reported Outcome (ePRO) tool.
7. Female patients of childbearing potential must agree to the protocol specified pregnancy testing and to practice abstinence from heterosexual intercourse in line with the preferred and usual lifestyle of the patient or to use a medically acceptable form of contraception methods from enrollment until 30 days after the last IMP administration. Methods acceptable for this study include male condom with or without spermicide, cervical cap, diaphragm or sponge with spermicide, a combination of male condom with cap, diaphragm, or sponge with

spermicide (double-barrier methods), combined or progestin-only hormonal methods (oral, injectable, or implantable), intrauterine device (IUD, all types), intrauterine hormone releasing systems (IUS).

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 and a follicle-stimulating hormone (FSH) test result indicative of post-menopausal status) do not require contraception during the study.

There are no contraceptive requirements for male patients.

8. The patient has provided informed consent.

4.3 Exclusion Criteria

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

1. Concomitant diagnosis of another form of chronic, recurrent angioedema, such as acquired angioedema (AAE) with C1-INH deficiency, angioedema with normal C1-INH levels (HAE type III), idiopathic nonhistaminergic angioedema, or recurrent angioedema associated with urticaria.
2. Participation in a clinical trial with any other investigational drug within the last 30 days or within 5 half-lives of IMP at screening (whichever was longer). Previous participation in the Study PHA022121-C201 is permitted.
3. Exposure to angiotensin-converting enzyme (ACE) inhibitors within 4 weeks of screening.
4. Receiving prophylactic treatment for HAE. Patients who have previously received prophylactic therapy but have stopped, can participate in this study provided a sufficiently long washout period is observed before the patient is screened. Exclusion includes use of:
 - a. long-term prophylactic therapy for HAE (C1-INH, oral kallikrein inhibitors, attenuated androgens, or anti-fibrinolytics) within 2 weeks prior to screening
 - b. long-term prophylactic monoclonal therapy for HAE (i.e., lanadelumab) within 11 weeks prior to screening
 - c. short-term prophylaxis for HAE within 7 days prior to screening

Short-term prophylaxis is defined as intravenous C1-INH, attenuated androgens, or anti-fibrinolytics to avoid angioedema complications from medically indicated procedures.

Note: Patients who are receiving long-term prophylactic treatment for HAE and are satisfied with this treatment, are not eligible for this 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 in Exclusion Criterion #4 for the different HAE therapies.

5. Clinically significant abnormal electrocardiogram (ECG), most notably a QTcF > 470 milliseconds (for women) or > 450 milliseconds (for men).
6. Any clinically significant history of angina, myocardial infarction, syncope, stroke, left ventricular hypertrophy or cardiomyopathy, uncontrolled hypertension (systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg), bradycardia (heart rate < 50 beats per minute) or any other cardiovascular abnormality within the previous year.

7. 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.
8. Any females who are pregnant, plan to become pregnant, or are currently breast-feeding.
9. Abnormal hepatic function (aspartate aminotransferase [AST] > 2×upper limit of normal [ULN], alanine aminotransferase [ALT] > 2×ULN, or total bilirubin > 1.5×ULN. Patients with Gilbert's syndrome, being defined as isolated increase of total bilirubin ≤3xULN and AST and ALT within the normal range, are not excluded.
10. Abnormal renal function (estimated glomerular filtration rate [eGFR] CKD-EPI < 60 mL/min/1.73 m²).
11. History of alcohol or drug abuse within the previous year, or current evidence of substance dependence or abuse.
12. Use of concomitant medications that are strong inhibitors of CYP3A4 such as clarithromycin, itraconazole, ketoconazole, ritonavir, and grapefruit as well as inducers of CYP3A4 such as phenobarbital, phenytoin, rifampicin, and St. John's Wort.

5 STUDY TREATMENTS

5.1 Description of Treatments

5.1.1 PHA-022121

PHVS416 is a soft capsule formulation containing PHA-022121.

The active IMP consists of 10 mg PHA-022121 soft capsules for oral use with a concentration of

5.1.2 Placebo

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

5.2 Treatments Administered

Patients will record daily in the ePRO HAE diary each administration of IMP.

Part 1

The treatments to be administered in Part 1 consist of 10 mg PHA-022121 soft capsules and matching placebo soft capsules for oral use.

The capsules are to be swallowed with at least 200 mL of water after breakfast and dinner, with 12 ± 2 hours between each dose.

Patients will randomly be assigned to one of three treatment groups and will receive blinded IMP as indicated:

- 10 mg BID: one capsule of 10 mg PHA-022121 and one placebo capsule after breakfast and dinner
- 20 mg BID: two capsules of 10 mg PHA-022121 after breakfast and dinner
- Placebo: two placebo capsules after breakfast and dinner.

Part 2

The treatment to be administered in Part 2 is open-label PHA-022121 20 mg BID, which consists of two capsules of 10 mg PHA-022121 to be administered orally after breakfast and dinner.

The capsules are to be swallowed with at least 200 mL of water after breakfast and dinner, with 12 ± 2 hours between each dose.

5.3 Selection and Timing of Dose for Each Patient

In Part 1, all randomized patients will self-administer orally blinded IMP BID after breakfast and dinner for the duration of the double-blind treatment period.

In Part 2, all patients will self-administer open-label PHA-022121 20 mg BID after breakfast and dinner for the duration of the open-label treatment period.

Further details on patient dosing, including the supply of IMP provided to each patient at study visits, are included in the schedule of events in [Appendix 1 \(Table 4 and Table 5\)](#).

5.4 Method of Assigning Patients to Treatment Groups

For Part 1, randomization will be performed using an interactive response technology (IRT) system.

Enrolled patients will be randomized in a 1:1:1 ratio to receive placebo or one of two dose regimens of PHA-022121 (10 mg or 20 mg BID). Approximately 10 patients will be assigned to each of the 3 dose regimens. Randomization to treatment groups will be stratified by the documented baseline attack rate prior to screening or confirmed during the screening period (1 to < 2 attacks, 2 to < 3 attacks, or ≥ 3 attacks per 4 weeks).

For Part 2, no randomization will occur; all patients will be assigned the same open-label treatment of 20 mg BID of PHA-022121. An individual patient's dose in Part 2 may be modified based on a benefit-risk assessment and recommendation from the investigator after consultation with and approval by the Sponsor's Medical Lead.

5.5 Blinding

Part 1

Patients, investigators and site personnel, and the sponsor will be blinded to treatment assignment.

Blinding of the treatment administered is achieved with the identical appearance of PHA-022121 capsules and placebo capsules. Each administered dose (twice daily) consists of a combination of 2 capsules of 10 mg PHA-022121 and/or placebo as described in [Section 5.2](#).

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

Access to treatment assignment will be available if the investigator or designee 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. The investigator will have the option of contacting the Medical Monitor to discuss the situation which has arisen and resulted in the need for unblinding of the patient. However, unblinding procedures can be initiated by the investigator without the need to contact the Medical Monitor in an emergency situation. The Medical Monitor will not be involved in the decision to unblind.

The IDMC, in consultation with the Medical Monitor, may also request unblinding of an individual patient's treatment assignment for safety reasons.

In the event of a drug-related, serious, unexpected adverse event (AE), the sponsor's Drug Safety department/designee will be provided with the patient's treatment assignment for the purpose of regulatory reporting. The treatment code will be broken before reporting each expedited event (e.g., suspected unexpected serious adverse reaction [SUSAR]) to regulatory authorities. The IRT will be used by the Drug Safety department/designee to perform regulatory unblinding to identify treatment allocation for each potentially expedited report (i.e., those that meet the

criteria for unblinding, which includes SAEs that are related and unexpected). The treatment allocation will be filed in a secure electronic repository.

Sites will be informed of each patient's treatment allocation in Part 1 once the study is completed.

The unblinding procedures are detailed in the safety management plan (SMP).

Part 2

Part 2 is open-label treatment period; no blinding will be used.

5.6 Prior and Concomitant Therapy

All non-study treatments (including but not limited to all prescription, over-the-counter medications, vitamins and supplements, herbal treatments, nonpharmacological treatments and procedures) administered to patient from the time of signing informed consent through the final study contact (i.e., end-of-study visit) are regarded as prior and/or concomitant therapies and must be documented as such in the electronic case report form (eCRF).

Additionally, all HAE medications (on-demand and/or prophylactic therapy) received by the patient within 3 months of the screening visit will also be documented in the eCRF.

The IMP is not known to be immunosuppressive, therefore the sponsor does not have any restriction to COVID-19 vaccination for study participants. 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.

5.6.1 Management of HAE Attacks

Patients enrolling in the study must have reliable access to and ability to use standard of care acute treatments to manage any HAE attack that requires pharmacological intervention. In accordance with the WAO guidelines, standard of care acute treatments include:

- Icatibant (Firazyr or generic equivalent)
- Ecallantide (Kalbitor)
- Plasma-derived or recombinant C1-INH concentrates (eg, Cinryze, Berinert, Ruconest)

Use of standard of care acute treatments will follow local regulatory approval mandates.

Icatibant is an oligopeptide drug that is metabolised by proteolytic enzymes, while ecallantide and the C1-INH concentrates are all biologics. While there is no data available on the coadministration of PHA-022121 with other approved acute HAE medications, due to the differences in the pathways for drug metabolism, the potential for drug-drug interactions is considered unlikely.

Patients should continue to administer IMP and follow study procedures without alteration to the protocol schedule, even if they receive acute treatment for an HAE attack. All medications associated with the management of an acute attack must be recorded in the ePRO HAE diary.

5.6.2 Prohibited Concomitant Medications

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

- Any medications for long-term prophylactic use to prevent HAE attacks including kallikrein inhibitors, antifibrinolytics (tranexamic acid or epsilon-aminocaproic acid), attenuated androgens (e.g., danazol, stanozolol, and oxandrolone), or C1-INH concentrates.
- Angiotensin-converting enzyme (ACE) inhibitors.
- Strong inhibitors of CYP3A4 such as clarithromycin, itraconazole, ketoconazole, ritonavir, and grapefruit as well as inducers of CYP3A4 such as phenobarbital, phenytoin, rifampicin, and St. John's Wort. If a patient requires a short-term treatment with a moderate or strong inhibitor or inducer of CYP3A4 for an intercurrent illness or a procedure, the Medical Monitor should be consulted to advise on whether treatment with IMP should be suspended and a wash out period is needed and, if it is, for how long.
- Any other investigational drug or device.

The use of medications that are substrates of P-gp and BCRP transporters and have a small therapeutic window are not prohibited, but should be considered carefully.

5.6.3 Nonpharmacologic Treatments and Procedures

To the extent possible, patients should postpone elective procedures (e.g., dental procedures) while participating in Part 1 of the study.

Short-term HAE prophylaxis may be used as needed.

5.7 Restrictions

5.7.1 Contraception

Following completion of the EFD studies in pregnant animals, PHA-022121 is considered an IMP with unlikely human teratogenicity/fetotoxicity in early pregnancy according to the CTFG recommendations (CTFG, 2020). Therefore, this allows the use of medically acceptable, and not just highly effective, birth control methods. Female patients of childbearing potential must agree to practice abstinence from heterosexual intercourse in line with the preferred and usual lifestyle of the patient or must agree to or use medically acceptable contraception from enrollment until 30 days after the last IMP administration (see Section 4.2, inclusion criterion #7 for list of methods).

There are no contraceptive requirements for female patients not of childbearing potential or for male patients.

5.7.2 Fluid and Food Intake

The BID administration of IMP throughout the treatment periods should occur following breakfast and dinner, with 12 ± 2 hours between each dose. The capsules are to be swallowed with at least 200 mL of water.

No other restrictions on fluid or food intake apply during the study.

5.7.3 Patient Activity Restrictions

There are no restrictions for patients in activity.

5.8 Treatment Compliance

Patients will record daily in the ePRO HAE diary the administration of the IMP.

In addition, patients will be instructed to bring unused IMP and empty/used IMP packaging to every site scheduled visit. Treatment compliance will be assessed by the study personnel documenting details on used and unused IMP on the drug accountability form.

5.9 Packaging and Labeling

The IMPs (PHA-022121 or placebo) are packaged and labelled according to current Good Manufacturing Practice.

The IMPs are packaged in aluminium/aluminium (alu/alu) blisters. Blisters will be sealed into a wallet. The wallet will be labelled and rendered tamper evident.

Each wallet will contain multiple daily doses, which consists of a combination of 4 capsules of 10 mg PHA-022121 and/or placebo for administration in Part 1 and 4 capsules of 10 mg PHA-022121 for administration in Part 2. The wallet will clearly mark the patient's morning dose (2 capsules) and evening dose (2 capsules).

5.10 Storage and Accountability

The investigator or designee has overall responsibility for ensuring that the IMP is stored in a secure, limited-access location. Access to the IMP should be restricted to designated study personnel.

Patients will be instructed on appropriate storage of the IMP at their home location.

The IMPs should not be stored above 25°C. Further details on IMP storage will be provided in the Pharmacy Manual.

5.11 Investigational Product Retention at Study Site

Not applicable.

Details on the return or destruction of all used and unused IMP supply is provided in Section [6.9](#).

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 will be given both verbal and written information describing the nature and duration of the clinical study. Further details on patient consent are provided 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, the number of attacks in the last 3 consecutive months and if possible, within the last year, will be collected. For patients receiving prophylactic therapy prior to study participation, the number of attacks over any consecutive 3-month period prior to commencing prophylaxis will also be documented. Patients who were not on prophylactic treatment prior to screening and have a documented history of at least 3 HAE attacks within the last 3 consecutive months prior to screening can be randomized as soon as all screening results are available and once enrollment has been approved by the Sponsor as specified in Section 7.1. If the patient has no documentation or has less than 3 attacks in the 3 months before the screening visit, or was on prophylactic treatment and has completed an appropriate washout (see Exclusion Criterion #4), patient must experience a minimum of 2 HAE attacks during the screening period (up to 8 weeks). As soon as such a patient has experienced 2 attacks during the screening period, he/she can be randomized and does not have to wait for the 8 weeks of the screening period to be completed.

The diagnosis of HAE should be documented prior to randomization by a local or central laboratory value for C1-INH functional level below 50% documented in the medical records (see Inclusion Criterion 2 in Section 4.2).

6.3 Medical History

At screening, existing relevant 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 other time points specified in the schedule of events.

6.5 Physical Examination

A physical examination will be conducted at screening and at other time points specified in the schedule of events (Table 4 and Table 5). 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).

6.6 Vital Signs

Vital signs include blood pressure, heart rate, body temperature, and respiratory rate (screening and Part 1 visits only for respiratory rate). Vital signs will be measured at screening and at other time points specified in the schedule of events. Blood pressure (systolic and diastolic) and heart rate will be taken after the patient has rested in supine or sitting position for at least 5 minutes. 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 heart rate from the blood pressure or ECG machine.

6.7 Digital 12-Lead Electrocardiogram

A 12-lead ECG (digital triplicate) will be performed and recorded, after the patient has rested in the supine position for at least 5 minutes, at the screening visit, and at other time points specified in the schedule of events. 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 have safety laboratory testing performed at screening and at other time points specified in the schedule of events. Clinical laboratory tests for hematology, biochemistry, coagulation, and urinalysis are indicated in Table 3. Women of childbearing potential will have a serum (screening and Part 1 visits) or urine (Part 2 and end-of-study visits) pregnancy testing performed. Post-menopausal women (defined as 12 consecutive months of amenorrhea without an alternative medical cause), will have serum sampling to test for FSH levels at screening.

Blood and urine samples will be processed by a central laboratory, with the exception of urine pregnancy testing. 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 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation based on serum creatinine and patient characteristics (Levey et al. 2009).

Table 3 List of Safety Laboratory Tests

<u>Hematology:</u> • 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 differential count (absolute and relative values) <u>Coagulation:</u> • Prothrombin time (PT) • International normalized ratio (INR) <u>Urinalysis:</u> • Macroscopic analysis: • Bilirubin • Blood • Glucose • Ketones • Leukocyte esterase • Nitrite • pH • Protein • Specific gravity • Urobilinogen • Microscopic analysis:^b • Bacteria • Casts • Crystals • Epithelial cells • RBCs • WBCs • Yeast	<u>Biochemistry:</u> • Albumin • Alkaline phosphatase (AP) • Alanine aminotransferase (ALT; SGPT) • Aspartate aminotransferase (AST; SGOT) • Blood urea nitrogen (BUN) • Bicarbonate • Calcium • Chloride • Creatinine • Gamma-glutamyl transferase (GGT) • Glucose • Lactate dehydrogenase (LDH) • Magnesium • Phosphate • Potassium • Sodium • Total bilirubin • Direct bilirubin • Total protein • Uric acid • eGFR CKD-EPI (calculated)* <u>Pregnancy test (for women of childbearing potential):</u> • Serum or urine human chorionic gonadotropin (hCG)^a <u>Follicle-stimulating hormone (FSH) test (for confirming post-menopausal status)^c:</u> • Serum FSH
---	--

^a Serum pregnancy testing will be performed at screening and Part 1 visits and urine pregnancy testing will be performed at Part 2 and end-of-study visits.

^b Microscopic urinalysis to be performed at screening and Part 1 visits. No microscopic urinalysis is needed at Part 2 and end-of-study visits.

^c At screening only.

6.8.2 Pharmacokinetic Plasma Sample Collection, Storage, and Shipping

In Part 1, plasma samples for PK evaluation will be collected pre-dose and between 2-3 hours following the patient's morning dose on Day 0 (Visit 1), Day 42 (Visit 4), and Day 84 (Visit 6). Patients should be in a fasted state (fasting from midnight or for at least 8 h) for the pre-dose sample collection.

In Part 2, plasma samples for PK evaluation will be collected at Visits 7, 9 (if on-site), and 11. The time of the last dose of IMP and the last meal prior to the PK sampling is to be entered in the eCRF. (In Part 2, patients are not required to be in a fasted state at the time of PK sample collection.)

Collected plasma samples will be stored at $-80\pm 16^{\circ}\text{C}$. Plasma samples will be transferred frozen to the bioanalytical laboratory contracted by the sponsor.

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 IMP

The IMP must be dispensed under the supervision of the investigator or designee using the IRT system for assigning treatments, allocating IMP, 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 IMP 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 IMP that were supplied to the investigator's site.

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

Any medication errors, including incorrect dosage, using expired IMP, storage requirement excursions, administration errors etc., should be recorded as protocol deviations and the sponsor should be immediately informed.

6.10 Efficacy Assessments

Analyses of the efficacy endpoints in this study require documentation of specific information regarding the patient's symptoms of any HAE attacks experienced during the study.

6.10.1 Definition of an HAE Attack

The definition of an HAE attack provided in following criteria allows for the investigator to make an assessment if the events reported by the patient can be confirmed as an HAE attack.

To be confirmed as an HAE attack, the event must have signs or symptoms consistent with an attack in at least one of the following locations:

- Peripheral angioedema: cutaneous swelling involving an extremity, face, neck, torso and/or genitourinary region
- Abdominal angioedema: abdominal pain, with or without abdominal distension, nausea, vomiting, or diarrhea

- Upper airway angioedema: lump sensation, difficulty swallowing, throat tightening, difficulty speaking, hoarseness, stridor, dyspnea, or upper airways swelling on the tongue, palate, uvula, or larynx

Despite the presence of these symptoms, the investigator may still determine that the event does not represent an HAE attack if there are clinical features that strongly refute such a diagnosis (e.g., associated with wheals or longer in duration than the typical time course of an attack or alternate etiology such as recent trauma resulting swelling or pain).

To be counted as a unique HAE attack distinct from a previous attack, the new symptoms must occur at least 24 hours after complete resolution of symptoms of a prior attack (i.e., there must be a 24-hour symptom-free period to be considered a new attack).

Patient-reported occurrences of prodromal symptoms alone or pre-emptive use of acute treatments without swelling symptoms are not considered to meet the criteria of an HAE attack.

6.10.2 Reporting of HAE Attacks

Efficacy will be assessed based upon investigator-confirmation of patient-reported details of occurrences of HAE attacks. During screening, site personnel will discuss with patients the requirements for reporting attacks, including the information that is to be captured for each HAE attack.

Patients will use an ePRO HAE diary daily to record any symptoms and details of HAE attacks, including relevant treatments. Patients will receive training on how to use the ePRO HAE diary at the screening visit and throughout the study, as needed. Patients will be instructed to report details of any HAE attack to the study site within 72 hours of onset of symptoms of an attack.

The investigator will complete a separate eCRF for each confirmed attack based on their review of the data in the patient's ePRO HAE diary and in follow-up with the patient. Additional queries by the investigator or site personnel during patient follow-up will include questions such as: whether the patient only experienced prodromal symptoms, whether the symptoms experienced were typical or different from prior attacks, or whether there were possible alternative etiologies for the symptoms. Any patient-reported HAE attack that is not confirmed by the investigator as an HAE attack, must have an alternate AE diagnosis recorded.

Information recorded in the eCRF will include, but is not limited to, the following:

- Date and time of onset of symptoms of an HAE attack
- Location (site) of the swelling or pain (indicating all that apply)
 - upper airways (laryngeal, pharyngeal)
 - gastrointestinal/abdominal
 - genitourinary (including scrotum or vulva)
 - facial
 - truncal (extremity, peripheral, or torso)
- Severity (intensity) based on impact of symptoms on patient's daily activity
 - Mild: the HAE attack is noticeable but is easily tolerated by the patient and does not interfere with routine activities
 - Moderate: the HAE attack limits/interferes with the patient's ability to attend work/school or participate in family life and social/recreational activities

- Severe: the HAE attack significantly limits with the patient's ability to attend work/school or participate in family life and social/recreational activities
- Investigator assessment of symptom(s)
- Acute treatments administered for the HAE attack (date, time, and medication(s), including the number of doses administered)
- Date and time of resolution of HAE symptoms
- If the HAE attack resulted in hospitalization or a visit to the emergency department

HAE attacks and their associated symptoms will not be defined as AEs/SAEs per se. Some of the triggers for HAE attacks, such as an infection or trauma, may be considered as AEs or SAEs, and therefore should be reported per the usual AE reporting process. HAE attacks that meet criteria as defined in Section 6.12.1 are considered SAEs and should be reported per the usual SAE reporting process.

6.11 Health-related Quality of Life Assessments

6.11.1 Angioedema Quality of Life Questionnaire

The Angioedema Quality of Life (AE-QoL) questionnaire is symptom-specific tool developed and validated to assess health-related quality of life impairment in patients with recurrent angioedema (Weller et al. 2012). The AE-QoL consists of 17 questions across four domains/dimensions (functioning, fatigue/mood, fear/shame, nutrition). Each of the 17 items has a five-point Likert-type response scale ranging from 1 (Never) to 5 (Very Often). The AE-QoL is scored to produce a score for each domain and a total score ranging from 0 to 100, with higher scores indicating greater impairment.

6.11.2 Angioedema Quality of Life Anchor Questions

Two anchor questions will also be completed by patients: a patient global assessment of quality of life (PGA-QoL; also referred to as the Patient Global Impression of Severity [PGIS]) and a patient global assessment of change (PGA-change; also referred to as the Patient Global Impression of Change [PGIC]). The PGA-QoL question covers how much the patient's QoL was impacted by their HAE over the past 4 weeks with a four-point Likert response scale (not at all, slightly, moderately, highly). The PGA-change question covers the overall change in how the patient's QoL has been impacted by their HAE since starting to take the IMP with a five-point Likert response scale (much better, a little better, no change, a little worse, or much worse). Both anchor questions were developed according to the FDA standards (FDA, 2018b) and will be used to help interpretation of a clinically meaningful within-patient score change in the AE-QoL questionnaire.

6.11.3 Angioedema Control Test

The Angioedema Control Test (AECT) was developed and validated to retrospectively quantify disease control and to aid treatment decisions in patients with recurrent angioedema (Weller et al., 2020a; Weller et al., 2020b). The AECT has 4 questions with each question having 5 answer options (each scored 0 to 4 points), addressing the frequency of angioedema, angioedema-related QoL impairment, unpredictability of angioedema attacks, and angioedema control by the current

treatment approach. The AECT ranges from 0 to 16 points, with total scores of 0-9 points indicating poorly controlled disease and 10-16 points indicating well controlled disease. The AECT version with a 4-week recall period (i.e., AECT-4wk) will be used in this study.

6.11.4 Treatment Satisfaction Questionnaire for Medication Scores

The 11-item Treatment Satisfaction Questionnaire for Medication (TSQM) evaluates patient treatment satisfaction with the medication for the following scales: effectiveness, side effects, convenience, and overall satisfaction (Atkinson et al. 2004). Scale scores are transformed into scores ranging from 0 to 100 and can be used to calculate a total composite score.

6.12 Adverse Events and Serious Adverse Events

6.12.1 Definitions

An adverse event (AE) is defined as, any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Baseline medical history/conditions, or abnormal diagnostic/laboratory values present at the screening visit, are not considered to be AEs, and should be recorded in the eCRF as baseline medical history. However, any worsening in severity, or an increase in frequency, of a pre-existing baseline medical condition is considered to be an AE.

Per ICH E2A, "In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase 'responses to a medicinal products' means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out."

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

- results in death;
- is life-threatening (at the time of the event);
NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- 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.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the

definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse (SAE definitions and criteria above are per ICH E2A).

Details on the reporting of HAE attacks (including possible associated AEs/SAEs) are provided in Section 6.10.2.

6.12.2 Adverse Event and Serious Adverse Event Assessments

The investigator or qualified designee will be responsible for assessing AEs and SAEs. Reporting of AEs and SAEs (also referred to as “events”) 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. When assessing for potential AEs, questioning should be open-ended, without leading the patient. 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 AEs, SAEs, or findings that seem unusual (e.g., an abnormal laboratory test result), regardless of its relationship to IMP, and even if it may be considered to be an unanticipated beneficial effect.

AEs and SAEs 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 and are a component of the reached diagnosis should not be recorded (use the reached diagnosis). However, if a diagnosis is initially unknown or uncertain, any signs and symptoms (or diagnostic test results) must be recorded. As soon as diagnosis is known, the event term(s) must be adjusted to the final reached diagnosis.

All AEs and SAEs are to be recorded on the eCRFs from the time of signing informed consent until the end-of-study visit. In certain situations, AE and SAE information is collected after the end-of-study visit (as outlined below).

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

SAEs are to be followed until the event resolves (or resolves with sequelae/stabilizes), the patient withdraws from the study, or the patient is lost to follow-up. If the event is a Grade 1 or 2 event (see Section 6.12.3.1 for AE grading) and 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 and 4 events, and events assessed as related to the IMP, the event should be followed until it is resolved (or resolves with sequelae/stabilizes), the patient

withdraws from the study, or the patient is lost to follow-up. This may require reporting after the end-of-study visit occurs.

The sponsor/designee retains the right to request additional information later for any patient with ongoing AEs/SAEs that are present at the end-of-study visit, if judged necessary.

If a patient dies during study participation, or during a recognized follow-up period, in addition to the investigator immediately reporting the death as a SAE, the investigator should attempt to provide the sponsor/designee with detailed information regarding the death.

6.12.3 Classification of an Adverse Event

6.12.3.1 CTCAE Grade and Severity

The National Cancer Institute (NCI) CTCAE is a descriptive terminology which can be utilized for event/Adverse Event (AE) reporting. Adverse events (also referred to as "events") are classified by CTCAE grade/severity.

The CTCAE incorporates certain elements of the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The System Organ Class (SOC), is the highest level of the MedDRA hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., the SOC called "Investigations" is used for laboratory test results). An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE term is a MedDRA lowest level term.

Per NCI CTCAE, grade refers to the severity of the event. The CTCAE grade/severity should be evaluated and recorded on the eCRF according to the NCI CTCAE, version 5.0 (NCI, 2017).

The grade refers to the severity of the AE. CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this 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 (ADL)*.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

** Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*

*** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.*

6.12.3.2 Relationship to IMP

All AEs/SAEs (events) will be assessed to determine their relationship to the IMP (causality). The investigator must assess the causality using the binary choices of “Related” or “Unrelated,” and by considering the rationales listed below. Events should be considered “Related” only if there is a reasonable possibility of a causal relationship to the IMP. These rationales allow the investigator to more clearly support their own assessments. All AEs and SAEs should be reported, regardless of causality, including events that are thought to be “Related” to targeted disease and/or population.

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 IMP
- Biological plausibility

6.12.4 Reporting Serious Adverse Events

All SAEs after signing of the informed consent through the end-of-study visit must be reported to the sponsor/designee by the investigator within 24 hours of the investigator's knowledge of their occurrence, independent of the circumstances or suspected cause. Details on reporting of events are provided in Sections [6.12.1](#) through [6.12.3](#).

The SAE must be reported by immediately completing the appropriate fields of the eCRFs using acceptable medical terminology, written in English, and must include a causality assessment (relationship to IMP). Simultaneously, any other applicable eCRF pages, including relevant AE and concomitant medications eCRF pages, must also be completed. Supporting source documents such as hospital discharge summaries may be provided via the SAE reporting contact information provided below.

If the electronic data capture (EDC) system is unable to be accessed, utilize the Medpace Clinical Safety SAE Reporting contact information listed below. A paper SAE Report Form

should be completed and sent within 24 hours. 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 (North America)
+49 89 89 55 718 44 (EMEA)

Safety Fax: +1-866-336-5320 or
+1-513-570-5196 (North America)
+49 89 89 55 718 104 (EMEA)

Email: medpace-safetynotification@medpace.com

If a paper SAE Report Form was utilized, the original paper form, together with the fax confirmation sheet (if applicable), must be retained at the study site. If the initial SAE report is made verbally, via email, or by telephone, a written form of the SAE must follow within 24 hours (via eCRF entry or paper SAE Report Form). The investigator will be requested to provide 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 / AE eCRF. Accompanying signs or symptoms (e.g., physical exam findings, abnormal diagnostics test results, ECG findings, etc.) should not be reported as additional SAEs. However, if initially the diagnosis is unknown, the signs and symptoms should be reported. As soon as a reached diagnosis causing the signs and symptoms is known, the event term(s) should be amended 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 (resolved with sequelae), the patient withdraws from the study, or the patient is lost to follow-up. All follow-up should be reported to the sponsor/designee within 24 hours of awareness.

The Pharvaris Medical Lead will ultimately be responsible for determining whether an SAE is expected or unexpected utilizing the reference safety information (RSI) of the version of the Investigator's Brochure that is in place at the time of the event's occurrence and assessment. An SAE will be considered unexpected if the nature, grade/severity, or frequency of the event is not consistent with the list of expected adverse reactions.

If an SAE is assessed as unexpected per the Investigator's Brochure in place at the time of awareness of the event and is assessed as related to the IMP at any dose, then it is called a Suspected Unexpected Serious Adverse Reaction (SUSAR). All SUSARs will be subject to expedited reporting to the regulatory authorities by the sponsor or designee, per recognized regulatory timelines.

6.12.5 Events of Special Interest

Currently, there are no clearly identifiable events of special interest defined for PHA-022121.

6.12.6 Reporting of Pregnancy

Any treated female patient who becomes pregnant during the study will be withdrawn from the study, and IMP will be discontinued immediately. Procedures indicated at the end-of-study visit may be performed, if medically safe to do so. The pregnancy will then be followed until the pregnancy's outcome.

While pregnancy is not considered an AE per se, pregnancies must be reported immediately to the sponsor or designee using the Pregnancy Report Form and following SAE reporting timelines (i.e., reporting from the investigator/site to the sponsor/designee).

A pregnancy in a female patient who has received IMP should be followed to pregnancy outcome to assess for any potential occurrence of congenital anomalies or birth defects (discovered in-utero or at birth). Similarly, pregnancies that occur in female partners of treated male patients should also be reported immediately and followed to outcome (if consent is provided).

Pregnancy outcomes 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 elective).

If a spontaneous abortion occurs, or a congenital abnormality/birth defect is observed (including in utero detections), they must be reported immediately to the sponsor or designee.

Some pregnancy findings and outcomes (e.g., spontaneous abortion, stillbirth, congenital abnormality/birth defect, [including in utero detections]), may meet seriousness criteria, and may need to comply with SAE regulatory reporting timelines.

6.13 Concomitant Medication Assessments

The investigator or designee is responsible for assessing and reviewing the use of concomitant medication between the dates of signed informed consent through the end-of-study visit, inclusive (Section 5.6). 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 on-demand acute treatments to manage HAE attacks will also be recorded.

6.14 Removal of Patients from the Study or IMP

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 any of the following reasons:

- Pregnancy
- Significant IMP noncompliance
- If any clinical AE/SAE, laboratory abnormality, or other medical condition or situation occurs that negatively impacts that benefit-risk such that continued participation in the study would not be in the best interest of the patient

- If the patient meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

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 eCRF.

Patients who are discontinued from IMP prematurely will be encouraged to complete scheduled assessments through the end of the study, but at a minimum will be required to complete an end-of-study visit 4 weeks after the last treatment administration.

Patients who express an intent to withdraw from further study participation will be requested to complete an end-of-study visit 4 weeks after the last treatment administration.

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

To be eligible for continued treatment in Part 2, the patient must have completed Part 1, unless discontinued from Part 1 due to regulatory actions. If there is a gap in treatment between Parts 1 and 2, Visit 7 safety assessments are to be performed, with results reviewed by the Investigator, and patient eligibility reconfirmed before the patient may restart treatment in Part 2.

6.15 Premature Study Termination

This study will be prematurely terminated or suspended by the sponsor 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)

6.16 Appropriateness of Measurements

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

7 STUDY ACTIVITIES

All study procedures to be performed are described below by visit, with the schedule of events provided in [Appendix 1](#) ([Table 4](#) and [Table 5](#)).

Since the study is ongoing during the COVID-19 pandemic, unless identified as a mandatory on-site visit, some of the planned visits and assessments may be performed remotely by a visiting nurse or home healthcare provider, where applicable and permitted by local regulations. In addition, virtual visits via telehealth will also be performed at specified time points (see [Table 4](#) and [Table 5](#)). For remote visits, direct shipment of IMP to patients may be implemented, with IMP oversight and accountability performed by the visiting nurse or home healthcare provider, if permitted by local regulations. In Part 1, weekly check-in calls with patients by site personnel (investigator or designee) will be performed following any off-site visit through to the next on-site visit.

7.1 Screening

The screening period may take up to 8 weeks. The following assessments will be performed on-site. After the on-site screening visit, the investigator will confirm whether the patient is eligible for the study after the results of all safety laboratory tests have become available and after obtaining approval from the Sponsor to enroll the patient.

- Informed consent
- Review eligibility (inclusion/exclusion criteria)
- Demographics and HAE characteristics including serum sampling for laboratory assessment of C1q level, C4 level and, if a documented C1-INH functional level lower than 50% is not available, C1-INH functional level
- Medical history
- Weight and height
- Physical examination
- Vital signs
- Digital triplicate 12-lead ECG
- Clinical laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Pregnancy test (for women of childbearing potential), using serum sampling for hCG test
- FSH testing (for women who have 12 consecutive months of amenorrhea without an alternative medical cause and are considered post-menopausal), using serum sampling
- Adverse events (reporting of adverse events occurs from date of signed informed consent through the end-of-study visit, inclusive; see [Section 6.12](#) for details)
- Prior and/or concomitant medications
- ePRO HAE diary training: patient is introduced to the use of the ePRO HAE diary and their capability to complete the ePROs is confirmed

Enrollment: 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.

7.2 Part 1: Double-blind Treatment Period (Day 0 to Day 84)

Throughout the treatment period, patients will administer the IMP orally twice daily, following breakfast and dinner. Mandatory on-site visits that require study procedures to be performed prior to patient's morning dose and in a fasted state (e.g., pre-dose ECG recording and pre-dose PK sampling), are noted below.

7.2.1 Visit 1 (Day 0) Procedures

The following procedures will be performed on-site prior to the first dose IMP, with patients being in a fasted state:

- Eligibility check
- Randomization
- Weight
- Vital signs
- Digital triplicate 12-lead ECG (ECG recordings should occur prior to plasma PK samplings)
- Clinical laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Pregnancy test (if applicable)
- Adverse events
- Prior and/or concomitant medications
- Dispense IMP
- PK plasma sampling
- Continued ePRO HAE diary training: patient will receive additional training on the use of the ePRO HAE diary at this visit and throughout the study, as needed
- AE-QoL questionnaire
- PGA-QoL question (PGA-QoL question is to be completed by the patient after the AE-QoL questionnaire)
- AECT-4wk

The following procedures will be performed on-site 2-3 hours after the patient's first dose IMP:

- Digital triplicate 12-lead ECG (ECG recordings should occur prior to plasma PK samplings)
- PK plasma sampling

In addition, symptoms/occurrences of HAE attacks and medications administered for the treatment of HAE attacks are to be documented daily in the ePRO HAE diary throughout the treatment period.

7.2.2 Visit 2 (Day 14) Procedures

The following procedures will be performed at Visit 2 (option to occur remotely if feasible and approved by the site, and where permitted by local regulations):

- Vital signs
- Clinical laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Adverse events
- Concomitant medications
- Dispense IMP
- HAE diary (daily)

7.2.3 Visit 3 (Day 28) Procedures

This is a virtual visit whereby site personnel (investigator or designee) will contact patients by telephone or videoconference to ensure the following procedures are performed at Visit 3:

- Adverse events
- Concomitant medications
- HAE diary (daily)
- AE-QoL questionnaire
- AECT-4wk
- TSQM score

7.2.4 Visit 4 (Day 42) Procedures

The following procedures will be performed on-site at Visit 4, with patients being in a fasted state prior to dosing with IMP:

- Vital signs
- Digital triplicate 12-lead ECG (ECG recordings should occur prior to plasma PK samplings)
- Clinical laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Pregnancy test (if applicable)
- Adverse events
- Concomitant medications
- Dispense IMP
- PK plasma sampling
- HAE diary (daily)

The following procedures will be performed on-site 2-3 hours after the patient's morning dose of IMP:

- Digital triplicate 12-lead ECG (ECG recordings should occur prior to plasma PK samplings)
- PK plasma sampling

7.2.5 Visit 5 (Day 56) Procedures

This is a virtual visit whereby site personnel (investigator or designee) will contact patients by telephone or videoconference to ensure the following procedures are performed at Visit 5:

- Adverse events
- Concomitant medications
- HAE diary (daily)
- AE-QoL questionnaire
- AECT-4wk
- TSQM score

7.2.6 Visit 6 (Day 84, End of Part 1) Procedures

The following procedures will be performed on site at Visit 6, with patients being in a fasted state prior to dosing with IMP:

- Weight
- Physical examination
- Vital signs
- Digital triplicate 12-lead ECG (ECG recordings should occur prior to plasma PK sampling)
- Clinical laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Pregnancy test (if applicable)
- Adverse events
- Concomitant medications
- PK plasma sampling
- HAE diary (daily)
- AE-QoL questionnaire
- PGA-QoL and PGA-change questions (PGA-QoL and PGA-change questions are both to be completed by the patient after the AE-QoL questionnaire, with PGA-QoL being completed first followed by PGA-change)
- AECT-4wk
- TSQM score

The following procedures will be performed on-site 2-3 hours after the patient's last dose of IMP. (This will be the last IMP administration in Part 1):

- PK plasma sampling
- Dispense IMP for Part 2

Note: Part 2 of the study will begin with the patient's administration of IMP dispensed at Visit 6. The patient's first dose of open-label IMP should occur after dinner on the same day as Visit 6 unless there is a gap in dosing between Parts 1 and 2 in which case the first dose of open label IMP will be administered in the morning of Visit 7.

7.3 Part 2: Open-label Treatment Period

The study allows patients to receive continuous treatment with IMP from Part 1 (double-blind period) to Part 2 (open-label period). In the event that a patient cannot continuously receive treatment between Part 1 and Part 2 or any time during Part 2, the patient may continue participation in this study after signing the ICF for the latest approved amendment.

To be eligible for continued treatment in Part 2, the patient must have completed Part 1, unless discontinued from Part 1 due to regulatory actions. If there is a gap in treatment between Parts 1 and 2, Visit 7 safety assessments are to be performed, with results reviewed by the Investigator, and patient eligibility reconfirmed before the patient may restart treatment in Part 2.

Part 2 of the study will begin with the patient's administration of IMP dispensed at Visit 6. The patient's first dose of open-label IMP should occur after dinner on the same day as Visit 6 and the last dose of open-label IMP will be after breakfast on the same day as Visit 17. For patients with a gap between the completion of Part 1 and the beginning of Part 2, the first dose of open label extension drug will be administered after Visit 7 safety assessments have been reviewed and patient eligibility has been reconfirmed by the Investigator, and the last dose of open-label IMP will be after breakfast on the same day as Visit 17.

7.3.1 Visit 7 (Day 91) Procedures

The following procedures will be performed on-site at Visit 7:

- Physical examination
- Vital signs
- Digital triplicate 12-lead ECG (ECG recordings should occur prior to plasma PK samplings)
- Clinical laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Pregnancy test (if applicable)
- Adverse events
- Concomitant medications
- Dispense IMP
- PK plasma sampling (time of the last dose of IMP and the last meal prior to PK sampling is to be recorded in the eCRF)
- HAE diary (daily)
- AE-QoL questionnaire
- PGA-QoL and PGA-change questions (PGA-QoL and PGA-change questions are both to be completed by the patient after the AE-QoL questionnaire, with PGA-QoL being completed first followed by PGA-change)
- AECT-4wk
- TSQM

7.3.2 Visits 8 and 10 (Days 126 and 210) Procedures

These are virtual visits whereby site personnel (investigator or designee) will contact patients by telephone or videoconference to ensure the following procedures are performed at Visits 8 and 10:

- Adverse events
- Concomitant medications
- HAE diary (daily)
- AE-QoL questionnaire
- PGA-QoL and PGA-change questions (PGA-QoL and PGA-change questions are both to be completed by the patient after the AE-QoL questionnaire, with PGA-QoL being completed first followed by PGA-change)
- AECT-4wk
- TSQM score

7.3.3 Visit 9, 12, 14, and 16 (Days 168, 343, 525, and 777) Procedures

The following procedures will be performed at Visits 9, 12, 14, and 16 (option to occur remotely if feasible and approved by the site, and where permitted by local regulations):

- Vital signs
- Digital triplicate 12-lead ECG at Visit 9 only (ECG recordings should occur prior to plasma PK sampling)
- Clinical laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Pregnancy test (if applicable)
- Adverse events
- Concomitant medications
- Dispense IMP
- PK plasma sampling (Visit 9 only [if on-site]; time of the last dose of IMP and the last meal prior to PK sampling is to be recorded in the eCRF)
- HAE diary (daily)
- AE-QoL questionnaire
- PGA-QoL and PGA-change questions (PGA-QoL and PGA-change questions are both to be completed by the patient after the AE-QoL questionnaire, with PGA-QoL being completed first followed by PGA-change)
- AECT-4wk
- TSQM score

7.3.4 Visit 11, 13, 15, and 17 (Day 252, 434, 686, and 938) Procedures

The following procedures will be performed on-site at Visits 11, 13, 15, and 17.

- Physical examination
- Vital signs
- Digital triplicate 12-lead ECG at Visits 11, 15, and 17 (ECG recordings should occur prior to plasma PK sampling at Visit 11)

- Clinical laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Pregnancy test (if applicable)
- Adverse events
- Concomitant medications
- Dispense IMP at visits other than Visit 17.
- PK plasma sampling at Visit 11 (time of the last dose of IMP and the last meal prior to PK sampling is to be recorded in the eCRF)
- HAE diary (daily)
- AE-QoL questionnaire
- PGA-QoL and PGA-change questions (PGA-QoL and PGA-change questions are both to be completed by the patient after the AE-QoL questionnaire, with PGA-QoL being completed first followed by PGA-change)
- AECT-4wk
- TSQM

7.4 Early Discontinuation Procedures

Patients who are discontinued from IMP prematurely will be encouraged to complete scheduled assessments through the end of the study, but at a minimum will be required to complete an end-of-study visit 4 weeks after the last treatment administration.

Patients who express an intent to withdraw from further study participation will be requested to complete an end-of-study visit 4 weeks after the last treatment administration.

7.5 End-of-Study Procedures (Visit 18; Day 966)

An end-of-study visit will be performed 4 weeks after the last treatment administration. The following procedures will be performed at Visit 18 (option to occur remotely):

- Vital signs
- Clinical laboratory testing (hematology, biochemistry, coagulation, urinalysis)
- Pregnancy test (if applicable)
- Adverse events
- Concomitant medications
- HAE diary

This visit may be waived if patients continue in another clinical study 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 the sponsor or their representatives. In accordance with the sponsor's SOPs, this study may be subject to independent quality assurance (QA) Good Clinical Practice (GCP) audits at the study sites or at the relevant study contract reach organizations (CROs)/vendors.

The study CRO(s) will, with the support and input of the sponsor, create (before study initiation) and maintain (throughout the study) a Risk Assessment and Mitigation plan, which will allow the study team to assess key quality variables during the study, and take actions as needed.

The sponsor 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 independent ethics committee (IEC) / independent review board (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, safety laboratory tests will be analyzed at central laboratories, and ECG-readings will be centralized.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

Planned analyses for this study are summarized below. Details of the planned analyses, method of handling missing data, sensitivity analyses, subgroup analyses, and exploratory analyses will be provided in the SAP. The SAP will comply with the GCP requirements. Any deviations from the planned analyses will be justified in the clinical study report. All analyses will be carried out using SAS® software Version 9.4 or higher (SAS Institute, Cary, NC, United States).

9.2 Determination of Sample Size

Power analysis and sample size estimation were conducted by assuming a Poisson distribution for angioedema attacks. [REDACTED]

Approximately 30 patients will be enrolled with an equal allocation rate to each group, with a randomization ratio of 1:1:1. Randomization to treatment groups will be stratified by the documented baseline attack rate prior to screening or confirmed during the screening period (1 to < 2 attacks, 2 to < 3 attacks, or ≥ 3 attacks per 4 weeks). For a treatment effect of 60% reduction in attacks as compared to placebo, [REDACTED]

[REDACTED] a sample size of 10 patients per group receiving active treatment and 10 patients receiving placebo would provide an approximate 85% power, at a significance level of 0.05 for two-sided test comparing each dose of PHA-022121 to placebo, without multiplicity correction for the two comparisons. Assuming a larger treatment effect of 80% reduction in attack rate, the power would increase to approximately 98%. The sample size consideration is to support the statistical testing for data from the blinded, placebo-controlled treatment phase (i.e., Part 1 analysis).

9.3 Analysis Sets

The analysis sets for this study are defined below:

- Intent-to-treat (ITT) Analysis Set includes all randomized patients who received at least one dose of IMP (PHA-022121 or placebo). In the analyses performed on the ITT Analysis Set, unless otherwise specified, patients will be analyzed according to their assigned treatment group per randomization regardless of actual treatment received.
- Safety Analysis Set includes all randomized patients who received at least one dose of IMP (PHA-022121 or placebo), essentially the same set of patients included in the ITT Analysis Set. In analyses performed on the Safety Analysis Set, patients will be analyzed according to their actual treatment received.
- Pharmacokinetic Analysis Set includes as all randomized patients who contribute data to PK evaluations.

9.4 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized using descriptive statistics for each treatment group.

Descriptive statistics will be tabulated as follows:

- Categorical data will be summarized in frequency tables including 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 Safety Endpoints

In both Part 1 and Part 2 of the study, the evaluation of safety includes the following endpoints:

- Treatment-emergent adverse events (TEAEs), treatment-related AEs, and treatment-emergent SAEs
- Clinical laboratory tests
- Vital signs
- ECG data

Adverse events will be coded using MedDRA. The safety endpoints will be summarized using the Safety Analysis Set. Treatment-emergent AEs (TEAEs) are defined as AEs that start or pre-existing AEs that have worsened after the initiation of IMP treatment. For patients with no gap between Part 1 and Part 2, Part 1 TEAEs are AEs that start or pre-existing AEs that have worsened during the time period between the first dose of IMP in Part 1 to the first dose in Part 2; Part 2 TEAEs are AEs that start or pre-existing AEs that have worsened during the time period between the first dose of IMP in Part 2 and 4 weeks after the last dose of IMP in Part 2 or the End of Study visit, whichever is later. For patients with a gap between Part 1 and Part 2, Part 1 TEAEs are AEs that start or pre-existing AEs that have worsened during the time period between the first dose of IMP in Part 1 and 4 weeks after the last dose of IMP in Part 1. Part 2 TEAEs are AEs that start or pre-existing AEs that have worsened during the time period between the first dose of IMP in Part 2 and 4 weeks after the last dose of IMP in Part 2 or the End of Study visit, whichever is later. The number and percentage of patients with TEAEs in Part 1 will be displayed for each treatment group by body SOC and preferred term. Summaries in terms of CTCAE grade/severity and relationship to IMP will also be provided. Serious AEs (SAEs) will be summarized separately in a similar fashion. Patient listings of TEAEs leading to discontinuation of IMP, AEs/SAEs leading to death, patient withdrawals, pregnancies, and SAEs will also be produced.

Usage of concomitant medications (other than rescue medications) in Part 1 will be summarized descriptively for each of the treatment groups and the combined active treatment group. Concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD).

Clinical laboratory data, vital signs, physical examination, and ECG data will be presented in summary tables and/or individual listings.

The safety analyses will be analyzed separately for Part 1. Safety data from Parts 1 and 2 will be combined for a long-term safety assessment.

9.6 Efficacy Endpoints

Part 1

The primary efficacy endpoint will be the number of investigator-confirmed HAE attacks during the treatment period in Part 1 (Day 0 through Day 84) and will be expressed as the normalized number of attacks per month (4 weeks) of exposure. The monthly attack rate is calculated for each patient as number of HAE attacks occurring during the treatment period divided by the number of days the patient contributed to the treatment period multiplied by 28 days.

The analysis of primary efficacy endpoint will be performed based on the ITT Analysis Set, and will compare each PHA-022121 dose group with the placebo group using a generalized linear model (GLM) assuming a Poisson distribution with a log link function and Pearson chi-square scaling of standard errors to account for potential dispersion. The model will include fixed effects for treatment group (categorical), the normalized baseline attack rate (continuous), the stratification factor of baseline attack rate (categorical), and an offset term of the logarithm of patient's follow-up time (in days) during the efficacy evaluation period. The estimated least squares (LS) mean rate for each PHA-022121 dose group and the mean rate ratios relative to the placebo group will be provided with 95% confidence intervals. These estimates will be reported as monthly attack rates (mean numbers of events per 4 weeks) by transforming the estimates using the exponential function and scaling by the unit of time. The treatment effect in the primary efficacy endpoint will be tested using a Wald-based chi-square test. Analysis using a negative binomial GLM will be performed as sensitivity analysis. In addition, Wilcoxon two-sample test will also be conducted comparing each PHA-022121 dose group with the placebo group.

The secondary efficacy endpoints in Part 1 of the study are listed below. The responder endpoints (e.g., achieving $\geq 50\%$ reduction in attack rate relative to baseline during the treatment period in Part 1) are derived for subjects with at least 4 weeks of study drug in Part 1. Summary statistics on the number of events, event rates, and number and proportion of patients will be provided. Similar methods used for the primary efficacy endpoint will be performed for the endpoints, if applicable. Fisher's exact test will be used for testing responder proportions. Kaplan-Meier method will be used to analyze the time to first investigator-confirmed HAE attack.

- Number of investigator-confirmed moderate or severe HAE attacks during the treatment period in Part 1 (Day 0 to Day 84).
- Number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period in Part 1.
- Number of patients achieving $\geq 50\%$ reduction in attack rate relative to baseline during the treatment period in Part 1.
- Number of patients achieving $\geq 70\%$ reduction in attack rate relative to baseline during the treatment period in Part 1.
- Number of patients achieving $\geq 90\%$ reduction in attack rate relative to baseline during the treatment period in Part 1.
- Number of patients that are attack-free during the treatment period in Part 1.
- Number and proportion of days with angioedema symptoms during the treatment period in Part 1.

- Time to first investigator-confirmed HAE attack in the treatment period in Part 1.
- Number of investigator-confirmed HAE attacks resulting in a visit to the emergency department or an admission to hospital during the treatment period in Part 1.

The analyses of these secondary efficacy endpoints are considered supportive, all statistical tests comparing treatments are descriptive in nature and will be made without adjustment for multiplicity.

Part 2

The efficacy endpoints in Part 2 of the study are:

- Number of investigator-confirmed angioedema attacks during the treatment period in Part 2 (from time of the first open-label dose to the last dose, excluding the treatment gap in Part 2).
- Number of investigator-confirmed moderate or severe angioedema attacks during the treatment period in Part 2.
- Number of investigator-confirmed angioedema attacks requiring acute treatment during the treatment period in Part 2.
- Incidence of HAE attacks during the treatment period in Part 2 (attack rate trend over time).
- Number and proportion of days with angioedema symptoms during the treatment period in Part 2.

The analysis of the efficacy endpoints in Part 2 will be performed based on the ITT analysis set. The number of investigator-confirmed HAE attacks during the treatment period in Part 2 will be expressed as the normalized number of attacks per month (4 weeks) of exposure. The normalized number of investigator-confirmed HAE attacks during the treatment period in Part 2 will be descriptively summarized. Similarly, normalized number of investigator-confirmed moderate or severe HAE attacks during the treatment period in Part 2, normalized number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period in Part 2, and proportion of days with HAE symptoms during the treatment period in Part 2 will be summarized.

All efficacy analyses in Part 2 will be descriptive.

9.7 Pharmacokinetic and Quality of Life Endpoints

Additional endpoints to be evaluated during each part of the study include:

- Pharmacokinetic parameters based on plasma concentration of PHA-022121
- Change from baseline in the AE-QoL questionnaire
- PGA-QoL and PGA-change questions
- AECT-4wk scores
- TSQM scores

Since only sparse PK sampling will be obtained for patients, PK parameters will be determined using an existing population PK model for PHA-022121.

For AE-QoL, the raw domain scores (mean of the item scores within each domain) and the raw total score (mean of all item scores) will be computed. All raw domain scores and total score will be transformed into percentage scores (0 – 100) prior to analyses. All four domain scores will be summarized as continuous variables.

The PGA-QoL, PGA-change, AECT-4wk, and TSQM scores will be summarized descriptively for each of the treatment groups. Change from baseline in AE-QoL questionnaire scores, change from baseline in AECT-4wk scores, and TSQM scores will be descriptively summarized by visit.

9.8 Planned Analyses

There will be no formal interim analysis in this study.

The primary efficacy analysis (PA) will be conducted after all patients have completed Part 1 of the study or have been discontinued from the study, at which point the unblinded analysis will be performed based on all data through the end of Part 1 (12-week assessment). Additionally, some Part 2 data available at the time of the PA may be included in the PA to provide supportive information.

The final analysis for the study will occur at the end of the entire study when all patients have completed Part 2 of the study or have been discontinued from the study and the study database final lock is completed.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

Coordinating Investigators:	Europe Emel Aygören-Pürsün, MD Department of Children and Adolescents University Hospital Frankfurt, Goethe University Theodor-Stern-Kai 7 D-60590 Frankfurt, Germany	US Marc Riedl, MD Division of Rheumatology, Allergy & Immunology US HAEA Angioedema Center University of California, San Diego 8899 University Center Lane, Suite 230 San Diego, CA 92122
Investigators:	Names and contact details of participating investigators are available in the electronic trial master file (eTMF)	
Sponsor:	Pharvaris Netherlands B.V. J.H. Oortweg 21 2333 CH Leiden The Netherlands	
Sponsor Representatives:	██████ MD PhD Chief Medical Officer	██████, MD Sponsor Medical Expert
Medical Monitor:	IQVIA Biotech Ltd	
Study Monitoring:	IQVIA Biotech Ltd	
Randomization and IMP Allocation:	IQVIA Biotech Ltd	
IMP Supplies:	Catalent	
Central Laboratory (Safety):	Q ² Solutions	
Central Laboratory (Pharmacokinetics):	Ardena Bioanalysis (The Netherlands)	
Data Management:	IQVIA Biotech Ltd	
Statistician (protocol):	Pharvaris Netherlands B.V. Efficient Pharma Management Corp. (EffPha)	
Statistician (analysis):	TigerMed Inc	
Safety Management:	Medpace Inc IQVIA Biotech Ltd (supportive)	
IDMC:	Names and contact details of IDMC members are available in the eTMF	

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

In accordance with GCP, the protocol, informed consent form(s), recruitment materials, and all patient materials will be submitted to an appropriate IEC/IRB for review and approval. Approval of both the protocol and the ICF must be obtained before any patient is enrolled. 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 Conference on Harmonisation GCP (ICH GCP E6[R2]) and other 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 will have completed ICH GCP training.

Patient insurance will be provided according to local regulations.

10.4 Patient Information and Consent

At the screening visit, a signed ICF must be obtained from each patient prior to performing any study-related procedures. Each patient will be given both verbal and written information describing the nature and duration of the clinical study.

The ICF must describe in detail the study 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 contents 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.

The sponsor will use the information obtained during the conduct of this study for the development of PHA-022121. The investigator is obliged to provide the sponsor 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 EMA, the 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

The sponsor 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 or designee 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 will be performed to confirm appropriate study conduct. If applicable by local regulations, monitoring visits may be performed remotely as a result of any COVID-19-related restrictions. Monitoring or remote monitoring may include the following:

- 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 accurately recorded in the CRFs
- IMP 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 an 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. The ePRO data will be considered source data.

10.8 Independent Data Monitoring Committee

An IDMC will be assembled prior to the study start to review safety data on a regular basis (and ad-hoc in case of unexpected safety issues) throughout the study. The review of unblinded safety data will be performed according to an IDMC charter, which will be prepared before data collection starts. 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 recommend 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

All deviations to the protocol will be recorded. 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 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 the sponsor or their representatives as well as inspections from the IEC/IRB and relevant regulatory authorities. Source documents may be reviewed remotely using regulatory-compliant and documented computerized systems when agreed upon with the investigator and study site, as applicable by local regulations. In these instances, they 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 the sponsor's procedures, this study may be subject to an independent QA GCP audit at the study sites.

10.11 Data Generation and Analysis

The investigator or designee must enter all protocol-required data in the available 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 trained on the use of the ePRO device, which should be carried with them at all times in order to collect information on symptoms and details of HAE attacks. The ePRO device is a validated "21 Code of Federal Regulations (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 MedDRA and medications will be coded with the 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(s) will be filed in an eTMF according to ICH-GCP. The eTMF will be transferred to the sponsor after the study and will be archived for at least 25 years or as otherwise required by local regulations. 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 or as otherwise required by local regulations. The Investigators will also retain source documents under their control for at least 25 years or as otherwise required by local regulations. All medical records will be retained by the medical center according to their own internal procedures.

10.13 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54.2(b) (1998).

10.14 Publication and Disclosure Policy

All data generated from this study are the property of the sponsor and shall be held in strict confidence along with all information provided by the sponsor. Except as provided through written agreement between the sponsor, 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 the sponsor. Such consent will not be withheld unreasonably. The sponsor is in agreement with the principle of full disclosure of clinical trial results.

11 REFERENCE LIST

- Ariano A, D'Apolito M, Bova M, et al. A myoferlin gain-of-function variant associates with a new type of hereditary angioedema. *Allergy*. 2020;75(11):2989-2992.
- Atkinson MJ, Sinha A, Hass SL, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. *Health Qual Life Outcomes*. 2004;2(1):12.
- Aygören-Pürsün E, Magerl M, Maetzel A, Maurer M. Epidemiology of bradykinin-mediated angioedema: a systematic investigation of epidemiological studies. *Orphanet J Rare Dis*. 2018;13(1):73
- Bafunno V, Firinu D, D'Apolito M, et al. Mutation of the angiopoietin-1 gene (ANGPT1) associates with a new type of hereditary angioedema. *J Allergy Clin Immunol*. 2018;141(3):1009-1017.
- Banerji A, Riedl MA, Bernstein JA, et al. Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks. *Jama*. 2018;320(20):2108.
- Banerji A, Davis KH, Brown TM, et al. Patient-reported burden of hereditary angioedema: findings from a patient survey in the United States. *Ann Allergy Asthma Immunol*. 2020;124(6):600-607.
- Binkley KE, Davis A. Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema. *J Allergy Clin Immunol*. 2000;106(3):546–50.
- Bönnner G, Preis S, Schunk U, Toussaint C, Kaufmann W. Hemodynamic effects of bradykinin on systemic and pulmonary circulation in healthy and hypertensive humans. *J Cardiovasc Pharmacol*. 1990;15(Suppl 6):S46-S56.
- Bork K, Barnstedt S-E, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet*. 2000;356(9225):213–217.
- Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol*. 2012;130(3):692–697.
- Bork, K., Wulff, K., Steinmüller-Magin, L., et al. Hereditary angioedema with a mutation in the plasminogen gene. *Allergy*. 2018;73(2):442-450.
- Bork, K., Wulff, K., Rossmann, H., et al. Hereditary angioedema cosegregating with a novel kininogen-1 gene mutation changing the N-terminal cleavage site of bradykinin. *Allergy*. 2019a;74(12):2479-2481.
- Bork K, Aygören-Pürsün E, Baş M, et al. Guideline: Hereditary angioedema due to C1 inhibitor deficiency. *Allergo J Int*. 2019b;28:16–29.
- Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. *J Allergy Clin Immunol Pract*. 2021;9(1):132-150.
- Busse PJ, Christiansen SC. Hereditary angioedema. *N Engl J Med*. 2020;382(12):1136-1148.
- Bygum A. Hereditary angio-oedema in Denmark: a nationwide survey. *Br J Dermatol*. 2009;161(5):1153-1158.

- Caballero T, Aygören-Pürsün E, Bygum A, et al. The humanistic burden of hereditary angioedema: results from the burden of illness study in Europe. *Allergy Asthma Proc.* 2014;35(1):47-53.
- Caballero T, Aberer W, Longhurst HJ, et al., IOS Study Group. The Icatibant Outcome Survey: experience of hereditary angioedema management from six European countries. *J Eur Acad Dermatol Venereol.* 2017;31(7):1214-1222.
- Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *New Engl J Medicine.* 2010;363(6):532–541.
- Cicardi M, Zuraw BL. Angioedema due to bradykinin dysregulation. *J Allergy Clin Immunol Pract.* 2018;6(4):1132–1141.
- Cockcroft JR, Chowienczyk PJ, Brett SE, Bender N, Ritter JM. Inhibition of bradykinin-induced vasodilation in human forearm vasculature by icatibant, a potent B2-receptor antagonist. *Br J Clin Pharmacol.* 1994;38(4):317-321.
- CTFG. Clinical Trial Facilitation and Coordination Group: Recommendations related to contraception and pregnancy testing in clinical trials. v1.1. 2020. Accessed on 07 January 2021 at: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-about_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf
- Dewald, G. and Bork, K. Missense mutations in the coagulation factor XII (Hageman factor) gene in hereditary angioedema with normal C1 inhibitor. *Biochem Biophys Res Commun.* 2006;343(4):1286-1289.
- EMA-CHMP. European Public Assessment Report (ePAR) for Firazyr. 2008. Document reference: EMA/350457/2008; accessed on 01 September 2020 at https://www.ema.europa.eu/en/documents/assessment-report/firazyr-epar-public-assessment-report_en.pdf.
- FDA-CDER. Medical Review(s) NDA 22-150 Firazyr (icatibant acetate). 2011. Accessed 01 September 2020 at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022150_firazyr_toc.cfm.
- FDA. The voice of the patient. A series of reports from the U.S. Food and Drug Administration's Patient-Focused Drug Development Initiative. 2018a;1-31. Accessed on 09 December 2020 at: <https://www.fda.gov/media/113509/download>.
- FDA. Methods to identify what is important to patients & select, develop or modify fit-for-purpose clinical outcomes assessments. U.S. Food and Drug Administration's Patient-Focused Drug Development Guidance Public Workshop. October 15-16, 2018b. Accessed on 16 April 2021 at: <https://www.fda.gov/media/116276/download> and <https://www.fda.gov/media/116259/download> (Appendices).
- Honing ML, Smits P, Morrison PJ, Rabelink TJ. Bradykinin-induced vasodilation of human forearm resistance vessels is primarily mediated by endothelium-dependent hyperpolarization. *Hypertension.* 2000;35(6):1314-1318.
- Kaplan AP, Joseph K. The bradykinin-forming cascade and its role in hereditary angioedema. *Ann Allergy Asthma Immunol.* 2010;104(3):193–204.

Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604-612.

Longhurst H, Cicardi M, Craig T, et al. Prevention of hereditary angioedema attacks with a subcutaneous C1-inhibitor. *New Engl J Medicine.* 2017;376(12):1131–1140.

Lumry WR, Castaldo AJ, Vernon MK, et al. The humanistic burden of hereditary angioedema: Impact on health-related quality of life, productivity, and depression. *Allergy Asthma Proc.* 2010;31(5):407-414.

Maurer M, Longhurst HJ, Bouillet L, et al. Long-term effectiveness and safety of icatibant for the on-demand treatment of hereditary angioedema attacks: 10 years of the Icatibant Outcome Survey (EAACI abstract #1118). *Allergy.* 2020;75(S109):59–60.

Maurer M, Aygören-Pürsün E, Banerji A, et al. Consensus on treatment goals in hereditary angioedema: A global Delphi initiative. *J Allergy Clin Immunol.* 2021;148(6):1526-1532.

Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema—The 2021 revision and update. *Allergy.* 2022;77(7):1961-1990.

NCI. NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 2017.

Available from:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

Nordenfelt P, Dawson S, Wahlgren CF, et al. Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden. *Allergy Asthma Proc.* 2014;35(2):185-190.

Nordenfelt P, Nilsson M, Björkander J, et al. Hereditary angioedema in Swedish adults: report from the national cohort. *Acta Dermato Venereol.* 2016;96(4):540–545.

Orladeyo (berotralstat). US Prescribing Information. BioCryst Pharmaceuticals, Inc. 2020.

Accessed on 27 January 2021 at: https://biocryst.com/wp-content/uploads/2020/12/ORLADEYO_PI_V1_2020.pdf

Prasad A, Husain S, Schenke W, Mincemoyer R, Epstein N, Quyyumi AA. Contribution of bradykinin receptor dysfunction to abnormal coronary vasomotion in humans. *J Am Coll Cardiol.* 2000;36(5):1467–1473.

Weller L, Groffik A, Magerl M, et al. Development and construct validation of the angioedema quality of life questionnaire. *Allergy.* 2012;67(10):1289-1298.

Weller K, Donoso T, Magerl M, et al. Development of the Angioedema Control Test-A patient-reported outcome measure that assesses disease control in patients with recurrent angioedema. *Allergy.* 2020a;75(5):1165-1177.

Weller K, Donoso T, Magerl M, et al. Validation of the Angioedema Control Test (AECT)-A patient-reported outcome instrument for assessing angioedema control. *J Allergy Clin Immunol Pract.* 2020b;8(6):2050-2057.

Zanichelli A, Arcoleo F, Barca MP, et al. A nationwide survey of hereditary angioedema due to C1 inhibitor deficiency in Italy. *Orphanet J Rare Dis*. 2015;10(1):11.

Zuraw BL. Hereditary angioedema. *New Engl J Medicine*. 2008;359(10):1027–1036.

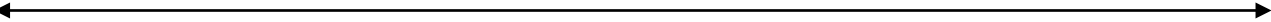
Zuraw BL, Kalfus I. Safety and efficacy of prophylactic nanofiltered C1-inhibitor in hereditary angioedema. *Am J Medicine*. 2012;125(9):938.e1-938.e7.

Zuraw BL, Banerji A, Bernstein JA, et al. US Hereditary Angioedema Association Medical Advisory Board. US Hereditary Angioedema Association Medical Advisory Board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. *J Allergy Clin Immunol Pract*. 2013;1(5):458-467.

Zuraw B, Lumry WR, Johnston DT, et al. Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: a randomized, double-blind, placebo-controlled phase 3 trial. *J Allergy Clin Immun*. 2021;148(1):164-172.

Appendix 1 Schedule of Events

Table 4 Part 1: Double-blind Treatment Period

	Screening (up to 8 weeks)	Treatment Period (12 weeks)					
Visit (Day)	Screening Visit (start of screening period)	Visit 1 Day 0	Visit 2 ¹ Day 14	Visit 3 ² Day 28	Visit 4 Day 42	Visit 5 ² Day 56	Visit 6 Day 84
Visit Location	On-site	On-site	On-site or Remote (if permitted by local regulations)	Virtual	On-site	Virtual	On-site
Assessments Window (days)	NA	NA	± 3	± 3	± 3	± 3	± 3
Informed consent ³	X						
Eligibility check	X	X					
Enrollment ⁴	X						
Randomization ⁵		X					
Demographics and HAE characteristics	X						
Medical history	X						
Weight and height ⁶	X	X					X
Physical examination ⁷	X						X
Vital signs ⁸	X	X	X		X		X
12-Lead ECG ⁹	X	X			X		X
Clinical laboratory testing ¹⁰	X	X	X		X		X
Pregnancy test ¹¹	X	X			X		X
FSH test ¹²	X						
Adverse events ¹³							
Prior / concomitant medications							
Dispense IMP ¹⁴		X	X		X		X
IMP administration ¹⁵							
PK plasma sampling ¹⁶		X			X		X

ePRO HAE diary training ¹⁷	X	X					
Visit (Day)	Screening Visit	Visit 1 Day 0	Visit 2 ¹ Day 14	Visit 3 ² Day 28	Visit 4 Day 42	Visit 5 ² Day 56	Visit 6 Day 84
ePRO: HAE diary ¹⁸							
ePRO: AE-QoL questionnaire		X		X		X	X
ePRO: PGA-QoL question ¹⁹		X					X
ePRO: PGA-change question ¹⁹							X
ePRO: AECT-4wk		X		X		X	X
ePRO: TSQM score				X		X	X

AECT-4wk=angioedema control test-4 week; AE-QoL=angioedema quality of life questionnaire; C1-INH=C1-inhibitor; ECG=electrocardiogram; EOT=end-of-treatment; ePRO=electronic patient report outcome (tool); HAE=hereditary angioedema; IMP=investigational medicinal product; NA=not applicable; TSQM=treatment satisfaction questionnaire for medication; PGA-QoL=patient global assessment of quality of life; PGA-change=patient global assessment of change; PK=pharmacokinetic

- ¹ Visit 2 may be performed either on-site or remotely by a visiting nurse or home healthcare provider (where applicable and permitted by local regulations). For remote visits, direct shipment of IMP to patients may be implemented (where applicable and permitted by local regulations), with IMP oversight and accountability performed by the visiting nurse or home healthcare provider. Weekly check-in calls with patients by site personnel (investigator or designee) will be performed following any off-site visit through to the next on-site visit.
- ² Visits 3 and 5 are virtual visits whereby site personnel (investigator or designee) will contact patients by telephone or videoconference to ensure the visit procedures are performed.
- ³ Informed consent form must be signed by the patient before any study-specific procedures are performed.
- ⁴ 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.
- ⁵ The diagnosis of HAE should be documented prior to randomization by a local or central laboratory assessment of a C1-INH functional level < 50% documented in the medical records (see Inclusion Criterion 2 in Section 4.2).
- ⁶ Height is only measured at the screening visit.
- ⁷ Physical examination at minimum to include the following body systems: gastrointestinal system; head/eyes/ears/nose/throat (HEENT); endocrine (including thyroid); respiratory system; cardiovascular system; integumentary system (skin); and nervous system (central and peripheral).
- ⁸ Blood pressure, heart rate, body temperature, and respiratory rate (see Section 6.6 for details).
- ⁹ ECGs (in triplicate) are to be performed at the study visits indicated. At Visits 1 and 4, an ECG recording is to be performed pre-dose and another recording is to occur at 2-3 hours after the patient's morning dose. The ECG recordings should occur prior to the plasma PK samplings.
- ¹⁰ Clinical laboratory testing includes hematology, biochemistry, coagulation, and urinalysis.
- ¹¹ For women of childbearing potential, a serum human chorionic gonadotropin (hCG) test must be performed.
- ¹² For post-menopausal women (defined as 12 consecutive months of amenorrhea without an alternative medical cause), a serum sampling to test for FSH levels must be performed.
- ¹³ Adverse events will be collected from the time of informed consent through to the last follow-up at the end-of-study visit (see Section 6.12).
- ¹⁴ Patients will receive a supply of IMP at each visit indicated to ensure coverage until the next study visit. Supply of IMP may be provided at the study site, or if the visit is performed remotely, may be provided by a visiting nurse or home healthcare provider, or direct shipment of IMP to the patient's home may occur, (where applicable and permitted by local regulations). At Visit 6, IMP will be dispensed for Part 2 of the study.
- ¹⁵ Throughout the treatment period, patients will administer the IMP orally twice daily, following breakfast and dinner. The last IMP administration in Part 1 will take place at the site during Visit 6.
- ¹⁶ PK plasma samples are to be collected at the study visits indicated. One plasma sample will be collected pre-dose and one sample will be collected between 2-3 hours following the patient's morning dose. Patients should be in a fasted state for the pre-dose sample collection.
- ¹⁷ Patients will receive training on how to use the ePRO HAE diary at the screening visit, Visit 1, and throughout the study, as needed.
- ¹⁸ Patients will use an ePRO HAE diary daily to record any symptoms and details of HAE attacks, including relevant treatments. Patients must report details of any HAE attack to the study site within 72 hours of onset of symptoms of an attack.
- ¹⁹ At Visit 1, patients are to complete the PGA-QoL question after the AE-QoL questionnaire. At Visit 6, patients are to complete both the PGA-QoL and PGA-change questions after the AE-QoL questionnaire, with PGA-QoL to be completed first followed by PGA-change.

Table 5 Part 2: Open-label Treatment Period

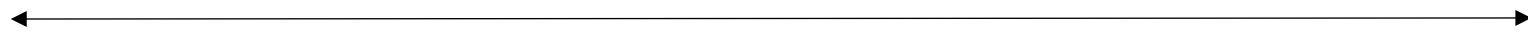
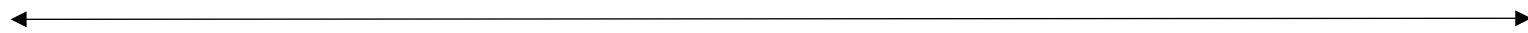
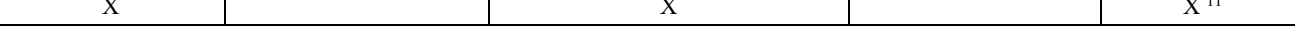
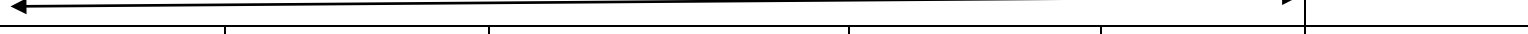
Visit (Day) ¹⁶	Treatment Period (30 months) ¹					Follow-up/EOS
	Visit 7 ¹⁷ Day 91 (Wk 13)	Visit 8 ² Day 126 (Wk 18)	Visit 9 ³ Day 168 (Wk 24)	Visit 10 ² Day 210 (Wk 30)	Visit 11 Day 252 (Wk 36)	Visit 18 ³ Day 966 (Wk 138)
			Visit 12 ³ Day 343 (Wk 49)		Visit 13 Day 434 (Wk 62)	
			Visit 14 ³ Day 525 (Wk 75)		Visit 15 Day 686 (Wk 98)	
			Visit 16 ³ Day 777 (Wk 111)		Visit 17/EOT Day 938 (Wk 134)	
Visit Location	On-site	Virtual	Onsite or Remote	Virtual	On-site	Onsite or Remote
Visit Window	± 1 week	± 2 weeks	± 2 weeks	± 2 weeks	± 1 week	± 2 weeks (±3 days in Germany)
Physical examination ⁴	X				X	
Vital signs ⁵	X		X		X	X
12-lead ECG (digital triplicate) ⁶	X		Visit 9 only		Visit 11, 15, and 17 only	
Clinical laboratory testing ⁷	X		X		X	X
Pregnancy test ⁸	X		X		X	X
Adverse events ⁹						
Concomitant medications						
Dispense IMP ¹⁰	X		X		X ¹¹	
IMP administration ¹²						
PK plasma sampling ¹³	X		Visit 9 only		Visit 11 only	
ePRO: HAE diary ¹⁴						
ePRO: AE-QoL questionnaire	X	X	X	X	X	
ePRO: PGA-QoL question ¹⁵	X	X	X	X	X	
ePRO: PGA-change question ¹⁵	X	X	X	X	X	

Table 5 Part 2: Open-label Treatment Period

Visit (Day) ¹⁶	Treatment Period (30 months) ¹					Follow-up/EOS
	Visit 7 ¹⁷ Day 91 (Wk 13)	Visit 8 ² Day 126 (Wk 18)	Visit 9 ³ Day 168 (Wk 24)	Visit 10 ² Day 210 (Wk 30)	Visit 11 Day 252 (Wk 36)	
			Visit 12 ³ Day 343 (Wk 49)		Visit 13 Day 434 (Wk 62)	
			Visit 14 ³ Day 525 (Wk 75)		Visit 15 Day 686 (Wk 98)	
			Visit 16 ³ Day 777 (Wk 111)		Visit 17/EOT Day 938 (Wk 134)	
Visit Location	On-site	Virtual	Onsite or Remote	Virtual	On-site	Onsite or Remote
Visit Window	± 1 week	± 2 weeks	± 2 weeks	± 2 weeks	± 1 week	± 2 weeks (±3 days in Germany)
ePRO: AECT-4wk	X	X	X	X	X	
ePRO: TSQM score	X	X	X	X	X	

AECT-4wk=angioedema control test-4 week; AE-QoL=angioedema quality of life questionnaire; ECG=electrocardiogram; EOS=end of study; EOT=end of treatment; ePRO=electronic patient-reported outcome; HAE=hereditary angioedema; IMP=investigational medicinal product; PGA-QoL=patient global assessment of quality of life; PGA-change=patient global assessment of change; PK=pharmacokinetic; TSQM=treatment satisfaction questionnaire for medication

¹ Part 2 of the study will begin with the patient's administration of IMP dispensed at Visit 6. The patient's first dose of open-label IMP should occur after the dinner on the same day as Visit 6 and the last dose of open-label IMP will be after breakfast on the same day as Visit 17. For patients with a gap in dosing between Part 1 and Part 2, the patient's first dose of open-label IMP should occur in the morning of Visit 7 and the last dose of open-label IMP will be after breakfast on the same day as Visit 17.

If there is a gap in treatment between Parts 1 and 2, safety assessments are to be performed and patient eligibility reconfirmed before the patient may restart treatment in Part 2.

² Visits 8 and 10 are virtual visits whereby site personnel (investigator or designee) will contact patients by telephone or videoconference to ensure the visit procedures are performed.

³ Visits 9, 12, 14, 16, and 18 may be performed either on-site or remotely by a visiting nurse or home healthcare provider (where applicable and permitted by local regulations).

⁴ Physical examination to include the following body systems: gastrointestinal system; head/eyes/ears/nose/throat (HEENT); endocrine (including thyroid); respiratory system; cardiovascular system; integumentary system (skin); and nervous system (central and peripheral). Additional physical examinations may be scheduled at the discretion of the investigator (or designee).

⁵ Blood pressure, heart rate, and body temperature (see Section 6.6 for details).

⁶ ECGs are to be performed at Visit 9 (if it is an on-site visit) and Visits 7, 11, 15, and 17. ECG recordings should occur prior to the PK sample collection.

⁷ Clinical laboratory testing includes hematology, biochemistry, coagulation, and urinalysis.

⁸ For women of childbearing potential, a urine human chorionic gonadotropin (hCG) test must be performed.

⁹ Adverse events will be collected from the time of informed consent through to the last follow-up at the end-of-study visit (see Section 6.12).

¹⁰ Patients will receive a supply of IMP at each visit indicated to ensure coverage until the next study visit. The provision may occur at the study site, or if the visit is performed remotely, may be provided by a home healthcare provider, or by direct shipment to the patient's home (where applicable and permitted by local regulations).

- ¹¹ IMP is not dispensed at Visit 17/EOT.
- ¹² Patients will administer IMP orally BID except for Visit 17, where the last dose of IMP will be after breakfast on the morning of Visit 17.
- ¹³ The time of the last dose of IMP and the last meal prior to PK sampling is to be recorded in the eCRF; PK samples are to be collected at Visits 7, 9 (if on-site), and 11.
- ¹⁴ Patients will use an ePRO HAE diary daily to record any symptoms and details of HAE attacks, including relevant treatments. Patients must report details of any HAE attack to the study site within 72 hours of onset of symptoms of an attack.
- ¹⁵ Patients are to complete both the PGA-QoL and PGA-change questions after the AE-QoL questionnaire, with PGA-QoL to be completed first followed by PGA-change.
- ¹⁶ Specified study days apply to patients who continue in the study without interruption.
- ¹⁷ If there is a gap in treatment between Parts 1 and 2, Visit 7 safety assessments are to be performed, with results reviewed by the Investigator, and patient eligibility reconfirmed before the patient may restart treatment in Part 2.

Appendix 2 Sponsor Signature

Study Title: A Phase II, Double-blind, Placebo-controlled, Randomized, Dose-ranging, Parallel Group Study to Evaluate the Safety and Efficacy of PHA-022121 Administered Orally for Prophylaxis Against Angioedema Attacks in Patients with Hereditary Angioedema due to C1-Inhibitor Deficiency (Type I or Type II)

Acronym CHAPTER-1

Study Number: PHA022121-C301

Original Protocol: Version 1.0 (09 February 2021)

Amendment 11: Version 7.0 (03 May 2023)

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

Signed: _____

Date: _____

██████████ MD
Sponsor Medical Expert
Pharvaris Netherlands B.V.

Appendix 3 Principal Investigator Signature

Study Title: A Phase II, Double-blind, Placebo-controlled, Randomized, Dose-ranging, Parallel Group Study to Evaluate the Safety and Efficacy of PHA-022121 Administered Orally for Prophylaxis Against Angioedema Attacks in Patients with Hereditary Angioedema due to C1-Inhibitor Deficiency (Type I or Type II)

Acronym CHAPTER-1

Study Number: PHA022121-C301

Original Protocol: Version 1.0 (09 February 2021)

Amendment 11: Version 7.0 (03 May 2023)

I have read all pages of this clinical study protocol for which Pharvaris Netherlands B.V. 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:

.....

.....