



Statistical Analysis Plan
for Study Part 1 of Clinical Study Protocol: PHA022121-C301
(Part 1 Data SAP)

Study Title: A Phase II, Double-blind, Placebo-controlled, Randomized, Dose-ranging, Parallel Group Study to Evaluate the Efficacy and Safety of PHA-022121 Administered Orally for Long-term 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

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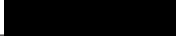
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APPROVAL

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VERSION HISTORY

SAP Version	Date	Primary Reasons for Amendment
1.0	October 27, 2023	Initial version

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LIST OF ABBREVIATIONS

AECT-4wk	angioedema control test 4-week
AE	adverse event
AE-QoL	angioedema quality of life (questionnaire)
BID	Twice per day
BQL	below quantification limit
C1-INH	C1-esterase inhibitor
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
EOS	End of study
ePRO	Electronic patient-reported outcomes
FA	Final analysis
HAE	Hereditary angioedema
IMP	Investigational Medicinal Product
ITT	intent-to-treat
LS	least squares (mean)
MedDRA	Medical Dictionary for Regulatory Activities
OLE	open-label extension
PA	primary analysis
PGA-change	patient global assessment of change (question)
PGA-QoL	patient global assessment of quality of life (question)
PD	Pharmacodynamic(s)
PK	pharmacokinetic(s)
PPS	Per Protocol Analysis Set (PPS)
QoL	Quality of life
SAE	serious adverse event

SAP	statistical analysis plan
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TSQM-II	treatment satisfaction questionnaire for medication
US	United States
WAO	World Allergy Organization
WCBP	Women of child-bearing potential

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the Primary Analysis (PA) using data from the double-blind treatment period (Part 1 data) up through protocol PHA022121-C301 version 7, dated 03 May, 2023. Therefore, this SAP is referred to as the Part 1 data SAP. It will be finalized prior to the PA database lock. Analysis related to Part 2 data or combined datasets of Part 1 and Part 2 will be described in the Final Analysis (FA) SAP. Any deviations from this SAP after PA database lock and release of treatment code will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives and Endpoints

The objectives and endpoints are separately described by Part 1 and Part 2 because the study consists of 2 parts, with participants completing 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. Further details are outlined in Section 2.2. Part 2 analysis is not covered in this SAP.

2.1.1 The Primary Objectives

Part 1

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

Part 2

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

2.1.2 The Secondary Objectives

Part 1

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

2.2 Study Design

2.2.1 Overview

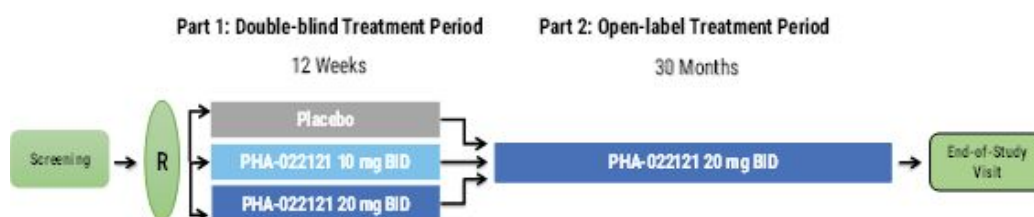
- This is a Phase II, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, parallel group, 2-part study to evaluate the safety and efficacy of PHA-022121 soft capsules (PHVS416) administered orally for long-term prophylaxis against angioedema attacks in participants with HAE due to C1-inhibitor (C1-INH) deficiency (type I or type II) (see study design schematic in Figure 1).

The study consists of 2 parts, with participants completing 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 participants 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. Such an extension will impact Part 2 analysis but not Part 1. Any participant who withdraws consent or is discontinued from the study at any time will complete an end-of-study visit approximately 4 weeks after the last treatment administration.

- Following signing of informed consent, participants will undergo screening assessments. The screening period may last up to 8 weeks.
- For Part 1, eligible participants 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 participant will receive blinded investigational medicinal product (IMP) (i.e., PHA-022121 or placebo) to be administered orally BID after breakfast and dinner with 12 ± 2 hours between doses for a duration of 12 weeks of treatment.
- For Part 2, participants 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 participant 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 participant eligibility reconfirmed before the participant 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 and questionnaires for QoL endpoints (see 4.7). Participants will have access to standard of care on-demand acute therapies and will be able to treat any HAE attack that may occur using such therapies in accordance with World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI) 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.

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

Figure 1 Study Design Schematic



BID=twice daily; R=randomization

2.2.2 Sample Size Considerations

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

For a treatment effect of 60% reduction in attacks as compared to placebo, [REDACTED] a sample size of 10 participants per group receiving active treatment and 10 participants 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%.

2.3 Study Endpoints

2.3.1 Safety Endpoints for Part 1

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

2.3.2 Efficacy Endpoints for Part 1

Primary Efficacy Endpoint:

- Number of investigator-confirmed HAE attacks (expressed as the normalized number of attacks per month [4 weeks] of exposure) during the treatment period in Part 1.

Secondary Efficacy Endpoints:

- 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 participants achieving $\geq 50\%$ reduction in attack rate relative to baseline during the treatment period in Part 1.
- Number of participants achieving $\geq 70\%$ reduction in attack rate relative to baseline during the treatment period in Part 1.
- Number of participants achieving $\geq 90\%$ reduction in attack rate relative to baseline during the treatment period in Part 1.
- Number of participants 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.

2.3.3 Pharmacokinetic and Health-related quality of life Endpoints for Part 1

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

3 DEFINITIONS

3.1 Investigational Medicinal Product (IMP)

In Part 1, both double-blinded PHA-022121 and placebo are referred to as investigational medicinal product (IMP).

The treatments to be administered in Part 1 consist of 10 mg PHA-022121 soft capsules (PHVS416) and matching placebo soft capsules for oral use.

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.

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

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

3.2 Dates, Periods, and Points of Reference

Baseline

Study baseline result refers to the results at randomization. Specifically, it is defined as the last assessment result prior to the first dose of IMP, i.e., the IMP administration in study Part 1 to assess efficacy, safety and PK. For electrocardiogram (ECG), the baseline is defined as the mean of the last recorded triplicate before the first IMP administration. If no triplicate is available before the first dose of IMP, the last ECG value before the first IMP administration will be considered as baseline. For AE-QoL, the baseline may be measured within two days of the first dose of IMP.

Study Day

The first IMP administration date is defined as the first day on which the participant took the first dose of the IMP as recorded on the CRF.

For assessments on or after the first IMP administration, study day is assessment date – the first IMP administration date + 1. As such, the first IMP administration date is study Day 1 and it is used for all the outputs. Note that protocol refers to the first IMP administration date as Day 0.

For assessments before the first IMP administration date, study day is calculated as assessment date – the first IMP administration, therefore, the day before the first IMP administration day is Day -1.

Analysis Periods

The screening period is defined as the period from the date and time of informed consent to the time before randomization, i.e., Visit 1 Day 0. The duration of the screening period is calculated as: Date of Randomization (i.e., Visit 1 Day 0) – date of informed consent +1.

The study period in Part 1 is defined as the period from randomization, (i.e., Visit 1, Day 0) to the date/time prior to the first IMP administration in Part 2 for participants who enrolled in Part 2, or to the end of study (EOS) date for participants who do not enroll in Part 2.

The treatment period in Part 1 is defined as the date and time of first IMP administration to the date and time of last IMP administration in Part 1. The duration of the treatment period is calculated as date of last IMP administration in Part 1 – date of first IMP administration of IMP +1.

The treatment period without substantial IMP non-compliance in Part 1 is defined as the treatment period excluding all substantial IMP non-compliance periods in Part 1. A participant may have multiple IMP non-compliance periods. An instance of substantial IMP non-compliance occurs when 4 or more consecutive doses of IMP are missing. The duration of non-compliance period is calculated (in days) as the total number of missed doses during non-compliance periods divided by 2. The substantial IMP non-compliance period is defined as the time period that starts from 12 hours after the most recent dose of IMP before the instance of substantial IMP-non-compliance and with duration defined as above.

The treatment period censored at first substantial IMP non-compliance in Part 1 is defined as the period from the date and time of first IMP administration to the start date and time of first substantial IMP non-compliance period in Part 1.

3.3 Analysis Sets

Intent-to-treat (ITT) Analysis Set

ITT analysis set includes all randomized participants who received at least one dose of IMP (PHA-022121 or placebo). In the analyses performed on the ITT Analysis Set, unless otherwise specified, participants will be analyzed according to their assigned treatment group per randomization regardless of actual treatment received.

Safety Analysis Set

Safety Analysis Set includes all randomized participants who received at least one dose of IMP (PHA-022121 or placebo), essentially the same set of participants included in the ITT

Set. In Part 1 analyses performed on the Safety Analysis Set, participants will be analyzed according to their actual treatment received. In cases where the participants received different doses during Part 1, the actual treatment is defined as the highest dose level that is >5% of the actual drug the participant has taken.

Per Protocol (PP) Analysis Set

The PP analysis set includes all participants in the ITT Analysis Set without any major items that could influence the validity of the data for the primary efficacy evaluations. Major items that may impact the key efficacy assessment include, but are not limited to:

- Major violations of inclusion/exclusion criteria
- Actual treatment is different from assigned at randomization
- Use of prohibited medications during the treatment period

All criteria to exclude participants from the PP analysis set will be finalized based on a blinded review of the data prior to Part 1 primary database lock.

Pharmacokinetic (PK) Analysis Set

PK Analysis Set includes all randomized participants who undergo plasma PK sampling and have evaluable concentration data for analysis. Participants will be analyzed according to the actual treatment received.

3.4 Study-Specific Definitions and Key Derived Variables

3.4.1 Attack rate related definitions

Unless otherwise specified, “HAE attack” refers to Investigator confirmed attacks. An attack will be counted as in Part 1 if it occurs after the first IMP administration and before 24 hours after the last IMP administration in Part 1 or before the first IMP administration in Part 2, whichever comes earlier.

Baseline attack rate

- For participants who were not on long-term prophylactic treatment and have documented history of at least 3 HAE attacks within the last 12 weeks prior to the screening visit, the baseline attack rate will be calculated as: Attacks per 4 weeks = number of attacks in the past 3 months (12 weeks) prior to screening divided by 3.
- Participants who were on long-term prophylactic treatment, had no documentation of their attacks or had fewer than 3 attacks in the 12 weeks prior to the screening visit must experience a minimum of 2 HAE attacks during the screening period of up to 8 weeks to be eligible. For these participants, the baseline attack rate will be calculated as follows:

$$\text{baseline attack rate (per 4 weeks)} = \frac{\text{Number of attacks during screening period}}{\text{Duration in days of screening period} \div 28}.$$

According to the protocol, randomization to treatment groups is stratified by baseline attack rate into 3 categories: 1 to < 2 attacks, 2 to < 3 attacks, or ≥ 3 attacks per 4 weeks. Due to the small group size for 2 to < 3 attacks as observed in the data, the baseline attack rate categories are regrouped to the two categories: 1 to < 2 attacks, or ≥ 2 attacks (i.e., 2 to < 3 attacks and or ≥ 3 attacks are combined to one category)

Monthly attack rate

The monthly attack rate in Part 1 is the primary endpoint of the study, i.e., the number of Investigator-confirmed HAE attacks during the treatment period in Part 1 expressed as the normalized number of attacks per month (4 weeks) of exposure. The monthly attack rate is calculated for each participant as number of HAE attacks occurring during the treatment period divided by the number of days the participant contributed to the treatment period multiplied by 28 days.

Attack rate by month-interval

For each month-interval, the attack rate for a participant will be calculated using the number of HAE attacks with onset date within each month-interval during the treatment period in Part 1. Monthly intervals in Part 1 are Day 0 to Day 27, Day 28 to Day 55 and Day 56 until end of Part 1. Note for participants whose monthly period is more or less than 28 days, the monthly attack rate will be normalized based on the actual days within the period multiplied by 28.

Percent reduction in attack rate during the treatment period in Part 1

Percent reduction in attack rate during the treatment period in Part 1 relative to baseline will be calculated as follows:

$$\frac{\text{Baseline attack rate} - \text{Attack rate during treatment period}}{\text{Baseline attack rate}} \times 100$$

A positive reduction from baseline indicates improvement.

3.4.2 AE-QoL

The AE-QoL questionnaire (Weller K, 2016) consists of 17 items across four domains/dimensions as shown below. Each of the 17 questions has a five-point response scale ranging from 0 to 4.

Table 1: AE-QoL questionnaire

Dimensions	Item
Functioning	1. Impairment of work
	2. Impairment of physical activity
	3. Impairment of spare time activities
	4. Impairment of social relations
Fatigue/Mood	6. Difficulties of falling asleep
	7. Waking up during the night
	8. Feeling tired during the day
	9. Difficulties in concentrating
	10. Feeling downhearted
Fears/Shame	12. Feeling burdened at having swellings
	13. Fear of new suddenly appearing swellings
	14. Fear of increased frequency of swellings
	15. Ashamed to visit public places
	16. Embarrassed by the appearance of swellings
	17. Fear of long term negative drug effects
Nutrition	5. General limitations in foods and eating
	11. Limitations in the selection of food and beverages

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 calculated. Missing items are excluded from the raw domain/total score calculation.

All raw domain scores and total score will be transformed into percentage scores (referred as AE-QoL domain scores and total score in following section) prior to analyses by using the formula below. The AE-QoL domain scores and total score range from 0 – 100. A higher score means worse, while a lower score indicates better health-related QoL.

AE-QoL domain and total score formula:

$(\text{Sum of all completed items} / \text{Max. possible sum of all completed items}) \times 100$.

The AE-QoL domain score will not be calculated if more than one item is missing in that domain. The AE-QoL total score will not be calculated if more than 25% of items (> 4 items) are missing.

3.4.3 TSQM-II

TSQM Version II has 11 items across four specific domains of Effectiveness, Side Effects, Convenience, and Global Satisfaction. Scores for each domain are computed by adding the TSQM items in each domain and then transforming the composite score into a value ranging from 0 to 100. Of note, a score can be computed for a domain only if no item is missing. If the participant answers 'yes' to item 3, he/she will be prompted to answer items 4-6. If the answer to question 3 is 'no', items 4-6 are skipped, and the participant moves right to question 7 and the Side Effects domain score will not be calculated. The calculations specific to each domain are presented in detail below (taken from TSQM User Manual Version 2.2 dated 12Jan2021):

- Global Satisfaction
 - $[(\text{Sum}(\text{Item 10 to Item 11}) - 2) \text{ divided by } 12] * 100$
 - If one item is missing:
 - $[(\text{Use the completed item}) - 1] \text{ divide by } 6) * 100$
- Effectiveness
 - $[(\text{Item 1} + \text{Item 2}) - 2] \text{ divide by } 12) * 100$
 - If one item is missing:
 - $[(\text{Use the completed item}) - 1] \text{ divide by } 6) * 100$
- Side Effects
 - All 'NA' responses are coded as '5' indicating 'Not at all Dissatisfied'
 - $[(\text{Sum}(\text{Item 4 to Item 6}) - 3] \text{ divide by } 12) * 100$
 - If one item is missing:
 - $[(\text{Sum}(\text{the two completed items})) - 2] \text{ divide by } 8) * 100$
- Convenience
 - $[(\text{Sum}(\text{Item 7 to Item 9}) - 3] \text{ divided by } 18) * 100$
 - If one item is missing:
 - $[(\text{Sum}(\text{the two completed items})) - 2] \text{ divided by } 12) * 100$

3.5 Timing and Scope of Milestone Analyses

3.5.1 Primary Analysis (End of Part 1 Analysis)

The Primary Analysis (PA) will be conducted after all participants 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 (approximately 12-week assessment).

3.5.2 Final Analysis (End of Part 2 Analysis)

The Final Analysis (FA) for the study will occur at the end of the entire study when all participants have completed Part 2 of the study or have been discontinued from the study and the study database final lock is completed. Details on planned statistical analyses will be specified in a separate SAP, namely, the FA SAP.

4 STATISTICAL METHODS FOR PLANNED ANALYSES

4.1 General Principles

Data displays produced for this study will include summary tables, figures, and data listings (TFLs).

In TFLs, the treatment “PHA-022121 10 mg BID” and “PHA-022121 20 mg BID” will be displayed in abbreviations of “PHA 10 mg” and “PHA 20 mg”, respectively. Unless described otherwise in following sections, in TFLs based on Part 1 data, results will be presented by treatment groups: Placebo, PHA 10 mg, and PHA 20 mg. Continuous data will be summarized with the number of participants, mean, standard deviation (SD), median, 25th percentile, 75th percentile, minimum, and maximum. Categorical data will be summarized with the number and percentages of participants in each category.

Data listings will include the data recorded on the CRF or derived variables for each record. They will be ordered by treatment (IMP), site, participant number, and time of assessment. When expedient, additional levels of ordering hierarchy may reflect subsets of assessments within the participant.

Unless otherwise specified, the ITT and the PP Analysis Sets will be used for analysis of efficacy and health-related QoL endpoints, and the Safety Analysis Set will be used for analysis of safety endpoints. The PK Analysis Set will be used for PK Analysis.

4.1.1 Analysis Visit Window

All assessments including scheduled, unscheduled, and early termination visits will be assigned to analysis visits using analysis visit windows based on the study day. If more than one assessment (scheduled, unscheduled, or early termination) occurs within a single visit window, then the analysis will be based on the assessment that is closest to the target day of the visit with the planned assessment. If there are multiple assessments that are equidistant from the target day, the visit with the later date and time will be used.

The analysis visit windows will be applied to all efficacy and safety visits. The details can be found in Appendix A.

4.1.2 Handling Missing Data and Partial Dates

Unless stated otherwise, missing data will not be imputed. When deemed necessary, sections below will address how missing data will be handled for the particular analyses.

Partial dates are allowed on the CRF for adverse events and prior and concomitant medications. Dates from these forms will be reported in listings as collected. Every effort will be made to query completely missing and partially missing dates.

For medications with completely missing dates, no imputation will be performed, and they will be treated as both prior and concomitant medications.

For the purposes of handling partially reported start and stop dates for medication the following algorithm will be applied:

- Missing start day, but month and year present:
The start day will be set to the first day of the month.
- Missing start day and month, but year present:
The start day and month will be set to 01 January.
- Missing end day, but month and year present:
The day will be set to the last day of the month, or the end of study date, whichever is earlier.
- Missing end day and month, but year present:
The end day and month will be set to the data cut-off date, end of study date or December 31 of the year, whichever is earliest.

For the purposes of handling partially reported start and stop dates for adverse events the following algorithm will be applied:

- Missing start day, but month and year present: If the first IMP dose had been taken in the same month and year as the occurrence of the adverse event, then the start day of the adverse event will be assigned to the day of first dose of IMP. Otherwise, the start day will be set to the first day of the month.
- Missing start day and month but year present: If the first IMP dose had been taken in the same year as the occurrence of the adverse event, then the start day of the adverse event will be assigned to the day of first dose of IMP. Otherwise, the start day will be set to the first day of the year.
- Missing end day, but month and year present: The day will be set to the last day of the month, the end of study date or data cutoff, whichever is earliest.
- Missing end day and month but year present: The day will be set to the last day of the year, the end of study date or data cutoff, whichever is earliest.

4.2 Disposition

Frequencies and percentages of participants' summary table and listings will be generated for the following disposition categories:

- Screened
- Screen failures
- Randomized
- Analysis Sets

- Completed the Part 1 treatment
- Reason for Part 1 treatment discontinuation.
- Reason for Part 1 study discontinuation
- Participants with Early Study Discontinuation Impacted by COVID

4.3 Protocol Deviations

Protocol deviations will be defined in the Protocol Deviation Plan. Frequencies and percentages of participants with CSR reportable protocol deviations by deviation category will be summarized by treatment group and in total, grouped by eligibility deviations and on-study protocol deviations, based on ITT.

All CSR reportable protocol deviations will be listed with the flag of whether they are related to COVID-19 pandemic.

4.4 Demographic and Baseline Characteristics

Participant characteristics defined below will be presented in summary tables and data listings for participants in the ITT Analysis Set. Percentages will be based on the number of participants in the ITT Analysis Set.

Demography

- Age: (years)
- Age group: <65, ≥ 65 years
- Sex
- Race
- Ethnicity
- Country of enrollment

Baseline Characteristics

- Height (cm)
- Weight (kg)
- BMI (kg/m²)
- Childbearing potential (Yes, No) for WCBP only
- HAE Type I or II
- Baseline HAE Attack Rate (per month)
- Baseline HAE Attack Rate Categories (both actual categories and stratification factor in randomization):
- Family History Consistent with HAE Type I or II
- Subjects with HAE long-term prophylactic treatment in the three months prior to screening

Medical History

Medical history will be coded using MedDRA version 24.0 or higher. Medical Histories will be summarized for the ITT Analysis Set by system organ class (SOC) and preferred term (PT) using frequencies and percentages.

4.5 IMP Exposure and Concomitant Medications

4.5.1 Exposure and Compliance

Exposure and compliance regarding PHA-022121 or placebo will be summarized using the following parameters based on the data collected in the EDC:

- Duration of the treatment period in Part 1 (days, defined in Section 3.2)
- Total number of capsules taken in Part 1, calculated as total number of capsules dispensed in Part 1 minus total number of capsules returned from those dispensed in Part 1. If the wallet is not returned, all the capsules contained in that wallet are assumed to be taken.
- Average Daily Dose of IMP in Part 1 (capsules/day), calculated as total # of capsules taken in Part 1 divided by duration of the treatment period in Part 1
- Percent compliance in Part 1, calculated as:

$$\frac{\text{Total \# of Capsules Taken in Part 1}}{\text{Treatment Duration of IMP in Part 1 (days) * 4 - 2}} \times 100$$

- Percent compliance categories: < 80%, 80-110%, >110%

The above parameters will be summarized for treatment group and overall (i.e., all treatment groups pooled together). A listing of the exposure and compliance parameters will also be provided. Participant diary data will also be presented in listings.

4.5.2 Prior and Concomitant Medications

Prior and concomitant medications, including prohibited medications, will be coded using the World Health Organization Drug Dictionary (WHO-DD) version B3 Global March 2021.

Prior medications are defined as any medications taken prior to the start of the IMP. Concomitant medications are defined as medications with a start date/time during the Part 1 treatment period, or medications with a start date/time prior to first IMP administration but ongoing during Part 1 treatment period. If the start or stop dates/times of medications are missing completely, the medication will be deemed as both prior and concomitant. If it is partially missing, the missing imputation rules from Section 4.1.2 will be applied to determine if it is prior or concomitant medication.

The number and percentage of participants with prior and concomitant medications in Part 1 will be summarized by WHO-DD Anatomical-Therapeutic-Chemical (ATC) classification and PT by treatment groups. For each PT, a participant will only be counted once if he/she has more than one medication. A separate summary of concomitant HAE acute and long-term prophylaxis medications in Part 1 will also be provided.

4.5.3 Prior and Concomitant Procedures

Prior and concomitant procedures will be coded using version 24.0 or higher of MedDRA. Any missing dates will be imputed using the rules from Section 4.1.2.

Prior procedures are defined as any procedures that started prior to the start of the IMP. Concomitant procedures are defined as procedures with a start date/time during the Part 1 study period.

4.6 Efficacy Endpoints

4.6.1 General Analysis Methods for Efficacy Endpoints

Efficacy data will be summarized by randomized treatment based on the ITT Analysis Set.

All statistical tests are carried out 2-sided (with 5% significance level). No multiplicity adjustments will be applied. The statistical test for the primary endpoint will be performed to compare each dose of PHA-022121 to placebo without multiplicity correction for the two comparisons. For the analyses of secondary efficacy endpoints, all statistical tests comparing treatments are descriptive in nature and will be made without adjustment for multiplicity.

4.6.2 Primary Efficacy Endpoint

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 in Part 1 is calculated for each participant as the number of HAE attacks occurring during the treatment period in Part 1 divided by the number of days the participant contributed to the treatment period in Part 1 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 randomized stratification factor of baseline attack rate (categorical), and an offset term of the logarithm of participant's follow-up time (in months) during the efficacy evaluation period. The stratification factor of baseline attack rate will be

combined into two groups (1 to < 2 attacks vs. ≥ 2 attacks) due to small sample size for certain category. 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. In addition, Wilcoxon two-sample test and the Hodges-Lehman estimate will be conducted comparing each PHA-022121 dose group with the placebo group. In the event that Poisson regression has model fitting issues due to limited sample size and excessive zero counts, the Wilcoxon two-sample test will be used as the primary analysis method to test the treatment effect.

The SAS code for Poisson Model, Wilcoxon rank sum test and Hodges-Lehman estimator are presented in Appendix B.

Primary Estimand

The primary estimand of interest is defined by the following attributes:

- Treatment: 2 PHA-022121 dose levels (10 and 20 mg BID) vs placebo
- Population: Patients with HAE due to C1-INH deficiency (type I or type II) as defined by the inclusion/exclusion criteria in the protocol
- Endpoint: Number of Investigator-confirmed HAE attacks, expressed as a time normalized number of attacks, i.e., monthly attack rate in Part 1
- Intercurrent events:
 - Discontinuation of IMP is considered as an intercurrent event: hypothetical strategy will be taken with the missing at random (MAR) assumption for participants who discontinue IMP early, the observed data up to the date of last IMP administration +1 will be included in the primary endpoint analysis.
- Population-level summary: Ratios of investigator-confirmed HAE attack rate comparing PHA-022121 to placebo groups.

Sensitivity Analyses

To evaluate the robustness of the assumption of Poisson regression, a sensitivity analysis will be performed on the primary efficacy endpoint using a negative binomial GLM, if feasible.

If there are differences between the actual baseline attack rate and the stratification factor used for randomization, the primary efficacy analysis may be repeated by using the actual baseline attack rate category in the model.

Supplementary Analyses

- The primary analysis above will be repeated using the PP Analysis Set.

- The primary analysis will be repeated using the attacks during the treatment period without substantial IMP non-compliance in Part 1.
- The primary analysis may be repeated using the attacks during the treatment period censored at first substantial IMP non-compliance in Part 1.

4.6.3 Secondary Efficacy Endpoints

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

HAE attack endpoints:

The following secondary efficacy endpoints will be analyzed in a similar manner to the primary endpoint using a Poisson regression model if applicable:

- Number of patient-reported HAE attacks.
- Number of Investigator-confirmed moderate or severe HAE attacks during the treatment period in Part 1.
- Number of Investigator-confirmed HAE attacks requiring acute treatment during 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.

In the event that Poisson regression has convergence issues, non-parametric test, Wilcoxon two-sample test, and the Hodges-Lehman estimate will also be conducted comparing each PHA-022121 dose group with the placebo group.

Depending on the observed counts of the endpoints above, an additional analysis based on the negative binomial GLM may be conducted, if feasible.

Descriptive summary statistics that include the number of events, subject-time (months) contribution to the treatment period, and average event rates will also be provided by treatment groups. Similar supplementary analyses as primary endpoint may be conducted.

Binary endpoints:

For the following binary secondary endpoints, descriptive summary statistics that include the number and proportion of participants will be provided by treatment groups for participants with at least 4 weeks of study drug:

- Number of participants achieving $\geq 50\%$ reduction in attack rate relative to baseline during the treatment period in Part 1.
- Number of participants achieving $\geq 70\%$ reduction in attack rate relative to baseline during the treatment period in Part 1.

- Number of participants achieving $\geq 90\%$ reduction in attack rate relative to baseline during the treatment period in Part 1.
- Number of participants that are attack-free during the treatment period in Part 1.

In addition, Fisher's exact test will be used for testing responder proportions.

Days with angioedema symptoms endpoint:

Number and proportion of days with Investigator-confirmed angioedema symptoms during the treatment period in Part 1 by treatment groups will be summarized using descriptive summary statistics by treatment groups.

In addition, the proportion of days with Investigator-confirmed angioedema symptoms will be analyzed using Wilcoxon two-sample test comparing each PHA-022121 dose group with the placebo group among participants with at least 4 weeks of time on study drug. The Hodges-Lehman estimate of the median difference between treatment and placebo groups will also be provided.

Time-to-event endpoint:

The time to first Investigator-confirmed HAE attack during the treatment period in Part 1 will be summarized using the Kaplan-Meier (KM) Method. The estimated median time, 25th, and 75th quantile time to event, and the KM figures will be provided if applicable. For participants with HAE attack(s), this is defined as days from Day 0 until the onset date of first investigator-confirmed HAE attack. Participants without an Investigator-confirmed HAE attack during the treatment period in Part 1 will be censored at the date of the last dose of IMP +1 day in Part 1.

4.6.4 Subgroup Analyses

Data from subgroups of participants in the ITT Analysis Set may be analyzed for the primary and selected secondary efficacy endpoint if applicable. These analyses will comprise descriptive summaries. Such analyses will be considered exploratory.

Prespecified subgroups are:

- Baseline HAE attack rate (1 to < 2 attacks, or ≥ 2 attacks per 4 weeks)
- Baseline categorical age (< 65, ≥ 65)
- Sex (Male, Female)

4.7 QoL Endpoints

The following health-related QoL endpoints will be analyzed:

- Actual values and change from baseline in the domain (functioning, fatigue/mood, fear/shame, nutrition) and total AE-QoL questionnaire scores
- PGA-QoL scores and PGA-change questions scores
- AECT-4wk scores and change from baseline
- TSQM-II individual item and total composite scores

AE-QoL

All four domains and total scores at each timepoint as well as their change from baseline values will be summarized descriptively by treatment groups and by visit.

PGA-QoL and PGA-change

PGA-QoL and PGA-change values will be summarized using counts and percentages of participants with responses in each category by treatment groups and by visit.

AECT-4wk

For AECT-4wk, the total score (ranging from 0 to 16 points) will be computed as the sum of the 4 AECT questions scored on a 0 to 4 scale. Observed values and change from baseline will be summarized as continuous variables by treatment groups and by visit. In addition, the total score will be categorized as either poorly controlled disease (total scores between 0 to 9 points) or well controlled disease (total scores between 10 to 16 points) and the dichotomized score will be summarized using counts and percentage of participants in each category by treatment groups and by visit.

TSQM_II

Each TSQM-II domain score will be summarized by treatment groups and by visit.

4.8 Safety Endpoints

Part 1 safety analysis for a given participant will include the participant's data from the period of the first dose of IMP in Part 1 to end of study if the participant withdrew before completing Part 1. Otherwise, safety analysis will include data from the first dose of IMP to last dose of IMP in Part 1 plus 4 weeks or till the first dose of IMP in Part 2, whichever comes earlier. All the safety analysis will be performed on the Safety Analysis set.

4.8.1 Adverse Events

AEs will be coded using version 24.0 or higher of MedDRA to System Organ Class (SOC) and Preferred Term (PT). Treatment-emergent AEs (TEAEs) are defined as AEs that occur at any point after the first administration of IMP, or medical conditions that are present prior to the first administration of IMP but increase in severity or frequency following the first administration of IMP. Should there be insufficient data for AE start date, stop date, and time to make this comparison, the AE will be considered treatment-emergent.

The severity of all AEs will be graded using the latest version of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Missing severity will be summarized as separate category.

If the relationship to the study drug is missing, the event will conservatively be assigned as related to IMP.

An overall AE summary will be presented and separated TEAE summaries will be produced by SOC and PT with the number and percent of participants by treatment group:

- All TEAEs
- Treatment-related AE's and SAE's
- Serious TEAE's
- TEAEs leading to IMP discontinuation
- TEAEs leading to discontinuation from study
- TEAEs leading to death
- TEAEs with CTCAE Grade ≥ 3
- TEAEs by maximum CTCAE Grade
- TEAEs by relationship to the study drug

The tables will display the number and percentages of participants by SOC and PT for those who reported at least one TEAE. The outputs will be presented by descending frequency of a given SOC and PT in the PHA-022121 20 mg BID group. The severity grade and relationship to the IMP will be summarized in a similar manner. If a participant reports multiple TEAEs, the participant will be counted once in the most severe category or relationship to the IMP for that AE.

All AEs will be listed by IMP and participant, detailing the verbatim term, the preferred term, system organ class, onset date and time, end date and time, CTCAE grade, outcome, relationship to IMP, seriousness and criteria for seriousness, action taken with IMP, other action taken, and trigger for an HAE attack.

4.8.2 Clinical Laboratory Results

Descriptive analysis for laboratory test results (including hematology, serum chemistry, coagulation, and urinalysis) will be presented. Summaries of observed values at each timepoint and changes from baseline will be presented by the treatment group at each visit. In addition, shift from baseline of reference range indicators as reported by central lab at each

post-baseline visit will be summarized using counts and percentages of participants. Labs where the result is not numerical but given as less than a minimal detectable level will be given half the minimum detectable level for use in analysis. Listings will be presented for all the central and local lab results.

Pregnancy test results will be listed.

4.8.3 Vital Signs and Physical Examination

Vital signs will be summarized descriptively using actual values and changes from baseline by treatment group and each visit/at scheduled timepoint. Any abnormal or clinically significant findings will be entered in the participant's Medical History or Adverse Events eCRF as appropriate.

Height from the screening visit, weight, and vital sign results (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse, body temperature, and respiratory rate) will be presented in data listings by treatment group and participant.

4.8.4 12-Lead Electrocardiogram (ECG)

The 12-Lead ECG will be collected in triplicate. The mean over the triplet will be calculated for each parameter. Observed values of PR, QRS, and QTcF as well as change from baseline values of QTcF will be flagged as potential clinically notable results as shown in the table below:

Table 2: Potential Clinically Notable ECG Results

Parameter	Potential Clinically Notable ECG Results
PR	< 110 ms and > 210 ms
QRS	> 110 ms
QTcF	< 350 ms and Abnormal: > 450 ms for male or >470 ms for female Markedly abnormal: > 500 ms
QTcF Change from baseline	≥ 30 ms and ≥ 60 ms

ECG parameters (PR, RR, QRS, QT, QTcF and QTcB intervals) will be summarized descriptively using observed values and change from baseline by treatment groups and scheduled visits. In addition, the number and percentage of participants in each potential clinically notable results categories will be included in the summary.

In addition, shift from baseline of investigator's overall ECG evaluation (i.e., normal, abnormal not clinically significant, abnormal clinically significant, indeterminate) at each post-baseline visit will be summarized using counts and percentages of participants.

All ECG results and overall ECG evaluation will be presented in data listings by treatment group and participant.

4.9 Pharmacokinetic Endpoints in Part 1

Sparse PK sampling data pre-dose and 2 to 3 hours post dose on Days 1, 42, and 84 in Part 1 will be listed and summarized descriptively by IMP, analyte, and nominal time points for the two PHA-022121 treatment groups.

Descriptive statistics for plasma concentration data will include the number of participants (n), mean, SD, coefficient of variation (CV%), median, minimum and maximum.

Concentration values below the limit of quantification (BLOQ) will be treated as 0 if this is first or last observations, and missing if it is between two measurable concentrations.

The detailed derivation for the pharmacokinetic parameters based on plasma concentrations data will be described in a separate PK analysis plan.

5. CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

The Poisson GLM model (Section 4.6.2) was planned as the primary approach to analyzing the primary endpoint. During analysis preparation, simulation results indicate that potential model fitting issue may present with the limited sample size and excessive zero counts. Therefore, in the SAP, it is planned that if the Poisson regression does not converge, a two-sample Wilcoxon rank sum test will be used as the primary approach to test the treatment effects for the Primary Analysis.

6. SUMMARY OF CHANGES FROM THE PREVIOUS VERSION OF THE SAP

Not applicable

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APPENDIX A: ANALYSIS WINDOW FOR PART 1

Endpoints	Visit	Week	Target Day	Analysis Window (Days) ¹
AE-QoL; AECT-4wk	Baseline (Visit 1 Day 0)	Baseline	1	On or prior to Day 3 (within 2 days of first dose)
	Visit 3 Day 28	Week 4	28	(4, 42]
	Visit 5 Day 56	Week 8	56	(42, 70]
	Visit 6 Day 84	Week 12	84	>70 and before 1 st OLE dose
TSQM-II	Visit 3 Day 28	Week 4	28	(1, 42]
	Visit 5 Day 56	Week 8	56	(42, 70]
	Visit 6 Day 84	Week 12	84	>70 and before 1 st OLE dose
PGA-QoL	Baseline (Visit 1 Day 0)	Baseline	1	On or prior to Day 1
	Visit 6 Day 84	Week 12	84	>1 and before 1 st OLE dose
PGA-change	Visit 6 Day 84	Week 12	84	>1 and before 1 st OLE dose
Vital sign (including weight); clinical lab	Baseline (Visit 1 Day 0)	Baseline	1	On or prior to Day 1
	Visit 2 Day 14	Week 2	14	(1, 28]
	Visit 4 Day 42	Week 6	42	(28, 63]
	Visit 6 Day 84	Week 12	84	>63 and before 1 st OLE dose
Pregnancy Test	Baseline (Visit 1 Day 0)	Baseline	1	On or prior to Day 1
	Visit 4 Day 42	Week 6	42	(1, 63]
	Visit 6 Day 84	Week 12	84	>63 and before 1 st OLE dose
ECG	Baseline (Visit 1 Day 0)	Baseline	1	On or prior to Day 1
	Visit 4 Day 42	Week 6	42	(1, 63]
	Visit 6 Day 84	Week 12	84	>63 and before 1 st OLE dose

Note that TSQM and PGA-change are not collected at baseline.

APPENDIX B: SAMPLE SAS CODE

