MEDPACE

STATISTICAL ANALYSIS PLAN

Protocol Title:	A Phase II, double-blind, placebo-controlled, **R**andomized, cross-over, dose-ranging study of oral PHA-022121 for **A**cute treatment of angioedema attacks in **P**atients with hereditary angioedema due to C1-**I**nhibitor **D**eficiency type I and II
Protocol Number:	PHA022121-C201
Protocol Version/Date:	Version 3.0 / 25 April 2022
Investigational Product:	PHVS416 (PHA-022121 soft capsules)
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SIGNATURE PAGE

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VERSION HISTORY

Version	Version Date	Description
1.0	13 May 2022	Original signed version

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ATC	Anatomical therapeutic chemical
AUC	Area under plasma concentration-time curve
AUC_{0-12h}	AUC from time 0 to 12 h post dosing (non-BQL) concentration, calculated by the linear-linear trapezoidal summation
AUC_{0-24h}	AUC from time 0 to 24 h post dosing (non-BQL) concentration, calculated by the linear-linear trapezoidal summation
AUC_{inf}	AUC from time 0 to infinity of the last measurable (non-BQL) concentration, calculated by the linear-linear trapezoidal summation
AUC_{last}	AUC from time 0 to the time of the last measurable (non-BQL) concentration, calculated by the linear-linear trapezoidal summation
CI	Confidence interval
CL/F	total apparent systemic clearance of drug after extravascular administration, calculated as Dose/ AUC_{inf}
C_{max}	maximum observed analyte concentration
COVID-19	Coronavirus disease 2019
CRF	Case report form
CSR	Clinical Study Report
CTCAE	Common terminology criteria for adverse events
ECG	Electrocardiogram
HAE	Hereditary Angioedema
ICE	Intercurrent event
IDMC	Independent data monitoring committee
IMP	Investigational medicinal product
IRT	Interactive response technology
KM	Kaplan-Meier
KSE	Key secondary endpoints
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MSCS	Mean symptom complex severity
NCI	National Cancer Institute
PA	Primary analysis
PCSA	Potentially Clinically Significant Abnormality
PK	Pharmacokinetics
PP	Per-Protocol
PRO	Patient reported outcome
SAE	Serious adverse event
SAP	Statistical Analysis Plan
$t_{1/2}$	apparent terminal elimination half-life, calculated as 0.693/λz
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
t_{max}	actual sampling time to reach the maximum observed analyte concentration

Abbreviation	Definition
TOS	Treatment outcome score
TSQM	Treatment satisfaction questionnaire for medication
VAS	Visual analogue scale
VAS-3	3-symptom composite visual analogue scale
V_z/F	apparent volume of distribution, based on terminal phase after a single dose
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from Pharvaris Netherlands BV, protocol number PHA022121-C201. The SAP will be finalized prior to unblinding database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

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

2.1.2 Secondary Objectives

The key secondary objectives of the study are:

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

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

Other secondary objectives of the study are:

- To evaluate the clinical efficacy of three different single doses of PHA-022121 versus placebo with regards to:
    - Time to onset of primary symptom relief by visual analogue scale (VAS)
    - The proportion of investigational medicinal product (IMP)-treated attacks requiring the use of HAE rescue medication
    - Time to the first use of HAE rescue medication
    - Change in the individual VAS scores (skin pain, skin swelling, abdominal pain) from pre-treatment to 4 h post-treatment
    - Change in MSCS score at 24 h post-treatment
    - TOS at 24 h post-treatment
- To evaluate the safety of three different single doses of PHA-022121 versus placebo
- To evaluate the pharmacokinetics (PK), dose-effect relationship, and concentration-effect relationship of PHA-022121

- To evaluate the treatment satisfaction questionnaire for medication (TSQM) scores at 48 h post-treatment

2.2 Study Design

2.2.1 Overview

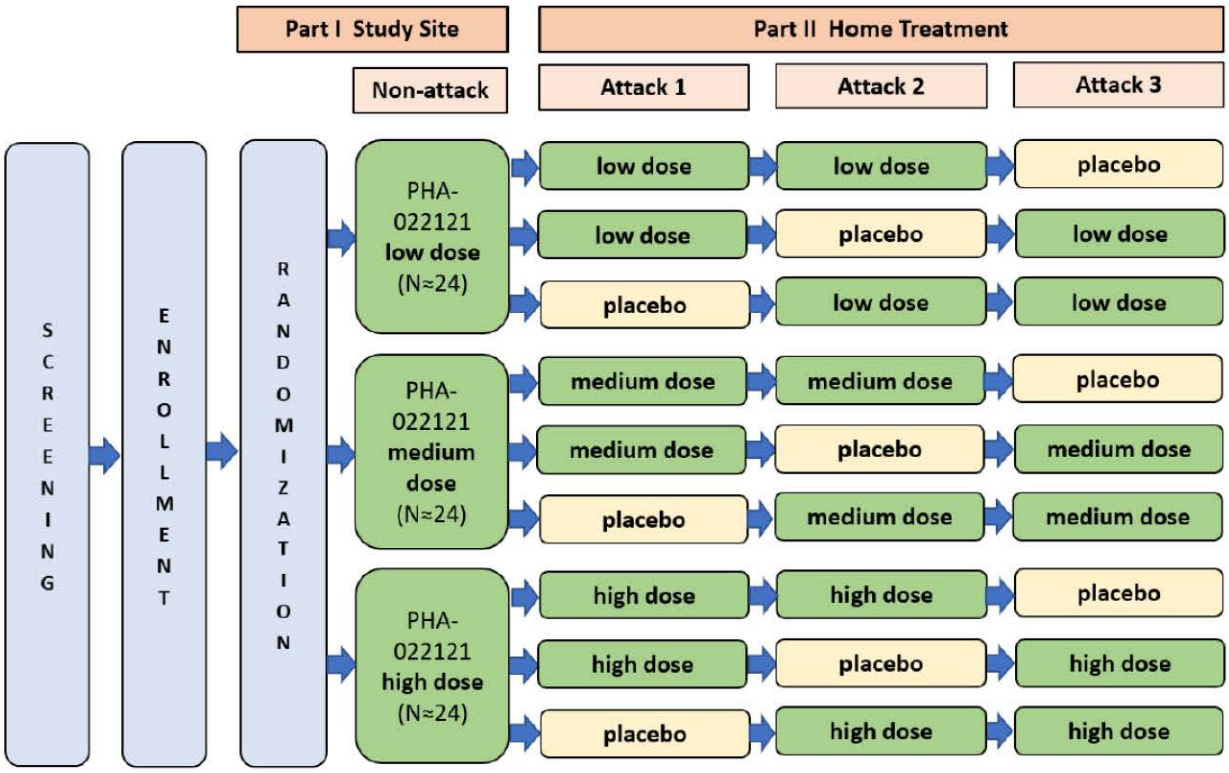
- After signing informed consent, patients will be screened for eligibility. Eligible patients will be enrolled in the study.
- Enrolled patients will be randomized to one of the three dose levels (low, medium, high) first, then based on the assigned cohort randomized to one of nine treatment sequences comparing three single doses of PHA-022121 (low, medium, high) with placebo treatment. During Part I (at the study site), patients in quiescent state will receive the assigned active single dose of PHA-022121 (dose is blinded) to assess PK and safety.
- In Part II of the study, patients will self-administer blinded investigational medicinal product (IMP) in the assigned treatment sequence at home to treat three qualifying HAE attacks, which should be consulted and confirmed by the investigator or designee via remote contact. The blinded IMP should be taken when at least one attack symptom (skin pain, skin swelling, or abdominal pain) becomes of moderate intensity (VAS score ≥ 30). When the attack reaches this VAS intensity threshold, blinded IMP should preferably be taken during the remote contact with the investigator or designee. If the patient cannot take the blinded IMP within 3 h after reaching the VAS intensity threshold, the attack does not qualify for blinded IMP treatment and should be treated with the patient's standard HAE medication. In addition, treatment of the attack should happen within 6 h after onset of symptoms at any location. If the blinded IMP cannot be administered within 6 h after onset of symptoms, the attack does not qualify for blinded IMP treatment and should be treated with the patient's standard HAE medication. Any symptoms involving the internal head and neck, regardless of intensity, also render an attack non-qualifying for treatment with blinded IMP and should be treated with the patient's standard HAE medication.

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

  Patient-reported outcomes (PROs) are collected from blinded IMP intake (including pre-treatment) until 48 h post-treatment. After each attack treated with blinded IMP, a safety follow-up visit will take place within 5 days post-treatment. Meanwhile, pharmacokinetic plasma samples are planned to be collected within 24 h post-treatment (preferably within 12 h) from a subset of patients for at least 50 attacks treated with PHA-022121 or placebo.

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

Figure 1. Flowchart of Study Design



2.2.2 *Randomization and Blinding*

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

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

Blinding is achieved because PHA-022121 capsules and placebo capsules have an identical appearance, and each treatment consists of a combination of three capsules of 10 mg PHA-022121 and/or placebo.

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

Access to blinded IMP assignment will be available if the Investigator deems it necessary to break the study blind in the interest of a patient's medical safety, in case of a medical emergency, to meet regulatory reporting obligations, or if warranted during scheduled safety reviews. Where medically appropriate, the Investigator will contact the Medical Monitor to

discuss the situation which has arisen and resulted in the need for unblinding of the patient. The Medical Monitor will not be involved in the decision to unblind.

2.2.3 Blinded IMP

The blinded IMP, also referred as study drug, is PHA-022121 or placebo administered in a double-blind fashion as soft capsules for oral use. The IMP consists of 10 mg PHA-022121 soft capsules and matching placebo soft capsules for oral use:

- Low dose (10 mg): one capsule of 10 mg PHA-022121 and two placebo capsules
- Medium dose (20 mg): two capsules of 10 mg PHA-022121 and one placebo capsule
- High dose (30 mg): three capsules of 10 mg PHA-022121
- Placebo: three placebo capsules

In Part I of the study, each patient receives a single dose of PHA-022121 (10, 20, or 30 mg) in quiescent state. In Part II, patients will be treated with blinded IMP for 3 qualifying attacks, including 2 attacks treated with a single dose of PHA-022121 (10, 20, or 30 mg) and 1 attack treated with placebo according to the randomized sequence.

According to Figure 1 (protocol Figure 2), the study has 3 cohorts and 9 treatment sequences. From top to bottom in Figure 1, the 3 Cohorts consisting of 9 treatment sequences based on the ordered treatment per randomization assignment are summarized in Table 1, with "L", "M", "H", and "P" denote low dose (10 mg), medium dose (20 mg), high dose (30 mg), and placebo, respectively.

Table 1. Summary of Treatment Cohorts and Treatment Sequences

Cohort by dose level	Sequence by assigned treatment to: Non-Attack → Attack 1 → Attack 2 → Attack 3
Cohort 1 (Low Dose Cohort)	Sequence 1: L → L → L → P Sequence 2: L → L → P → L Sequence 3: L → P → L → L
Cohort 2 (Medium Dose Cohort)	Sequence 4: M → M → M → P Sequence 5: M → M → P → M Sequence 6: M → P → M → M
Cohort 3 (High Dose Cohort)	Sequence 7: H → H → H → P Sequence 8: H → H → P → H Sequence 9: H → P → H → H

2.2.4 Sample Size Determination

The study is powered for the expected treatment effect on the VAS-3 score at 4 h post-treatment, assuming a treatment difference between PHA-022121 and placebo of 10 in VAS-3 score change from pre-treatment to 4 h post-treatment with a standard deviation of 11, based on the previous HAE studies with oral on-demand (Longhurst et al. 2019) and with icatibant treatment (Lumry et al. 2011). With the cross-over design, there are nine different treatment sequences twice comparing the same active and placebo treatment within the same patient. Assuming a very low correlation of 0.2 between the within-patient measurements on the different attacks, a total of 72 randomized patients, i.e. 8 patients per sequence randomized to the nine sequences, will provide approximately 90% power to detect a difference of 10 in VAS-3 score change from pre-treatment to 4 h post-treatment between a PHA-022121 treatment group

(medium dose or high dose) and the placebo group at a conservative significance level of 2.5% for a 2-sided test, and the power will reach 94% for a significance level of 5% for a 2-sided test. This sample size is adjusted to take into account a 20% attrition rate for evaluable attacks and 5% of attacks that will be treated with rescue medication within 4 h post-treatment.

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

2.3 Study Endpoints

2.3.1 Primary and Key Secondary Efficacy Endpoints

The primary efficacy endpoint of the study is:

- The change of the VAS-3 score from pre-treatment to 4 h post-treatment.

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

- Time to onset of symptom relief by a ≥30% reduction in VAS-3 score from the pre-treatment score
- Time to almost complete or complete symptom relief by VAS-3 score
- Time to a ≥50% reduction in VAS-3 score from the pre-treatment score
- Change in MSCS score from pre-treatment to 4 h post-treatment
- TOS at 4 h post-treatment

The detailed definitions are included in Section 3.1.1.6, and the estimand framework of the primary and key secondary endpoints are included in Section 3.4.

2.3.2 Other secondary efficacy endpoints

- Time to onset of primary symptom relief assessed by a 30% reduction in the VAS for the primary symptom, and time to 50% reduction in the VAS for the primary symptom
- Proportion of IMP-treated attacks requiring HAE rescue medication within 12 h, within 24 h, and within 48 h post-treatment
- Time to first HAE rescue medication use for IMP-treated attacks, if applicable.

  An IMP-treated attack refers to an attack treated with blinded IMP (study drug).
- Change in the VAS score for individual symptoms (skin pain, skin swelling, abdominal pain) from pre-treatment to 4 h post-treatment
- Change in MSCS score from pre-treatment to 24 h post-treatment
- TOS at 24 h post-treatment
- TSQM scores at 48 h post-treatment

2.3.3 Safety Endpoints

The safety endpoints of the study are:

- Treatment-emergent adverse events (TEAEs), treatment-related TEAEs, and treatment-emergent serious adverse events (TESAEs), and treatment-related TESAEs

- Clinical laboratory tests
- Vital signs
- Electrocardiogram (ECG)

2.3.4 Pharmacokinetic Endpoints

The PK endpoints of the study are:

- PK parameters based on plasma profiles of PHA-022121 and metabolite M2-D: C_{max}, t_{max}, area under plasma concentration-time curve $(AUC)_{0\text{-}12h}$, $AUC_{0\text{-}24h}$, AUC_{last}, AUC_{inf}, $t_{1/2}$, V_z/F (PHA-022121 only) and CL/F (PHA-022121 only).

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Study Specific Definitions

3.1.1.1 Analysis Day

Analysis day will be calculated from the date of the first dose of blinded IMP. The day of the first dose of blinded IMP will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.1.2 Analysis Visits and Analysis Timepoint

Scheduled visits will be assigned to analysis visits as recorded on the case report form (CRF). The expected schedule of events is as follows:

- Screening Visit
- Part I Non-Attack Visit
- Part II Post-Attack 1 On-site Visit
- Part II Post-Attack 2 On-site Visit
- Part II Post-Attack 3 On-site Visit

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

The followings will be conducted remotely:

- Part II Home Treatment Attack 1
- Part II Home Treatment Attack 2
- Part II Home Treatment Attack 3
- End of study

The details of each visit are described in the protocol Section 7.

The analysis timepoint is defined in Appendix E.

3.1.1.3 Definition of 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 I in which patients are in quiescent state and receive the assigned active single blinded dose of PHA-022121 to assess PK and safety. For electrocardiogram (ECG), the baseline is defined as the mean of the last recorded triplicate before the first blinded IMP administration. If no triplicate is available before the first dose of study medication intake, the last ECG value before the first blinded IMP administration will be considered as baseline.

3.1.1.4 Qualifying attacks

According to the protocol, in Part II of the study, qualifying HAE attacks are to be consulted and confirmed by the investigator or designee via remote contact. Attacks qualify for administration of the blinded IMP if all four following criteria are met:

- At least one attack symptom (skin pain, skin swelling, or abdominal pain) has become of moderate intensity (VAS score ≥ 30)
- No symptoms involving the internal head and neck are present
- Treatment with blinded IMP is administered within 6 hours after onset of symptoms and within 3 hours of the VAS score reaching the threshold of 30
- If treatment was administered at the non-attack visit or for a previous attack (either blinded IMP or the patients standard HAE medication), the date of treatment occurred more than 5 days earlier

3.1.1.5 Study Periods and Results by Points of Reference

Pre-Treatment and Post-Treatment Results

In Part II of the study, the patient self-administers blinded IMP in the assigned treatment sequence at home to treat three qualifying HAE attacks, remotely guided by the investigator. For VAS, MSCS and TOS, the pre-treatment value is defined as follows.

Unless otherwise specified, in the analyses description, pre-treatment result refers to the latest assessment result prior to IMP administration in the non-attack phase or prior to each IMP administration to treat an attack in the attack phase.

Post-treatment result refers to the result for any assessment performed after the IMP administration in the non-attack phase or after each IMP administration to treat an attack in the attack phase.

For VAS, among all assessments during the time period from 30 min before through 5 min after the time the blinded IMP is taken, the one with the assessment time that is closest to the time the blinded IMP is taken will be selected as the pre-treatment VAS.

For MSCS/TOS, among all assessments during the time period from 30 min before through 10 min after the time the blinded IMP is taken, the one with the assessment time that is closest to the time the blinded IMP is taken will be selected as the pre-treatment MSCS/TOS.

A delay of up to 5 min (for VAS) and up to 10 min (for MSCS/TOS) between treatment-taken time and baseline-assessment time may be due to differences between the patient's clock and the ePRO device clock and is, therefore, only an apparent delay. The longer window for

MSCS/TOS reflects the order in which the patients are instructed to complete the PRO (VAS completed 1st) and the longer time needed to complete MSCS/TOS.

For VAS, MSCS and TOS, the analysis timepoint is defined in Appendix E.

Attack Periods for Efficacy Analyses

In the descriptions of efficacy analyses and statistical models, each attack period refers to the time window enclosing all efficacy measures (VAS, MSCS, TOS, TSQM) for an attack that is treated with IMP. The time window covers the pre-treatment and all post-treatment efficacy assessments. These attack periods in efficacy analyses are labeled as Attack 1, Attack 2, and Attack 3.

3.1.1.6 Endpoint Related Definitions

The 3-symptom composite visual analogue scale (VAS-3) score

The VAS-3 score is the mean of the patient-reported VAS scores of the three major HAE symptoms: skin swelling, skin pain, and abdominal pain. The VAS score of each of the three major HAE symptoms ranges between 0 and 100 (Lumry et al. 2011; Kusuma et al. 2012). According to the protocol, the VAS scores must be reported pre-treatment at the time the investigator is consulted to confirm eligibility of the attack for blinded IMP treatment. Thereafter, if the attack is confirmed as a qualifying attack, the VAS scores will be reported every 30±10 min from 0 to 4 h post-treatment, and at 5±0.5, 6±0.5, 8±1, 24±4 and 48±6 h post-treatment. If the 5 h and/or 6 h timepoints fall during the overnight/sleeping hours, these timepoints are optional to report. All other time points are required. Handling of missing VAS-3 results is detailed in Section 3.1.5. The statistical methods for analyzing VAS-3 with missing data are discussed in Section 3.4.

Time to Onset of Symptom Relief by VAS-3 and Time to ≥ 50% reduction in VAS-3 score

Symptom relief by VAS-3 is a sustained VAS-3 reduction defined as a reduction of ≥ 30% from pre-treatment value of VAS-3 score for at least 2 consecutive reported VAS assessments post-treatment. Symptom relief is considered as achieved regardless of whether any scheduled assessment with a missing result presents between the 2 consecutive VAS assessments that meet the ≥30% reduction condition. Symptom relief is also considered as achieved if the ≥30% reduction condition is met for the single VAS assessment result at the last scheduled time point (48 h) provided no rescue medication used within 12 h after the last time point. The time to symptom relief by VAS-3 is the time from IMP administration to the earliest reported VAS assessment meeting the ≥ 30% reduction in sustained VAS-3 reduction. As detailed in Section 3.4.2, if rescue medication is taken before symptom relief is achieved, the time to symptom relief by VAS-3 will be censored at the time of the last post-treatment VAS-3 assessment prior to rescue medication taken. If a patient did not reach symptom relief in an attack period, the time will be censored at the last post-treatment VAS-3 assessment for that attack.

Time to a ≥ 50% reduction in VAS-3 score from pre-treatment value is defined similarly.

Symptom relief for individual VAS score with pre-treatment value >10 is defined as a reduction of ≥ 30% from pre-treatment value. Time to onset of individual VAS symptom relief and time to a ≥ 50% reduction in individual VAS score from pre-treatment value is defined similarly as the time to onset of symptom relief by VAS-3.

Time to Almost Complete or Complete Symptom Relief by VAS-3

Almost complete symptom relief by VAS is an outcome of sustained low VAS, defined as all 3 individual VAS scores (skin swelling, skin pain, and abdominal pain) having a value of 0-10 for at least 2 consecutive reported VAS assessments post-treatment. Complete symptom relief is defined as all 3 individual VAS scores of the VAS-3 having a value of 0. Almost complete or complete symptom relief is considered as achieved regardless of whether any scheduled assessment with missing result presents between the 2 consecutive VAS assessments that meet the individual VAS condition of 0-10. Almost complete or complete symptom relief is also considered as achieved if the individual VAS condition of 0-10 is met for the single VAS assessment result at the last scheduled time point (48 h) provided no rescue medication used within 12 h after the last time point. The time to almost complete or complete symptom relief by VAS is the time from IMP administration to the earliest reported VAS assessment meeting the ≤ 10 threshold in the sustained low VAS case. As detailed in Section 3.4.2, if rescue medication is taken before symptom relief is achieved, the time to almost complete or complete symptom relief by VAS-3 will be censored at the time of the last post-treatment VAS assessment prior to rescue medication taken. If a patient did not reach almost complete or complete symptom relief in an attack period, the time will be censored at the last post-treatment VAS assessment for that attack. The definition of complete symptom relief is the same except that the condition changes from requiring all individual VAS values of 0-10 to requiring all individual VAS values of 0.

Almost complete or complete symptom relief in an individual VAS symptom is an outcome of sustained low individual VAS score, defined as the individual VAS score (skin swelling, skin pain, or abdominal pain) having a value of 0-10 for at least 2 consecutive reported VAS assessments post-treatment. The definition of complete symptom relief in a VAS individual symptom is the same except that the condition changes from requiring the individual VAS value of 0-10 to requiring the individual VAS value of 0.

Time to onset of primary symptom relief by VAS

The symptom with the highest pre-treatment VAS score is considered as the primary symptom. If skin pain and abdominal pain tie at pre-treatment, abdominal pain is taken forward as primary symptom. If skin pain and skin swelling tie, then skin pain is taken forward as primary symptom. In the event that all are tied, abdominal pain would be taken forward as primary symptom.

Primary symptom relief is defined as a ≥ 30% reduction from the pre-treatment in the score for the primary VAS symptom for at least 2 consecutive reported VAS assessments post-treatment. Primary symptom relief is also considered as achieved if the ≥30% reduction condition is met for the single VAS assessment result at the last scheduled time point (48 h) provided no rescue medication used within 12 h after the last time point. The time to onset of primary symptom relief is defined similarly as the time to the onset of symptom relief by VAS-3.

Time to ≥ 50% reduction in the VAS primary symptom is defined similarly.

Mean symptom complex severity (MSCS)

The MSCS score is made up of two components: (1) symptom complex identification; and (2) severity assessment of each symptom complex. Patients are asked to identify where on the body they are experiencing symptoms including pain, swelling, rash, etc. Patients do not identify specific symptoms (e.g., rash), but rather identify symptom complexes (body areas) where symptoms are occurring. There are 5 symptom complexes: internal head/neck, stomach/gastrointestinal, genital/buttocks, external head/neck, and cutaneous. After sites are

identified, the patient is asked to rate the severity of symptoms within each complex (called the severity assessment). Severity options include: normal = 0, mild = 1, moderate = 2, severe = 3.

The MSCS score is calculated by taking the arithmetic mean of the individual symptom complex severity assessments. Zeros are not included in the pre-treatment scoring but can be included in the post-treatment scoring if they refer to symptom complexes experienced at pre-treatment.

Treatment outcome score (TOS)

The TOS score is made up of three components: (1) symptom complex identification pre-treatment; (2) severity assessment of each symptom complex pre-treatment; and (3) response assessment post-treatment. Pre-treatment, patients are asked to identify where on the body they are experience symptoms including pain, swelling, rash, etc. Patients do not identify specific symptoms (e.g., rash), but rather identify symptom complexes (body areas) where symptoms are occurring. There are 5 symptom complexes: internal head/neck, stomach/gastrointestinal, genital/buttocks, external head/neck, and cutaneous. After sites are identified, the patient is asked to rate the severity of symptoms within each symptom complex. Severity options include: severe = 3, moderate = 2, mild = 1, normal = 0.

After treatment and at the specified time points, patients are asked to rate change in the affected symptom complexes they identified pre-treatment (called the response assessment). The response assessment options include: significant improvement = 100, improvement = 50, the same = 0, worsening = -50, or significant worsening = -100.

The pre-treatment TOS is calculated as the mean of the symptoms with non-missing and non-zero pre-treatment severity.

The post baseline TOS is calculated as the sum of individual symptom complex (internal head/neck, stomach/gastrointestinal, genital/buttocks, external head/neck, and cutaneous) response assessments multiplied by the symptom complex severity assessment at pre-treatment, divided by the sum of all individual symptom complex severity assessments at pre-treatment, that is ([internal head/neck]*[pre-treatment internal head/neck] + [stomach/gastrointestinal]*[pre-treatment stomach/gastrointestinal] + [genital/buttocks]*[pre-treatment genital/buttocks] + [external head/neck]*[pre-treatment external head/neck] + [cutaneous]* [pre-treatment cutaneous]) divided by ([pre-treatment internal head/neck] + [pre-treatment stomach/gastrointestinal] + [pre-treatment genital/buttocks] + [pre-treatment external head/neck] + [pre-treatment cutaneous]).

Treatment satisfaction questionnaire for medication (TSQM)

The TSQM is an 11-item treatment satisfaction questionnaire consisting of four scales: (1) effectiveness; (2) side effects; (3) convenience; and (4) overall satisfaction. The scores for each domain are computed by adding the items in each domain and then transforming the composite score into a value ranging from 0 to 100 using the following methods. Note, a score can be computed for a scale only if no more than one item is missing from that scale.

- Effectiveness = ([(Item #1 + Item #2) – 2] / 12) * 100
    - If one item is missing use: ([(Completed item) – 1] / 6) * 100

- Side effects = ([(Item #4 + Item #5 + Item #6) – 3] / 12) * 100
    - If one item is missing use: ([(Sum of 2 Completed items) – 2] / 8) * 100
    - Note: all “NA” responses are coded as ‘5’ indicating “Not at all Dissatisfied”

- Convenience = ([(Item #7 + Item #8 + Item #9) – 3] / 18) * 100
  - If one item is missing use: ([(Sum of 2 Completed items) – 2] / 12) * 100

- Global Satisfaction = ([(Item #10 + Item #11) – 2] / 12) * 100
  - If one item is missing use: ([(Completed item) – 1] / 6) * 100

Use of rescue medication and time to first use of rescue medication for a treated attack

The time to first rescue medication use within 48 h post-treatment is

- Either the time rescue medication is taken minus the time blinded is IMP taken if use of rescue medication = Yes
- Or the time is censored at 48 h post-treatment or at the new attack start time (as defined below), whichever is earlier, if use of rescue medication = No.

An attack is considered as "new" if it started at least 24 hours after the end time of the previous attack. Otherwise, it will be considered as the same attack as the previous one.

- Use of rescue medication=Yes, if there is a rescue medication taken date/time within 48 hours after the time blinded IMP is taken and prior to a new attack starting time. Otherwise, use of rescue medication=No.

The definitions of rescue medication use within 12 h and 24 h post-treatment are similar, but with different timing thresholds, 12 h and 24 h.

3.1.2 Summary Statistics

Categorical data will generally be summarized in frequencies and percentages of patients. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized using number of non-missing values (n), mean, standard deviation, median (25^{th}, 75^{th}), minimum, and maximum values.

3.1.3 Multiplicity

The study primary endpoint and key secondary endpoints (KSEs) are listed in the Table 2 along with the statistical hypotheses for testing PHA-022121 versus placebo with respect to the high, medium, and low dose of PHA-022121.

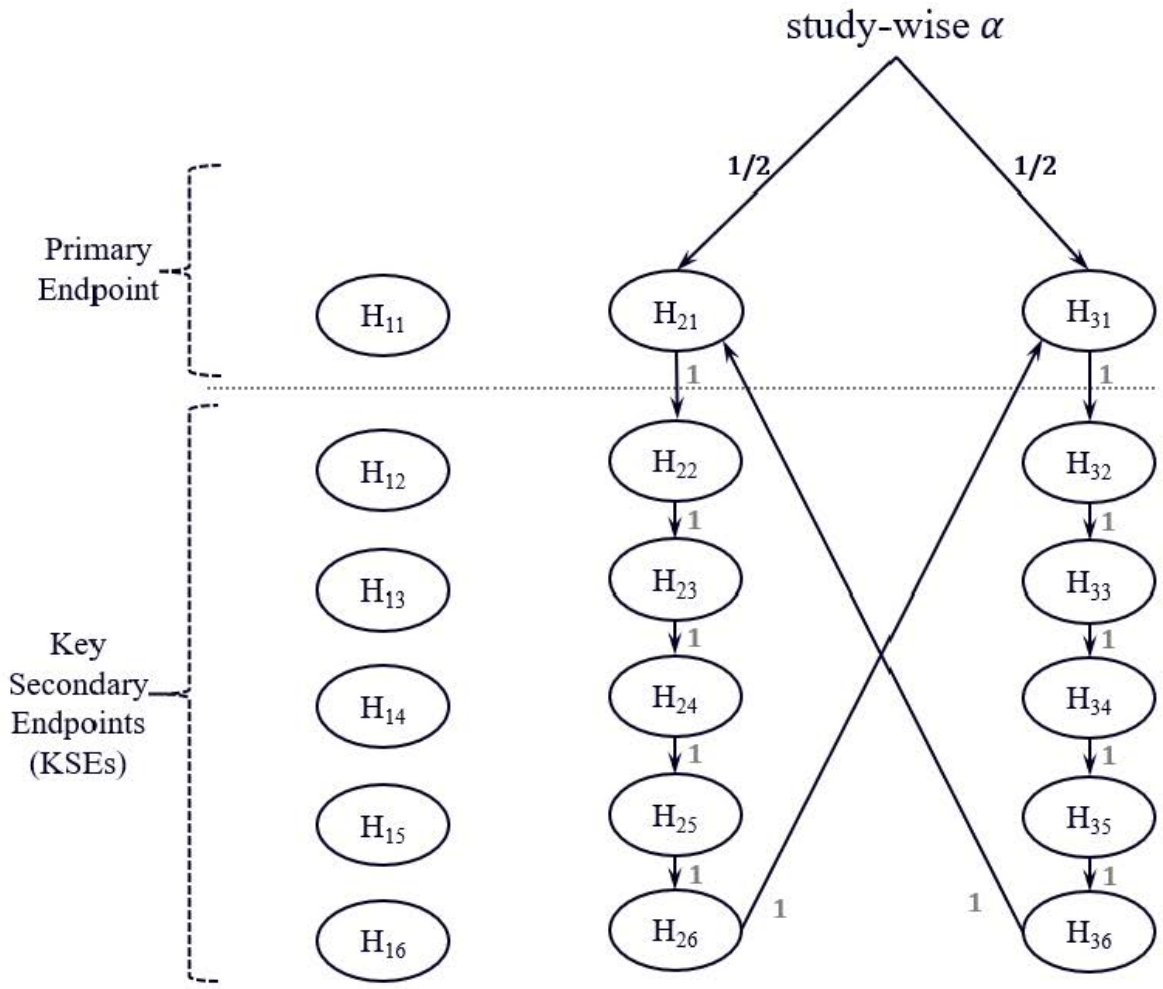
Table 2. Study Endpoints and Associated Statistical Hypotheses

Endpoint	Hypothesis ID for testing High, Medium, Low Dose
Primary Endpoint: Change of VAS-3 score from pre-treatment to 4 h post-treatment	H_{11}, H_{21}, H_{31}
KSE: Time to onset of symptom relief by a ≥30% reduction in VAS-3 score from the pre-treatment score	H_{12}, H_{22}, H_{32}
KSE: Time to almost complete or complete symptom relief by VAS-3 score	H_{13}, H_{23}, H_{33}
KSE: Time to a ≥50% reduction in VAS-3 score from the pre-treatment score	H_{14}, H_{24}, H_{34}
KSE: Change in MSCS at 4 h post-treatment	H_{15}, H_{25}, H_{35}
KSE: TOS at 4 h post-treatment	H_{16}, H_{26}, H_{36}

The study-wise type I error rate for statistical hypothesis testing of the primary and key secondary endpoints will be controlled at 5% significance level for 2-sided test. The testing strategy is described below and illustrated in Figure 2. The low dose will be included in the analysis for evaluating dose response but will not spend α in the multiplicity control procedure; the nominal p values for testing the 10-mg dose will be provided.

To control the overall type I error rate for hypotheses testing among the primary endpoint and KSEs and across the medium and high doses in this study, a graphical multiple testing procedure (Bretz et al 2011) will be applied. As shown in Figure 2, initially the full α will be equally split and allocated to 2 branches of hypotheses testing for the high and medium doses. Within each branch, the endpoints are ordered according to Table 2 and Figure 2, hypotheses can only be tested in sequential order as indicated by the arrows. In the graphical testing procedure, the nodes are individual hypotheses, the numbers labeled on the edges indicate the weights of α to be propagated to testing the next hypothesis pointed by the arrow if the preceding hypothesis testing is passed. If all the hypotheses are successfully passed within a branch (i.e., a dose level), the remaining α will be allocated to testing the hypotheses of the primary endpoint in the other dose level.

Figure 2. Multiple Testing Procedure Controlling for Study-wise Type I Error Rate



3.1.4 Evaluation of Site Effect

The average number of patients projected to be enrolled in each site is too small to evaluate site effect. No additional analyses on site effect will be performed.

3.1.5 Handling of Missing Data

For primary and key secondary endpoints, the handling of missing data is detailed in section 3.4 with the details for each respective endpoint.

The electronic PRO device does not allow for individual items within VAS-3 to be skipped. Thus, the VAS-3 composite score will not have any imputed data since all items will be completed.

For concomitant medications/processes, if a medication has incomplete start or stop dates, dates will be imputed to determine whether a medication should be considered prior or concomitant. If a medication start date is incomplete, the first day of the month will be imputed for the missing day and January will be imputed for the missing month. If a medication stop date is incomplete, the last day of the month will be imputed for the missing day and December will be imputed for the missing month. Incomplete start and stop dates will be listed as collected without imputation.

When deciding if an adverse event (AE) is a treatment-emergent adverse event (TEAE), the incomplete start date/time will be imputed by the latest possible date/time. When deciding if the TEAE starts within 48 h post-dose, the start date/time will be imputed by the earliest possible date/time.

3.2 Analysis Sets

3.2.1 Full Analysis Set (FAS)

The FAS includes all patients enrolled and randomized in the study. In analyses performed on the FAS, patients will be analyzed, based on the intention-to-treat principle, according to their randomized treatment assignment regardless of treatment received.

3.2.2 Modified Intent-to-Treat (mITT) Analysis Set

The mITT Analysis Set is a subset of FAS including all randomized patients who had at least one IMP-treated (blinded PHA-022121 or placebo) HAE attack and who had non-missing VAS results at both pre-treatment and at least 1 post-treatment time point of that attack. In analyses performed on the mITT Analysis Set, patients will be analyzed based on the intention-to-treat principle according to their randomized treatment assignment regardless of treatment received.

3.2.3 Safety Analysis Set

The Safety Analysis Set is a subset of FAS including all randomized patients who received any dose of IMP. In analyses performed on the Safety Analysis Set, patients will be analyzed according to their actual treatment received.

3.2.4 Per-Protocol (PP) Analysis Set

The PP Analysis Set is defined as all subjects' treated attacks in the mITT Analysis Set with no major protocol deviations or other non-compliance that may impact the key efficacy assessment, including data from the corresponding attack periods. The PP Analysis Set will be a secondary analysis set for analysis of the primary and key secondary efficacy endpoints, where the actual treatment will be used for the analyses. Major protocol deviations or other non-compliance that may impact the key efficacy assessment include but are not limited to:

- Failed to meet critical eligibility criteria
- Treatment with blinded IMP is not administered within 6 hours after onset of symptoms or is not administered within 3 hours of the VAS score reaching the threshold of 30
- More than half of VAS-3 scores are missing during the first 4 h
- Missed at least 1 out of 3 capsules of the IMP for the treated attack

A list of subjects with major protocol deviations or other non-compliance leading to exclusion from the PP Analysis Set will be finalized prior to unblinding the randomized treatment assignments.

3.2.5 Pharmacokinetic Analysis Set

The PK Analysis Set is defined as all patients for whom PK parameters can be estimated.

3.3 Patient Data and Study Conduct

3.3.1 Patient Disposition

Patients who were screened (signed informed consent) and discontinued early during screening (screen failures) will be listed with the reason of screen failure and if it is due to coronavirus disease 2019 (COVID-19).

Frequencies and percentages of patients will be summarized by dose cohort and in total based on FAS in at least each of the following disposition categories:

- Patients who completed the non-attack visit
- Patients who completed post-attack 1 visit
- Patients who completed post-attack 2 visit
- Patients who completed post-attack 3 visit
- Patients who completed the study
- Patients with early discontinuation

Reasons for early discontinuation will also be summarized and listed.

All attacks recorded will be listed, with flag of whether they are qualifying attacks.

3.3.2 Protocol Deviations

Protocol deviations will be defined in the Protocol Deviation Plan. Frequencies and percentages of patients with CSR reportable protocol deviations by deviation category will be summarized by dose cohort and in total, grouped by eligibility violations and on-study protocol deviations, based on FAS.

The CSR reportable protocol deviations will also be summarized by actual treatment.

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

3.3.3 Analysis Sets

Frequencies and percentages of patients in each analysis set will be summarized by dose cohort and in total based on FAS. Reasons for exclusions from the analysis sets will be listed.

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years) and age categories (<65 years, ≥65 years)
- Sex
- Childbearing potential
- Race
- Ethnicity
- Country
- Height (cm)
- Weight (kg)

- Body mass index (BMI) (kg/m^2) and BMI categories (<30 kg/m^2, ≥30 kg/m^2)
- Time since HAE diagnosis (year)
    - Time since HAE diagnosis (years) is calculated as (date of informed consent – date of diagnosis + 1)/365.25 if the dates are full; Month difference of (date of informed consent and date of diagnosis)/12 if only day is missing; year difference of (date of informed consent and date of diagnosis) if both month and day are missing;
- HAE Type
- Number of HAE attacks in the last 2 months prior to screening
- Number of HAE attacks in the last 4 months prior to screening
- Number of HAE attacks in the last 1 year prior to screening
- Number of patients with prophylactic HAE treatment history

Demographic and baseline characteristics will be summarized with summary statistics as appropriate by dose cohort and in total for mITT and safety analysis sets. Demographic and baseline characteristics will be listed.

3.3.5 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1 (or later version). Frequencies and percentages of patients with medical history by system organ class and preferred term will be summarized by dose cohort and in total based on Safety Analysis Set. Medical history will also be listed.

3.3.6 Concomitant Medications and Procedures

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and Drug Code of the Preferred Name using the WHO Drug B3 Global, September 2020 (or later version). For summary purposes, medications will be considered prior medications if they stopped prior to the first dose of blinded IMP and concomitant medications if they were taken at any time after the first dose of study drug (i.e. started prior to the first dose of blinded IMP and were ongoing or started after the first dose of blinded IMP). Please refer to Section 3.1.5 about how to handle incomplete dates.

Frequencies and percentages of patients taking prior (HAE/non-HAE) medications by ATC class and preferred term will be summarized by actual dose cohort and in total based on the Safety Analysis Set. The use of any prior or concomitant medication will be listed. The concomitant HAE/non-HAE medications, and rescue medications will be summarized separately similarly.

Prior or concomitant procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1 (or later version) and will be listed.

The concomitant medications will be reviewed by the study team to adjudicate which of them are HAE medications and which are rescue medications. This will be recorded in an excel spreadsheet and serve as a source data in the end of study for identifying the HAE medications and rescue medications, which can overwrite the same information collected in the CRF.

3.3.7 Blinded IMP Exposure and Compliance

Days in the study will be calculated as date of early discontinuation/end of study - date of first dose of blinded IMP + 1. Days in the study will be summarized by cohort based on the Safety

Analysis Set with frequencies and percentages of patients with exposure in the following categories:

- Treated with IMP at site for Part I
- Treated with IMP at home once for attack in Part II
- Treated with IMP at home twice for attacks in Part II
- Treated with IMP at home three times for attacks in Part II

Compliance with the blinded IMP regimen will be summarized by treatment based on the Safety Analysis Set at each visit/attack with frequencies and percentages of compliance in the following categories:

- 1 Capsule
- 2 Capsules
- 3 Capsules

3.4 Efficacy Analysis

Efficacy data will be summarized by randomized treatment (for the attack) based on the mITT Analysis Set. Unless otherwise specified, all analyses for efficacy endpoints will be based on assessment results from HAE attacks that have been treated with IMP.

Descriptive summary statistics will be presented for all study endpoints. For continuous endpoints, descriptive summary statistics will generally include number of subjects with data, the mean, standard deviation, median, interquartile range (Q1, Q3) and range (minimum, maximum). For categorical endpoints, this will generally include number and the percent of subjects with data in each category.

All efficacy endpoints will be evaluated primarily on the mITT Analysis Set. All statistical tests are carried out 2-sided (with 5% significance level).

For continuous efficacy endpoints, the evaluation of treatment effect will be based on mixed models for repeated measures (MMRM) allowing modeling for within-patient and between-patient variabilities. Unless otherwise specified, the MMRM will include fixed effects of treatment, time, treatment-by-time interaction, period (attacks 1, 2, 3), and period specific pre-treatment covariates as appropriate. The time referred to here is the categorical variable for the protocol specified assessment timepoints per treated attack. A heterogeneous Toeplitz covariance structure will be assumed to model the within-patient variability. Model convergence will be checked. If the MMRM with heterogeneous Toeplitz covariance fails to converge, the following tests will be used in sequence: heterogeneous autoregressive covariance structure, heterogeneous compound symmetry covariance structure, and compound symmetry covariance structure. Least-squares (LS) adjusted mean and its 95% confidence interval (CI) of each treatment group as well as treatment differences between PHA-022121 and placebo, for each dose of PHA-022121 respectively, will be provided with 95% CI and p-values. For the analysis of an efficacy endpoint using MMRM, the model will be based on the data up to the primary timepoint. For example, for the endpoint of change of VAS-3 from pre-treatment to 4 h post-treatment, all VAS-3 results from assessment timepoints up to 4 h post-treatment will be used to fit the MMRM for the main analysis.

For time-to-event efficacy endpoints, the evaluation of treatment effect will be based on marginal Cox proportional hazards models (CPHM) with a robust variance-covariance estimator to account

for the within-patient correlation. Unless otherwise specified, the model will include treatment, period, and period specific pre-treatment VAS-3 score as independent variables. Patients who have not had the event of interest at the time of the analysis will be censored, for example, a patient's time to symptom relief defined by VAS-3 will be censored at the last assessment of VAS-3 if no symptom relief has occurred. The estimated hazard ratio between PHA-022121 and placebo, for each dose of PHA-022121 respectively, will be provided with 95% CI and p-value.

For the binary efficacy endpoint, i.e., the proportion of attacks requiring HAE rescue medication, the analysis will be based on the generalized estimating equation (GEE) with a logit link. Unless otherwise specified, the model will include treatment, period, and period specific pre-treatment VAS-3 score as independent variables, and an identity matrix as the working correlation matrix of the robust empirical estimates of error (Jones and Kenward 2014, Section 6.3). The estimated odds ratio of requiring HAE rescue medication between PHA-022121 and placebo, for each dose of PHA-022121 respectively, will be provided with 95% CI and p-value.

For analysis using MMRM, the timepoint defined in Appendix E will be used. For time-to-event endpoints, the actual time length is used for the analysis. The actual time period is also used for defining the binary endpoint.

Any changes and specific detail will be provided for each endpoint in the following subsections.

3.4.1 Primary Efficacy Endpoint

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

Based on this primary objective, the primary estimand is described as follows according to the framework provided in ICH E9(R1) (FDA 2021). The treatment condition of interest for this study is a single dose of PHA-022121 10 mg (low dose), 20 mg (medium dose), 30 mg (high dose) or placebo in oral capsules as acute treatment for HAE attacks. The primary efficacy estimand on the treatment effect of PHA-022121 considers the patient population as defined through the study inclusion/exclusion criteria, with the primary efficacy endpoint being the change of VAS-3 score from pre-treatment to 4 h post-treatment. The population-level summary is the least squares means (LS-means) of the difference in VAS-3 score change from pre-treatment to 4 h post-treatment between PHA-022121 and placebo for each dose of PHA-022121, respectively, as estimated from the MMRM as described in Section 3.4.

The MMRM will include fixed effects of treatment, time (every 0.5 h from 0.5 to 4 h post-treatment), treatment-by-time interaction, period, and period specific pre-treatment VAS-3 value as covariate.

In addition, summary statistics of the changes from pre-treatment at the different post-treatment time points will be provided, for the different doses of PHA-022121. Frequencies and percentages of attacks in each location, severity will be provided with the summary statistics of the duration by cohort.

The intercurrent events (ICEs) by category and the corresponding strategies for addressing these ICEs are listed in Table 3.

If both Category 1 ICE and Category 2 ICE occur for the same patient, addressing Category 1 ICE takes precedence over Category 2 ICE. For example, if a patient took rescue medication at

2 h post-treatment, and subsequently dropped out at 3 h with no VAS-3 result after 3 h post-treatment, then VAS-3 results after initiation of rescue medication will all be set to missing with analysis following the specified approach for addressing Category 1 ICE.

The following sensitivity and supplementary analyses will be provided.

- VAS-3 results after the initiation of Category 1 or Category 2 ICE will be set to missing and be multiply imputed using copy reference method which is a control-based multiple imputation (Ratitch and O'Kelly 2011).
- In addition to mITT analysis set, the primary efficacy endpoint analyses will be repeated on the PP analysis set.
- The primary efficacy endpoint analysis may be repeated using the actual treatment received.

Table 3. ICEs by Category and Strategies for Addressing ICEs in the Primary Estimand

Category 1 ICE: Intake of allowed HAE rescue medication (protocol 5.6.1) or prohibited concomitant medications for treating the attack (protocol 5.6.2) within 4 h post-treatment timepoint	**Category 2 ICE:** Any event (e.g., ePRO device malfunction) causing subsequent VAS-3 results all missing through 4 h post-treatment timepoint
Hypothetical Strategy: VAS-3 results after the initiation of Category 1 ICE will firstly be set to missing, then the data will be analyzed using MMRM, which serves as the main analysis method assuming missing at random (MAR). Additionally, sensitivity analysis will be performed with missing not at random (MNAR) assumption. VAS-3 results after the initiation of Category 1 ICE will be set to missing and be multiply imputed using copy reference method which is a control-based multiple imputation (Ratitch and O'Kelly 2011). For every imputed data set an MMRM will be fitted. Overall inference will then be obtained by applying Rubin's rules (Rubin 1976) on the estimates obtained from every imputed data set.	**Hypothetical Strategy:** All available VAS-3 results up to 4 h post-treatment timepoint will be analyzed using MMRM with missing results after Category 2 ICE assumed as MAR. Additionally, sensitivity analysis will be performed with missing not at random (MNAR) assumption. VAS-3 results after the initiation of Category 2 ICE will be set to missing and be multiply imputed using copy reference method which is a control-based multiple imputation (Ratitch and O'Kelly 2011). For every imputed data set an MMRM will be fitted. Overall inference will then be obtained by applying Rubin's rules (Rubin 1976) on the estimates obtained from every imputed data set.

The following supportive analyses may be provided.

- The primary efficacy endpoint analysis may be conducted by excluding data with inconsistency in symptom reports between VAS and MSCS/TOS (defined in Appendix F). Note that if there is inconsistency in symptom reports between pre-treatment VAS and pre-treatment MSCS/TOS then all the post-treatment VAS-3 change scores will be excluded for that attack.
- The primary efficacy endpoint analysis may be repeated using only the data from the 1st treated HAE attack.

The example SAS code is provided in Appendix G.

3.4.2 Secondary Efficacy Endpoints

All secondary efficacy endpoints will be analyzed on the mITT Analysis Set. Analyses for the key secondary endpoints will also be conducted on the PP Analysis Set. For key secondary efficacy endpoints, a multiplicity control procedure will be applied as detailed in section 3.1.3. For other secondary efficacy endpoints, analyses are descriptive in nature and nominal p-values will be provided as applicable.

For KSEs, the estimands' attributes concerning treatment and population are the same as the ones described in Section 3.4.1. The KSEs are listed in Table 4, along with the descriptions in the estimand framework.

The example SAS code is provided in Appendix G.

Time-to-event outcomes

The time-to-event endpoints will be modeled using a marginal Cox proportional hazards model (CPHM) as described in Section 3.4. Patients who have not had the event of interest at the time of the analysis (i.e. 48 h ± 6h time period) will be censored at the last assessment time. Patients will also be censored at the time of the last post-treatment VAS assessment prior to intake of rescue medication (except for the endpoint Time to first HAE rescue medication). Estimated hazard ratio of each PHA-022121 dose versus placebo with 95% CI and p-value will be provided from the CPHM.

Additionally, Kaplan-Meier (KM) analyses will be provided with data from the 3 attack periods pooled together by assigned treatment. For example, the time-to-event data from Sequence 1 in Attack 1 and Attack 2, from Sequence 2 in Attack 1 and Attack 3, and from Sequence 3 in Attack 2 and Attack 3 will be pooled as the data for Low Dose group; the time-to-event data from Sequences 1, 4, 7 in Attack 3, from Sequences 2, 5, 8 in Attack 2, and from Sequences 3, 6, 9 in Attack 1 will be pooled as the data for placebo; and thus the standard KM analyses will be applied to compare the Low Dose group with placebo.

In addition, a supportive analysis only based on data from Attack 1 may be provided. For example, KM analyses will be applied to compare Low Dose with placebo by pooling the time-to-event data from Sequence 1 and 2 in Attack 1 as the data for Low Dose group, and pooling the data from Sequence 3, 6, and 9 in Attack 1 as the data for placebo group.

KM estimates of the survival function for time to symptom relief by VAS and time to complete or almost complete symptom relief by VAS may be graphically displayed for each treatment group. KM estimates of quartiles (median, 25^{th} and 75^{th} percentiles) with 95% CI will be calculated if applicable.

Time-to-event analyses will only be performed if at least one treatment group has a large enough number of events. Treatment groups that have a small number of events will be summarized.

Table 4. Key Secondary Endpoints and Corresponding Estimands

Endpoint	Population-Level Summary	Strategy of Addressing Category 1 ICE - Intake of rescue medication during assessment window	Strategy of Addressing Category 2 ICE - Any event causing subsequent missing result of the variable of interest
Time to onset of symptom relief by VAS-3 [a reduction of ≥30% from pre-treatment for VAS-3, which is the mean of the 3 VAS scores for skin swelling, skin pain, and abdominal pain]. Assessment window for this endpoint is from IMP dose to 48 h post-dose timepoint for each treated attack.	Hazard ratio between PHA-022121 and placebo in time to onset of symptom relief by VAS-3 using marginal CPHM.	**Hypothetical Strategy** – censor the time at the last VAS assessment prior to occurrence of Category 1 ICE; treatment effect of interest concerning the outcomes if rescue medication was not available.	**Hypothetical Strategy** – censor the time at the last VAS assessment prior to occurrence of Category 2 ICE. As results after Category 2 ICE are all missing, this is the standard approach to time-to-event analysis when event status is missing.
Time to complete or almost complete symptom relief by VAS (as defined in Section 3.1.1.6). Assessment window for this endpoint is from IMP dose to 48 h post-dose timepoint for each treated attack.	Hazard ratio between PHA-022121 and placebo in time to onset of almost complete or complete symptom relief by VAS-3 score using marginal CPHM.	**Hypothetical Strategy** – similar to above	**Hypothetical Strategy** – similar to above
Time to a ≥50% reduction in VAS-3 score from pre-treatment Assessment window for this endpoint is from IMP dose to 48 h post-dose timepoint for each treated attack.	Hazard ratio between PHA-022121 and placebo in time to ≥50% reduction in VAS-3 using marginal CPHM.	**Hypothetical Strategy** – similar to above	**Hypothetical Strategy** – similar to above
Change of MSCS at 4 h post-treatment. Assessment window for this endpoint is from IMP dose to 4 h post-dose timepoint for each treated attack.	LS-means of the difference in MSCS change from pre-treatment to 4 h post-treatment between PHA-022121 and placebo estimated from the MMRM.	**Hypothetical Strategy**: MSCS results after the initiation of Category 1 ICE will firstly be set to missing, then the data will be analyzed using MMRM assuming missing MAR.	**Hypothetical Strategy**: All available MSCS results up to 4 h post-treatment timepoint will be analyzed using MMRM with missing results after Category 2 ICE assumed as MAR.
TOS at 4 h post-treatment. Assessment window for this endpoint is from IMP dose to 4 h post-dose timepoint for each treated attack.	LS-means of the difference in TOS at 4 h post-treatment between PHA-022121 and placebo estimated from the MMRM.	**Hypothetical Strategy** – similar to above	**Hypothetical Strategy** – similar to above

Time to onset of symptom relief by VAS-3 score

The analysis of this endpoint is described above and in Table 4.

Similar analysis for the individual VAS symptom relief may be conducted if applicable. The individual VAS pre-treatment value will be adjusted in the marginal CPHM.

Supportive analysis:

The time to onset of symptom relief by VAS-3 score will be rederived by excluding data on or after the first timepoint with inconsistency in symptom reports between VAS and MSCS/TOS (defined in Appendix F). The KM analysis and marginal CPHM analysis may be conducted.

Time to almost complete or complete symptom relief by VAS

The analysis of this endpoint is described above and in Table 4.

Similar analysis for almost complete or complete relief in individual VAS symptom may be conducted if applicable. The individual VAS pre-treatment value will be adjusted in the marginal CPHM.

Supportive analysis:

The time to almost complete or complete symptom relief by VAS will be rederived by excluding data on or after the first timepoint with inconsistency in symptom reports between VAS and MSCS/TOS (defined in Appendix F). The KM analysis and marginal CPHM analysis may be conducted.

Time to a ≥50% reduction in VAS-3 score from pre-treatment

The analysis of this endpoint is described above and in Table 4.

Similar analysis for ≥50% reduction in individual VAS symptom may be conducted if applicable. The individual VAS pre-treatment value will be adjusted in the marginal CPHM.

Supportive analysis:

The time to ≥50% reduction in VAS-3 score from pre-treatment will be rederived by excluding data on or after the first timepoint with inconsistency in symptom reports between VAS and MSCS/TOS (defined in Appendix F). The KM analysis and marginal CPHM analysis may be conducted.

Time to first HAE rescue medication (if applicable)

The Time to first HAE rescue medication analysis will be performed if we observe enough IMP treated attacks with HAE rescue medication taken. Only the treatment arms with enough events will be included in the analysis.

The analysis is described above. Assessment window for this endpoint is from time of IMP dose to
48 h post-treatment for each treated attack.

Time to onset of primary symptom relief by VAS

The analysis is described above. The primary VAS symptom pre-treatment value will be adjusted in the marginal CPHM. Assessment window for this endpoint is from time of IMP dose

to
48 h post-treatment timepoint for each treated attack.

If rescue medication is taken during assessment window, time will be censored at the last corresponding VAS assessment prior to occurrence of the ICE.

If any event causing subsequent missing result of the variable of interest, time will be censored at the last corresponding VAS assessment prior to occurrence of the ICE.

Continuous secondary endpoints

Change of the individual VAS scores and MSCS, actual TOS and TSQM score, may be summarized using descriptive statistics by treatment arm at the specified time points. Analyses based on MMRM will be carried out similarly to the analysis for the primary endpoint if applicable. Note that for the individual VAS scores analysis, only symptom scores with a non-zero pre-treatment value will be considered and the individual VAS pre-treatment value will be adjusted in the MMRM.

Mean symptom complex severity (MSCS)

Scores and change from pre-treatment will be summarized using descriptive statistics by treatment arm at each scheduled time point. An analysis based on MMRM (in Section 3.4) will be carried out similarly to the analysis for the primary efficacy endpoint for timepoint 4 h post-treatment. The MMRM will include fixed effects of treatment, time (1, 2, and 4 h post-treatment), treatment-by-time interaction, period, and period specific pre-treatment MSCS value as covariate. Please refer to Table 4 for handling of ICEs.

The MSCS will also be analyzed at 24 h post-treatment as an other secondary endpoint. The analysis and method of handling ICEs are the same but the timepoint is changed from 4 h to 24 h, including the data used for analysis.

An emerging symptom complex(es) is any new symptom complex that develops symptoms after dosing with blinded IMP. Emerging symptoms in MSCS will be listed.

Supportive Analysis:

MMRM analysis for MSCS may be conducted by excluding data with inconsistency in symptom reports between VAS and MSCS/TOS (defined in Appendix F). Note that if there is inconsistency in symptom reports between pre-treatment VAS and pre-treatment MSCS/TOS then all the post-treatment MSCS change scores will be excluded for that attack.

Treatment outcome score (TOS)

Actual scores will be summarized using descriptive statistics by treatment arm at each scheduled time point. An analysis based on MMRM (in Section 3.4) will be carried out similarly to the analysis for the primary efficacy endpoint for timepoint 4 h post-treatment. The MMRM will include fixed effects of treatment, time (1, 2, and 4 h post-treatment), treatment-by-time interaction, period, and period specific pre-treatment MSCS value as covariate. Please refer to Table 4 for handling of ICEs.

The TOS will also be analyzed at 24 h post-treatment as an other secondary endpoint. The analysis and method of handling ICEs are the same but the timepoint is changed from 4 h to 24 h, including the data used for analysis.

Emerging symptoms in TOS will be listed.

Supportive Analysis:

MMRM analysis for TOS may be conducted by excluding data with inconsistency in symptom reports between VAS and MSCS/TOS (defined in Appendix F). Note that if there is inconsistency in symptom reports between pre-treatment VAS and pre-treatment MSCS/TOS then all the post-treatment TOS will be excluded for that attack.

Treatment satisfaction questionnaire for medication (TSQM)

Domain scores will be summarized using descriptive statistics by treatment arm at 48 hours post-treatment. An analysis based on MMRM (in Section 3.4) will be carried out, including the handling of Category 1 and Category 2 ICEs. The MMRM will include fixed effects of treatment, period, and period specific pre-treatment VAS-3 value as covariate.

Binary efficacy endpoint

Proportion of blinded IMP treated attacks requiring HAE rescue medication

A generalized estimating equation (GEE) with a logit link will be used to analyze the proportion of IMP treated attacks requiring HAE rescue medication within 12 h, within 24 h, and within 48 h post-treatment, based on binary outcome data. The model will include treatment, period, and pre-treatment VAS-3 score as fixed effects. An estimated odds ratio of each PHA-022121 dose versus placebo with its 95% CI and p-value will be provided. Please refer to Table 4 for handling of ICEs.

Additionally, the number of attacks requiring HAE rescue medication (after taking IMP) will be summarized using frequencies and percentages by treatment arm.

3.4.3 Subgroups

The primary efficacy endpoint will be summarized for the mITT Analysis Set by age (<65, ≥65), gender (male, female). The primary efficacy analysis may be repeated for each subgroup if sufficient data is available in each subgroup. Other subgroups may also be explored.

The corresponding subgroup analysis will be performed only if each category has at least 5 patients in each treatment group.

3.5 Pharmacokinetic Analysis

Pharmacokinetic analysis will be described in a separate document.

3.6 Safety Analysis

Safety data will be summarized by actual dose received (and in total for selected analyses) based on the Safety Analysis Set. The occurrence of an event is counted towards the treatment arm (dose) that the patient has taken prior to the event occurrence. Incidence summary tables will be by the actual dose cohort (L, M, H) during the non-attack period and by the actual dose during the attack periods (L, M, H, P). Selected incidence summary tables will be by the actual dose cohort and by the actual dose during the attack periods (L cohort (L, P), M cohort (M, P), H cohort (H, P), Total active, Total P). Summary tables for lab numeric parameters will be by the actual dose cohort (L, M, H, Total) during the non-attack period and by the actual dose (L, M, H, P) during the attack periods.

3.6.1 Adverse Events (AEs)

AEs will be captured from the date of the informed consent was signed until the end-of-study visit. All AEs will be coded to system organ class and preferred term using MedDRA version 23.1 (or later version). Treatment emergent adverse events (TEAEs) are defined as AEs that occur during the time window that starts from the first IMP administration through the end-of-study visit.

AE severity grade will be evaluated and recorded on the CRF according to the grading described in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on the 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

An overview of AEs within 48 hours post-treatment (of non-attack or attack period) will be provided including frequencies and percentages of patients (and event frequencies) with the following:

- Any TEAEs (overall and by maximum grade/severity)
- Any blinded IMP-related TEAEs (overall and by maximum grade/severity)
- Any treatment-emergent serious AEs (TESAEs)
- Any blinded IMP-related TESAEs (overall and by maximum grade/severity)
- Any TEAEs leading to discontinuation of blinded IMP
- Any TEAEs leading to discontinuation from study participation
- Any AEs leading to death

Frequencies and percentages of patients (and event frequencies) will also be presented by system organ class and preferred term for each of the categories in the overview. The Incidence summary tables described in Section 3.6 will be used.

Overview and frequencies and percentages of patients (and event frequencies) will be repeated including only those AEs that began (or worsened) within 5 days post-treatment (of non-attack or attack period), summarized by actual dose received (prior to the AEs) and in total.

The TEAE is counted towards the specific dose group (e.g., low dose) only if it started during the time period after the patient was administered IMP of that dose (or placebo) and prior to the administration of another different dose (or placebo), if there was any.

All AEs will be listed. Separate listings will be presented specifically for SAEs and TEAEs leading to discontinuation of blinded IMP or discontinuation from the study.

3.6.2 Clinical Laboratory Tests

Blood and/or urine sampling for blood chemistry, hematology, coagulation, urinalysis, and pregnancy test will be done at the Screening visit, the Non-attack visit (pre-dose), and the Post-attack visits. Blood sampling for viral testing will be done at Screening only. Blood and urine samples will be processed by a central laboratory. A list of laboratory tests to be performed along with reference ranges is included in Appendix B.

Observed values will be presented at each scheduled visit and baseline by laboratory test. The post attack visits may be pooled together for simplicity. The incidence of abnormalities (as defined by normal ranges) prior to the first dose of blinded IMP and after the first dose of blinded IMP may be summarized with frequencies and percentages of patients.

The incidence of worst post-attack lab abnormalities may be summarized with frequencies and percentages of patients for selected parameters using the grading scheme in the CTCAE Version 5.0. CTCAE criteria are detailed in Appendix C (CTCAE v5.0).

All laboratory data will be listed. Another list will be provided to show the corresponding values for the patient's laboratory parameters with at least one meeting the CTCAE criteria.

3.6.3 Vital Signs

Vital signs include blood pressure, heart rate, body temperature, and respiratory rate. The measurements will be taken at Screening, Non-attack visit, and Post-attack visits. Observed values and changes from baseline will be summarized. The post attack visits may be pooled together for simplicity.

The incidence of Potentially Clinically Significant Abnormalities (PCSA) will be summarized with frequencies and percentages of patients for selected parameters. PCSA criteria are defined in Appendix D.

Vital signs assessments will be listed. Clinically significant changes in vital signs reported as AEs will be flagged as well as the PCSA. Another list will be provided to show the corresponding values for the patient's vital signs with at least one potential clinically significant abnormality.

3.6.4 Electrocardiograms

A 12-lead Electrocardiogram (ECG) (digital triplicate) will be recorded at Screening and at the Non-attack visit. Clinically significant ECG findings will be reported as AEs. The mean over the triplet will be calculated for each parameter. Mean values will be derived during the statistical analysis. Only means will be reported in the summary tables.

The incidence of PCSA may be summarized with frequencies and percentages of patients. PCSA criteria are defined in Appendix D.

ECG readings and abnormalities will be listed. Another list will be provided to show only the corresponding values for the patient's ECG parameters with at least one PCSA. The ECG Medpace Core Laboratories interpretation may be summarized.

3.6.5 Physical Examinations

A physical examination will be conducted at Screening. Physical examination findings will be listed.

4 DATA MONITORING COMMITTEE

An Independent Data Monitoring Committee (IDMC) has been assembled to review safety data on a regular basis (and ad-hoc in case of unexpected safety issues) throughout the study. The review of safety data will be performed according to the IDMC charter.

5 ANALYSIS TIMING

No interim analysis is planned.

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

If a PA is conducted, all the formal statistical tests for the efficacy endpoints as specified in Section 3.1.3 will be performed for the PA. Following the PA, a Final Analysis (FA) will be conducted at the very end of the study once most patients have completed the assessments for 3 qualified attacks or have been discontinued from the study. The FA will include all data accumulated from the beginning of the study through the end of the entire study. All statistical analyses at the FA will be regarded as descriptive in nature.

After the database is locked and exclusions from analysis sets have been finalized, the randomized treatment assignments will be unblinded to a specific biostatistics team and designated sponsor team, and the pre-final analysis will be generated and reviewed only by the unblinded personnel.

After all comments on the pre-final analysis have been resolved and the study database is declared final, the final analysis will be generated. Final TFLs will be provided after the study database is declared final. If there were no changes to the pre-final analysis or the study database, the pre-final TFLs may be considered final.

6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

No change is made from the protocol.

7 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. All available data will be presented in patient data listings which will be sorted by patient and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

APPENDIX A: REFERENCES

[1] Longhurst H, Moldovan D, Bygum A, Cicardi M, Huissoon A, Aygoren-Pursun E, et al. Oral Plasma Kallikrein Inhibitor BCX7353 is Safe and Effective as an On-Demand Treatment of Angioedema Attacks in Hereditary Angioedema (HAE) Patients: Results of the ZENITH-1 Trial. J Allergy Clin Immun. 2019;143(2):AB36.

[2] Lumry WR, Li HH, Levy RJ, Potter PC, Farkas H, Moldovan D, et al. Randomized placebo-controlled trial of the bradykinin B2 receptor antagonist icatibant for the treatment of acute attacks of hereditary angioedema: the FAST-3 trial. Ann Allergy Asthma Immunol. 2011;107(6):529-537.e2.

[3] Bretz F, Posch M, Glimm E, Klinglmueller F, Maurer W, Rohmeyer K. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. Biometrical J. 2011;53(6):894–913.

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[5] Jones B, Kenward MG. Design and analysis of cross-over trials. 3rd ed. Boca Raton: CRC Press, Taylor & Francis Group; 2014.

[6] Ratitch B, O'Kelly M. Implementation of pattern-mixture models using standard SAS/STAT procedures. Proceedings of PharmaSUG. 2011 May.

APPENDIX B: LABORATORY TESTS

Hematology:

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

Coagulation:

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

Urinalysis:

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

Blood chemistry:

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

Pregnancy test (for women of childbearing potential):

- Serum human chorionic gonadotropin (hCG)

Menopause test (for post-menopausal women) **:

- Serum follicle-stimulating hormone (FSH)

Viral testing **:

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

* Non-attack visit only

** At Screening only

APPENDIX C: CTCAE V5.0

Laboratory	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Blood chemistry	Hypoalbuminemia	Albumin <LLN - 3 g/dL; <LLN - 30 g/L	Albumin <3 - 2 g/dL; <30 - 20 g/L	Albumin <2 g/dL; <20 g/L	-
	Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
	Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
	Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
	Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences
	Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences
	Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
	Hypoglycemia	Glucose <LLN - 55 mg/dL; <LLN - 3.0 mmol/L	Glucose <55 - 40 mg/dL; <3.0 - 2.2 mmol/L	Glucose <40 - 30 mg/dL; <2.2 - 1.7 mmol/L	Glucose <30 mg/dL; <1.7 mmol/L;
	Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences
	Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences
	Hyperkalemia	Potassium >ULN - 5.5 mmol/L	Potassium >5.5 - 6.0 mmol/L	Potassium >6.0 - 7.0 mmol/L	Potassium >7.0 mmol/L

Laboratory	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences
	Blood bilirubin increased	Total Bilirubin >ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	Total Bilirubin >1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	Total Bilirubin >3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	Total Bilirubin >10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Hema-tology	Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hemoglobin (Hgb) <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 – 80 g/L	Hemoglobin (Hgb) <8.0 g/dL; <4.9 mmol/L; <80 g/L	-
	Hemoglobin increased	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL	Increase in >4 g/dL	-
	Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L
	White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L
	Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L
	Lymphocyte count decreased	<LLN - 800/mm3; <LLN – 0.8 x 10e9/L	<800 - 500/mm3; <0.8 – 0.5 x 10e9/L	<500 200/mm3; <0.5 – 0.2 x 10e9/L	<200/mm3; <0.2 x 10e9/L
	Lymphocyte count increased	-	<4000 - 20000/mm3	>20000/mm3	-
Coagula-tion	INR increased	>1.2 - 1.5; >1 - 1.5 x baseline if on anticoagulation	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation	>2.5; >2.5 x baseline if on anticoagulation	-

This is for the derived CTCAE from the laboratory data without considering the medical input.

APPENDIX D: LIST OF PCSA CRITERIA

PCSA for Vital Signs parameters:

Parameter	PCSA
BMI (kg/m^2)	<18 or >30
Heart rate (bpm)	<50 or >100
Systolic blood pressure (mmHg)	< 100 or > 150
Diastolic blood pressure (mmHg)	< 50 or > 90
Temperature (C)	< 36 or > 37.5
Respiratory rate (breaths/min)	<12 or > 20

PCSA for ECG parameters:

Parameter	PCSA
Heart rate (bpm)	<50 or >100
PR (msec)	<120 or > 200
QRS (msec)	<80 or > 120;
QT (msec)	> 500
QTcF (msec)	> 450 for men and > 470 for women
RR (msec)	<0.6 or > 1.2

APPENDIX E: ANALYSIS TIMEPOINT WINDOWING PER TREATED ATTACK

For VAS-3, MSCS and TOS, the entry timing will be calculated as

"entry time" – "corresponding treatment time".

According to the calculated entry timing, the entries will be assigned to the following timepoints based on the timing window. Entries labeled as prior to the corresponding treatment in the data will not be used for post-treatment timepoint. Entries labeled as after the corresponding treatment will not be used for pre-treatment timepoint. If multiple entries fall into the same timing window, the one that is the closest to the target hour will be used for analysis. The later one will be used if two records are the closest to the target hour.

All VAS-3, MSCS and TOS data will be listed.

VAS-3 Timepoint	Target hour	Timing Window
Pre-treatment	0	[-30, 5] min
0.5	0.5	0.5 h ± 10 min
1	1	1 h ± 10 min
1.5	1.5	1.5 h ± 10 min
2	2	2 h ± 10 min
2.5	2.5	2.5 h ± 10 min
3	3	3 h ± 10 min
3.5	3.5	3.5 h ± 10 min
4	4	4 h ± 10 min
5	5	5 ± 0.5 h (excluding 5.5 h)
6	6	6 ± 0.5 h (including 5.5 h)
8	8	8 ± 1 h
24	24	24 ± 4 h
48	48	48 ± 6 h
MSCS/TOS Timepoint		
Pre-treatment	0	[-30, 10] min
1	1	1 ± 0.25 h
2	2	2 ± 0.25 h
4	4	4 ± 0.25 h
6	6	6 ± 1 h (excluding 7 h)
8	8	8 ± 1 h (including 7 h)
24	24	24 ± 4 h
48	48	48 ± 6 h

APPENDIX F. DISCREPANCY BETWEEN VAS AND MSCS/TOS AT THE SAME TIMEPOINT

- VAS skin pain > 0, but none of the following in MSCS/TOS: External Head/Neck, Cutaneous, Stomach/GI, or Genital/Buttocks is "Yes".
- VAS skin swelling > 0, but none of the following in MSCS/TOS: External Head/Neck, Cutaneous, Stomach/GI, or Genital/Buttocks in MSCS/TOS is "Yes".
- VAS abdominal pain > 0, but Stomach/GI in MSCS/TOS is "No".
- External Head/Neck= "Yes" in MSCS/TOS with severity Moderate or Severe but VAS skin pain = 0 and skin swelling = 0.
- Genital/Buttocks = "Yes" in MSCS/TOS with severity Moderate or Severe but VAS skin pain = 0 and skin swelling = 0.
- Stomach/GI = "Yes" in MSCS/TOS with severity Moderate or Severe but VAS Abdominal pain = 0.
- Cutaneous = "Yes" in MSCS/TOS with severity Moderate or Severe but VAS skin pain = 0 and skin swelling = 0.

APPENDIX G: SAS CODE

D1. Example SAS Code for MMRM

```
/*************************************************************************/
/* CHG: change from baseline                                             */
/* AVALB: baseline value                                                 */
/* trtpn: treatment assignment                                           */
/* ATPTN: timepoint                                                      */
/* APERIOD: treated attack number (1st, 2nd, 3rd)                        */
/*************************************************************************/
proc mixed DATA=MMRM;
      class USUBJID trtpn(ref="0") ATPTN APERIOD;
      model CHG = trtpn ATPTN trtpn*ATPTN APERIOD AVALB / solution residual
cl ddfm=kr outp = res;
      repeated ATPTN / sub=USUBJID*APERIOD  type=TOEPH;
      lsmeans trtpn*ATPTN / pdiff cl /*e*/;
      ods output lsmeans=lsmeans
                 diffs=diffs(where = ( ATPTN =_ATPTN & _TRTPN = 0));

run;
```

D2. Example SAS Code for CPHM

```
/*************************************************************************/
/* prevas: pre-treatment VAS-3 score                                     */
/* AVAL: time to event/censored                                          */
/* trtpn: treatment assignment                                           */
/* ATPTN: timepoint                                                      */
/* APERIOD: treated attack number (1st, 2nd, 3rd)                        */
/*************************************************************************/
proc phreg data=adtte(where=(prevas^=.)) covs(aggregate);
      class subjid trtpn(ref=first) aperiod;
      model aval*cnsr(1)=trtpn aperiod prevas / risklimits;
      id subjid;
      hazardratio "Treatment (Trt vs. Control)" trtpn/ diff=ref ;
      ods output ParameterEstimates=pe95 ;

run;
```

D3. Example SAS Code for GEE

```
proc genmod data=gee descending;
      class SUBJID trtpn(ref="0") APERIOD;
      model AVAL = trtpn APERIOD prevas/dist=bin link=logit;
      repeated subject=SUBJID/ type=ind ECOVB MCOVB CORRW;
      lsmeans trtpn /diff exp ilink cl;
      ods output  lsmeans=lsmeans
                        ConvergenceStatus = ConvergenceStatus
                        diffs=diffs(where = (  _TRTPN = 0));

run;
```

MEDPACE

STATISTICAL ANALYSIS PLAN

Protocol Title:	A Phase II, double-blind, placebo-controlled, **R**andomized, cross-over, dose-ranging study of oral PHA-022121 for **A**cute treatment of angioedema attacks in **P**atients with hereditary angioedema due to C1-**I**nhibitor **D**eficiency type I and II
Protocol Number:	PHA022121-C201
Protocol Version/Date:	Version 3.0 / 25 April 2022
Investigational Product:	PHVS416 (PHA-022121 soft capsules)
Sponsor:	Pharvaris Netherlands BV
SAP Version/Date:	Version 2.0 / 19 October 2022

SIGNATURE PAGE

Protocol Title:	A Phase II, double-blind, placebo-controlled, Randomized, cross-over, dose-ranging study of oral PHA-022121 for Acute treatment of angioedema attacks in Patients with hereditary angioedema due to C1-Inhibitor Deficiency type I and II
Protocol Number:	PHA022121-C201
SAP Version/Date:	Version 2.0 / 19 October 2022

We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature	Date
[redacted]	19-Oct-2022
Project Statistician ***Medpace, Inc.***	
[redacted]	20-Oct-2022
Medical Director ***Medpace, Inc.***	
[redacted]	19-Oct-2022
Director of Biostatistics ***Pharvaris Netherlands BV***	
[redacted]	19-Oct-2022
Head of Biometrics & Data Science ***Pharvaris Netherlands BV***	
[redacted]	20-Oct-2022
Executive Director, Clinical Development ***Pharvaris Netherlands BV***	

VERSION HISTORY

Version	Version Date	Description
1.0	13 May 2022	Original signed version
2.0	19 October 2022	The SAP aiming to guide the study Primary Analysis

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ATC	Anatomical therapeutic chemical
AUC	Area under plasma concentration-time curve
$AUC_{0\text{-}12h}$	AUC from time 0 to 12 h post dosing (non-BQL) concentration, calculated by the linear-linear trapezoidal summation
$AUC_{0\text{-}24h}$	AUC from time 0 to 24 h post dosing (non-BQL) concentration, calculated by the linear-linear trapezoidal summation
AUC_{inf}	AUC from time 0 to infinity of the last measurable (non-BQL) concentration, calculated by the linear-linear trapezoidal summation
AUC_{last}	AUC from time 0 to the time of the last measurable (non-BQL) concentration, calculated by the linear-linear trapezoidal summation
CI	Confidence interval
CL/F	total apparent systemic clearance of drug after extravascular administration, calculated as Dose/ AUC_{inf}
C_{max}	maximum observed analyte concentration
COVID-19	Coronavirus disease 2019
CRF	Case report form
CSR	Clinical Study Report
CTCAE	Common terminology criteria for adverse events
ECG	Electrocardiogram
HAE	Hereditary Angioedema
ICE	Intercurrent event
IDMC	Independent data monitoring committee
IMP	Investigational medicinal product
IRT	Interactive response technology
KM	Kaplan-Meier
KSE	Key secondary endpoints
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MSCS	Mean symptom complex severity
NCI	National Cancer Institute
PA	Primary analysis
PCSA	Potentially Clinically Significant Abnormality
PK	Pharmacokinetics
PP	Per-Protocol
PRO	Patient reported outcome
SAE	Serious adverse event
SAP	Statistical Analysis Plan
$t_{1/2}$	apparent terminal elimination half-life, calculated as 0.693/λz
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
t_{max}	actual sampling time to reach the maximum observed analyte concentration

Abbreviation	Definition
TOS	Treatment outcome score
TSQM	Treatment satisfaction questionnaire for medication
VAS	Visual analogue scale
VAS-3	3-symptom composite visual analogue scale
V_z/F	apparent volume of distribution, based on terminal phase after a single dose
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from Pharvaris Netherlands BV, protocol number PHA022121-C201. The study Primary Analysis (PA) will be carried out according to this version of the SAP. This SAP will be finalized prior to the PA unblinding database lock. Any deviations in the PA from this SAP after the PA database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

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

2.1.2 Secondary Objectives

The key secondary objectives of the study are:

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

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

Other secondary objectives of the study are:

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

- To evaluate the pharmacokinetics (PK), dose-effect relationship, and concentration-effect relationship of PHA-022121
- To evaluate the treatment satisfaction questionnaire for medication (TSQM) scores at 48 h post-treatment

2.2 Study Design

2.2.1 Overview

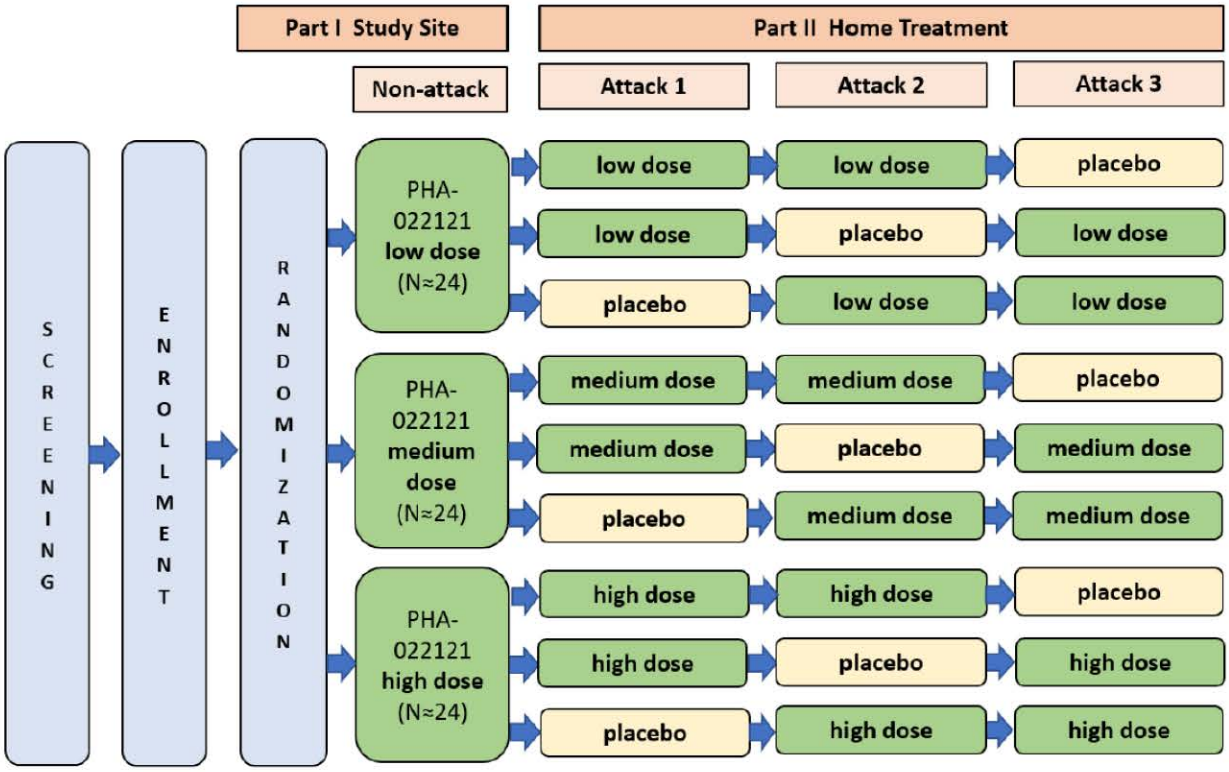
- After signing informed consent, patients will be screened for eligibility. Eligible patients will be enrolled in the study.
- Enrolled patients will be randomized to one of the three dose levels (low, medium, high) first, then based on the assigned cohort randomized to one of nine treatment sequences comparing three single doses of PHA-022121 (low, medium, high) with placebo treatment. During Part I (at the study site), patients in quiescent state will receive the assigned active single dose of PHA-022121 (dose is blinded) to assess PK and safety.
- In Part II of the study, patients will self-administer blinded investigational medicinal product (IMP) in the assigned treatment sequence at home to treat three qualifying HAE attacks, which should be consulted and confirmed by the investigator or designee via remote contact. The IMP should be taken when at least one attack symptom (skin pain, skin swelling, or abdominal pain) becomes of moderate intensity (VAS score ≥ 30). When the attack reaches this VAS intensity threshold, IMP should preferably be taken during the remote contact with the investigator or designee. If the patient cannot take the IMP within 3 h after reaching the VAS intensity threshold, the attack does not qualify for IMP treatment and should be treated with the patient's standard HAE medication. In addition, treatment of the attack should happen within 6 h after onset of symptoms at any location. If the IMP cannot be administered within 6 h after onset of symptoms, the attack does not qualify for IMP treatment and should be treated with the patient's standard HAE medication. Any symptoms involving the internal head and neck, regardless of intensity, also render an attack non-qualifying for treatment with IMP and should be treated with the patient's standard HAE medication.

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

  Patient-reported outcomes (PROs) are collected from IMP intake (including pre-treatment) until 48 h post-treatment. After each attack treated with IMP, a safety follow-up visit will take place within 5 days post-treatment. Meanwhile, pharmacokinetic plasma samples are planned to be collected within 24 h post-treatment (preferably within 12 h) from a subset of patients for at least 50 attacks treated with PHA-022121 or placebo.

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

Figure 1. Flowchart of Study Design



2.2.2 *Randomization and Blinding*

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

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

Blinding is achieved because PHA-022121 capsules and placebo capsules have an identical appearance, and each treatment consists of a combination of three capsules of 10 mg PHA-022121 and/or placebo.

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

Access to IMP assignment will be available if the Investigator deems it necessary to break the study blind in the interest of a patient's medical safety, in case of a medical emergency, to meet regulatory reporting obligations, or if warranted during scheduled safety reviews. Where medically appropriate, the Investigator will contact the Medical Monitor to discuss the situation

which has arisen and resulted in the need for unblinding of the patient. The Medical Monitor will not be involved in the decision to unblind.

2.2.3 Investigational Medicinal Product (IMP)

The IMP, also referred as study drug or blinded IMP, is PHA-022121 or placebo administered in a double-blind fashion as soft capsules for oral use. The IMP consists of 10 mg PHA-022121 soft capsules and matching placebo soft capsules for oral use:

- Low dose (10 mg): one capsule of 10 mg PHA-022121 and two placebo capsules
- Medium dose (20 mg): two capsules of 10 mg PHA-022121 and one placebo capsule
- High dose (30 mg): three capsules of 10 mg PHA-022121
- Placebo: three placebo capsules

In Part I of the study, each patient receives a single dose of PHA-022121 (10, 20, or 30 mg) in quiescent state. In Part II, patients will be treated with IMP for 3 qualifying attacks, including 2 attacks treated with a single dose of PHA-022121 (10, 20, or 30 mg) and 1 attack treated with placebo according to the randomized sequence.

According to Figure 1 (protocol Figure 2), the study has 3 cohorts and 9 treatment sequences. From top to bottom in Figure 1, the 3 Cohorts consisting of 9 treatment sequences based on the ordered treatment per randomization assignment are summarized in Table 1, with "L", "M", "H", and "P" denote low dose (10 mg), medium dose (20 mg), high dose (30 mg), and placebo, respectively.

Table 1. Summary of Treatment Cohorts and Treatment Sequences

Cohort by dose level	Sequence by assigned treatment to: Non-Attack → Attack 1 → Attack 2 → Attack 3
Cohort 1 (Low Dose Cohort)	Sequence 1: L → L → L → P Sequence 2: L → L → P → L Sequence 3: L → P → L → L
Cohort 2 (Medium Dose Cohort)	Sequence 4: M → M → M → P Sequence 5: M → M → P → M Sequence 6: M → P → M → M
Cohort 3 (High Dose Cohort)	Sequence 7: H → H → H → P Sequence 8: H → H → P → H Sequence 9: H → P → H → H

2.2.4 Sample Size Determination

The study is powered for the expected treatment effect on the VAS-3 score at 4 h post-treatment, assuming a treatment difference between PHA-022121 and placebo of 10 in VAS-3 score change from pre-treatment to 4 h post-treatment with a standard deviation of 11, based on the previous HAE studies with oral on-demand (Longhurst et al. 2019) and with icatibant treatment (Lumry et al. 2011). With the cross-over design, there are nine different treatment sequences twice comparing the same active and placebo treatment within the same patient. Assuming a very low correlation of 0.2 between the within-patient measurements on the different attacks, a total of 72 randomized patients, i.e. 8 patients per sequence randomized to the nine sequences, will provide approximately 90% power to detect a difference of 10 in VAS-3 score change from pre-treatment to 4 h post-treatment between a PHA-022121 treatment group

(medium dose or high dose) and the placebo group at a conservative significance level of 2.5% for a 2-sided test, and the power will reach 94% for a significance level of 5% for a 2-sided test. This sample size is adjusted to take into account a 20% attrition rate for evaluable attacks and 5% of attacks that will be treated with rescue medication within 4 h post-treatment.

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

2.3 Study Endpoints

2.3.1 Primary and Key Secondary Efficacy Endpoints

The primary efficacy endpoint of the study is:

- The change of the VAS-3 score from pre-treatment to 4 h post-treatment.

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

- Time to onset of symptom relief by a ≥30% reduction in VAS-3 score from the pre-treatment score
- Time to almost complete or complete symptom relief by VAS
- Time to a ≥50% reduction in VAS-3 score from the pre-treatment score
- Change in MSCS score from pre-treatment to 4 h post-treatment
- TOS at 4 h post-treatment

The detailed definitions are included in Section 3.1.1.6, and the estimand framework of the primary and key secondary endpoints are included in Section 3.4.

2.3.2 Other secondary efficacy endpoints

- Time to onset of primary symptom relief assessed by a 30% reduction in the VAS for the primary symptom, and time to 50% reduction in the VAS for the primary symptom
- Proportion of IMP-treated attacks requiring HAE rescue medication within 12 h, within 24 h, and within 48 h post-treatment
- Time to first HAE rescue medication use for IMP-treated attacks, if applicable.

  An IMP-treated attack refers to an attack treated with blinded IMP (study drug).
- Change in the VAS score for individual symptoms (skin pain, skin swelling, abdominal pain) from pre-treatment to 4 h post-treatment
- Change in MSCS score from pre-treatment to 24 h post-treatment
- TOS at 24 h post-treatment
- TSQM scores at 48 h post-treatment

2.3.3 Safety Endpoints

The safety endpoints of the study are:

- Treatment-emergent adverse events (TEAEs), treatment-related TEAEs, and treatment-emergent serious adverse events (TESAEs), and treatment-related TESAEs

- Clinical laboratory tests
- Vital signs
- Electrocardiogram (ECG)

2.3.4 Pharmacokinetic Endpoints

The PK endpoints of the study are:

- PK parameters based on plasma profiles of PHA-022121 and metabolite M2-D: C_{max}, t_{max}, area under plasma concentration-time curve $(AUC)_{0\text{-}12h}$, $AUC_{0\text{-}24h}$, AUC_{last}, AUC_{inf}, $t_{1/2}$, V_z/F (PHA-022121 only) and CL/F (PHA-022121 only).

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Study Specific Definitions

3.1.1.1 Analysis Day

Analysis day will be calculated from the date of the first dose of IMP. The day of the first dose of IMP will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.1.2 Analysis Visits and Analysis Timepoint

Scheduled visits will be assigned to analysis visits as recorded on the case report form (CRF). The expected schedule of events is as follows:

- Screening Visit
- Part I Non-Attack Visit
- Part II Post-Attack 1 On-site Visit
- Part II Post-Attack 2 On-site Visit
- Part II Post-Attack 3 On-site Visit

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

The followings will be conducted remotely:

- Part II Home Treatment Attack 1
- Part II Home Treatment Attack 2
- Part II Home Treatment Attack 3
- End of study

The details of each visit are described in the protocol Section 7.

The analysis timepoint is defined in Appendix E.

3.1.1.3 Definition of 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 I in which patients are in quiescent state and receive the assigned active single blinded dose of PHA-022121 to assess PK and safety. 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 intake, the last average ECG value before the first IMP administration will be considered as baseline.

3.1.1.4 Qualifying HAE Attacks

According to the protocol, in Part II of the study, qualifying HAE attacks are to be consulted and confirmed by the investigator or designee via remote contact. Attacks qualify for administration of the IMP if all four following criteria are met:

- At least one attack symptom (skin pain, skin swelling, or abdominal pain) has become of moderate intensity (VAS score ≥ 30)
- No symptoms involving the internal head and neck are present
- Treatment with IMP is administered within 6 hours after onset of symptoms and within 3 hours of the VAS score reaching the threshold of 30
- If treatment was administered at the non-attack visit or for a previous attack (either IMP or the patients standard HAE medication), the date of treatment occurred more than 5 days earlier

3.1.1.5 Study Periods and Results by Points of Reference

Pre-Treatment and Post-Treatment Results

In Part II of the study, the patient self-administers IMP in the assigned treatment sequence at home to treat three qualifying HAE attacks, remotely guided by the investigator. For VAS, MSCS and TOS, the pre-treatment value is defined as follows.

Unless otherwise specified, in the analyses description, pre-treatment result refers to the latest assessment result prior to IMP administration in the non-attack phase or prior to each IMP administration to treat an attack in the attack phase.

- For VAS, among all assessments during the time period from 30 min before through 5 min after the time the IMP is taken, the one with the assessment time that is closest to the time the IMP is taken will be selected as the pre-treatment VAS.
- For MSCS/TOS, among all assessments during the time period from 30 min before through 10 min after the time the IMP is taken, the one with the assessment time that is closest to the time the IMP is taken will be selected as the pre-treatment MSCS/TOS.

A delay of up to 5 min (for VAS) and up to 10 min (for MSCS/TOS) between treatment-taken time and baseline-assessment time may be due to differences between the patient's clock and the ePRO device clock and is, therefore, only an apparent delay. The longer window for MSCS/TOS reflects the order in which the patients are instructed to complete the PRO (VAS completed 1st) and the longer time needed to complete MSCS/TOS.

Post-treatment result refers to the result for any assessment performed after the IMP administration in the non-attack phase or after each IMP administration to treat an attack in the attack phase.

For VAS, MSCS and TOS, the analysis timepoint is defined in Appendix E.

Attack Periods for Efficacy Analyses

In the descriptions of efficacy analyses and statistical models, each attack period refers to the time window enclosing all efficacy measures (VAS, MSCS, TOS, TSQM) for an attack that is treated with IMP. The time window covers the pre-treatment and all post-treatment efficacy assessments. These attack periods in efficacy analyses are labeled as Attack 1, Attack 2, and Attack 3. The term attack period is referred to as attack, or period, interchangeably, in model descriptions.

3.1.1.6 Endpoint Related Definitions

The 3-symptom composite visual analogue scale (VAS-3) score

The VAS-3 score is the mean of the patient-reported VAS scores of the three major HAE symptoms: skin swelling, skin pain, and abdominal pain. The VAS score of each of the three major HAE symptoms ranges between 0 and 100 (Lumry et al. 2011; Kusuma et al. 2012). According to the protocol, the VAS scores must be reported pre-treatment at the time the investigator is consulted to confirm eligibility of the attack for treatment with IMP. Thereafter, if the attack is confirmed as a qualifying attack, the VAS scores will be reported every 30±10 min from 0 to 4 h post-treatment, and at 5±0.5, 6±0.5, 8±1, 24±4 and 48±6 h post-treatment. If the 5 h and/or 6 h timepoints fall during the overnight/sleeping hours, these timepoints are optional to report. All other time points are required. Handling of missing VAS-3 results is detailed in Section 3.1.5. The statistical methods for analyzing VAS-3 with missing data are discussed in Section 3.4.

For VAS based time-to-event endpoints, the following general derivation rules will be used.

- Only non-missing VAS assessment prior to any rescue medication taken and other HAE on-demand treatments (within 5 days after IMP taken) will be included in the derivation.
- Sustained events are defined as events occurring on 2 or more consecutive post-treatment assessments.
- If the event occurs at the last scheduled time point (48 h) and no rescue medication is used within 12 h after the last time point, this is also considered as a sustained event.
- The time to event is the time from IMP administration to the first observation of sustained events.
- If rescue medication or other HAE on-demand is taken before an event (e.g., symptom relief) is achieved, the time-to-event will be censored at the time of the last post-treatment VAS assessment prior to rescue medication or other HAE on-demand taken.
- If a patient did not achieve an event (e.g., symptom relief) in an attack period and did not take any rescue medications or other HAE on-demand treatment, the time will be censored at the last post-treatment VAS assessment with non-missing result for that attack.

For the VAS based time-to-event endpoints including

- Time to onset of symptom relief assessed by a ≥ 30% reduction in VAS-3 score from the pre-treatment score,
- Time to a ≥ 50% reduction in VAS-3 score from the pre-treatment score,
- Time to almost complete or complete symptom relief by VAS,
- Time to complete symptom relief by VAS,
- Time to onset of primary symptom relief assessed by a ≥ 30% reduction in the VAS for the primary symptom,
- Time to a ≥ 50% reduction in the VAS for the primary symptom,
- Time to individual VAS symptom relief assessed by a ≥ 30% reduction from pre-treatment for an individual VAS symptom with score >10 at pre-treatment,
- Time to a ≥ 50% reduction from pre-treatment for an individual VAS symptom with score >10 at pre-treatment,
- Time to almost complete or complete symptom relief for an individual VAS symptom with score >10 at pre-treatment,
- Time to complete symptom relief for an individual VAS symptom with score >10 at pre-treatment.

The time-to and event/censoring status will be derived following the above general rules, with endpoint-specific definitions provided in Table 2 and detailed censoring rules outlined in Table 3.

Table 2. Events of Interest

Event	Definition
Symptom relief by VAS-3	≥ 30% reduction in VAS-3 score from pre-treatment
≥ 50% reduction in VAS-3 score	≥ 50% reduction in VAS-3 score from pre-treatment
Individual VAS symptom relief	Individual VAS score at pre-treatment is >10 and ≥ 30% reduction in an individual VAS score from pre-treatment
≥ 50% reduction in individual VAS score	Individual VAS score at pre-treatment is >10 and ≥ 50% reduction in an individual VAS score from pre-treatment
Almost complete or complete symptom relief by VAS	All 3 individual VAS scores (skin swelling, skin pain, and abdominal pain) having a value of 0-10
Complete symptom relief by VAS	All 3 individual VAS scores (skin swelling, skin pain, and abdominal pain) are 0
Almost complete symptom or complete relief for an individual VAS symptom	Individual VAS score at pre-treatment is >10 and individual VAS post-treatment score is 0-10
Complete symptom relief for an individual VAS symptom	Individual VAS score at pre-treatment is >10 and individual VAS post-treatment score is 0

Primary symptom relief by VAS	The symptom with the highest pre-treatment VAS score is considered as the primary symptom. If skin pain and abdominal pain tie at pre-treatment, abdominal pain is taken forward as primary symptom. If skin pain and skin swelling tie, then skin pain is taken forward as primary symptom. If all are tied, abdominal pain would be taken forward as primary symptom. ≥ 30% reduction in primary symptom VAS-3 score from pre-treatment
≥ 50% reduction in the VAS primary symptom	The primary symptom is defined the same as for primary symptom relief by VAS. ≥ 50% reduction in primary symptom VAS-3 score from pre-treatment

Table 3. Censoring rules

Case	Outcome	Date/time of Event/Censoring
Had sustained events (e.g., symptom relief)	Event	Date/time of the first observation of sustained events
Had no sustained events and received rescue medication or other HAE on-demand treatments (within 5 days after IMP taken)	Censored	Date/time of the last post-treatment non-missing assessment prior to rescue medication or other HAE on-demand treatments taken
Had no sustained events and didn't receive rescue medication or other HAE on-demand treatments (within 5 days after IMP taken)	Censored	Date/time of the last post-treatment non-missing assessment

Mean symptom complex severity (MSCS)

The MSCS score is made up of two components: (1) symptom complex identification; and (2) severity assessment of each symptom complex. Patients are asked to identify where on the body they are experiencing symptoms including pain, swelling, rash, etc. Patients do not identify specific symptoms (e.g., rash), but rather identify symptom complexes (body areas) where symptoms are occurring. There are 5 symptom complexes: internal head/neck, stomach/gastrointestinal, genital/buttocks, external head/neck, and cutaneous. After affected symptom complexes are identified at pre-treatment, the patient is asked to rate the severity of symptoms within each complex (called the severity assessment). Severity options at post-treatment include: normal = 0, mild = 1, moderate = 2, severe = 3.

The MSCS score is calculated by taking the arithmetic mean of the severity from the individual symptom complexes identified as affected at pre-treatment. Zeros are not included in the pre-treatment scoring but can be included in the post-treatment scoring if they refer to symptom complexes experienced at pre-treatment. For example, if a patient reports pre-treatment symptoms at stomach/gastrointestinal and genital/buttocks, and does not experience internal head/neck, cutaneous, or external head/neck symptoms at pre-treatment, the MSCS score will

be calculated as the mean of severity score from stomach/gastrointestinal and genital/buttocks at each timepoint.

Treatment outcome score (TOS)

The TOS score is made up of three components: (1) symptom complex identification pre-treatment; (2) severity assessment of each symptom complex pre-treatment; and (3) response assessment post-treatment. Pre-treatment, patients are asked to identify where on the body they are experience symptoms including pain, swelling, rash, etc. Patients do not identify specific symptoms (e.g., rash), but rather identify symptom complexes (body areas) where symptoms are occurring. There are 5 symptom complexes: internal head/neck, stomach/gastrointestinal, genital/buttocks, external head/neck, and cutaneous. After affected symptom complexes are identified at pre-treatment, the patient is asked to rate the severity of symptoms within each symptom complex. Severity options at post-treatment include: severe = 3, moderate = 2, mild = 1, normal = 0.

After treatment and at the specified time points, patients are asked to rate change in the affected symptom complexes they identified pre-treatment (called the response assessment). The response assessment options include: significant improvement = 100, improvement = 50, the same = 0, worsening = -50, or significant worsening = -100.

The pre-treatment TOS is calculated as the mean of the symptom severity from the individual symptom complexes identified as affected with non-zero pre-treatment severity.

The post-baseline TOS is calculated as the sum of individual symptom complex response assessments multiplied by the symptom complex severity assessment identified as affected at pre-treatment, divided by the sum of all individual symptom complex severity assessments identified as affected at pre-treatment. For example, if a patient reports stomach/gastrointestinal symptom with moderate severity, genital/buttocks symptom with mild severity and cutaneous symptom with severe severity at pre-treatment, and does not experience internal head/neck and external head/neck symptoms at pre-treatment, then at 1 h post-treatment the patient reports response assessment same at stomach/gastrointestinal, improvement at genital/buttocks, significant improvement at cutaneous, the post-treatment TOS at 1 h post-treatment will be then calculated as (0 * 2 + 50 * 1 + 100 * 3) / (2 + 1 + 3) = 58.33.

Treatment satisfaction questionnaire for medication (TSQM)

The TSQM is an 11-item treatment satisfaction questionnaire consisting of four scales: (1) effectiveness; (2) side effects; (3) convenience; and (4) overall satisfaction. The scores for each domain are computed by adding the items in each domain and then transforming the composite score into a value ranging from 0 to 100 using the following methods. Note, a score can be computed for a scale only if no more than one item is missing from that scale. The 11-item questionnaire is described in Appendix F.

- Effectiveness = ([(Item #1 + Item #2) – 2] / 12) * 100
  - If one item is missing use: ([(Completed item) – 1] / 6) * 100

- Side effects = ([(Item #4 + Item #5 + Item #6) – 3] / 12) * 100
  - If one item is missing use: ([(Sum of 2 Completed items) – 2] / 8) * 100
  - Note: all “NA” responses are coded as ‘5’ indicating “Not at all Dissatisfied”

- Convenience = ([(Item #7 + Item #8 + Item #9) – 3] / 18) * 100
    - If one item is missing use: ([(Sum of 2 Completed items) – 2] / 12) * 100

- Global Satisfaction = ([(Item #10 + Item #11) – 2] / 12) * 100
    - If one item is missing use: ([(Completed item) – 1] / 6) * 100

Use of rescue medication and time to first use of rescue medication for a treated attack

Only rescue medications confirmed by blinded clinical manual review are considered in the analysis. Use of rescue medication=Yes if for a confirmed rescue medication, the medication date/time is within 48 hours after the IMP administration and before the starting time of a new attack, if there is any. Otherwise, use of rescue medication=No. An attack is considered as "new" if it started at least 24 hours after the end time of the previous attack. Otherwise, it will be considered as the same attack as the previous one.

The time to first rescue medication use within 48 h post-treatment is

- Either the time from the IMP administration to the first time that a rescue medication is taken after a treated attack if use of rescue medication = Yes
- Or the time is censored at 48 h post-treatment or at the new attack start time (as defined above), whichever is earlier, if use of rescue medication = No.

The definitions of rescue medication use within 12 h and 24 h post-treatment are similar, but with different timing thresholds, 12 h and 24 h.

3.1.2 Summary Statistics

Categorical data will generally be summarized in frequencies and percentages of patients. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized using number of non-missing values (n), mean, standard deviation, median (25^{th}, 75^{th}), minimum, and maximum values.

3.1.3 Multiplicity

The study primary endpoint and key secondary endpoints (KSEs) are listed in the Table 4 along with the statistical hypotheses for testing PHA-022121 versus placebo with respect to the high, medium, and low dose of PHA-022121.

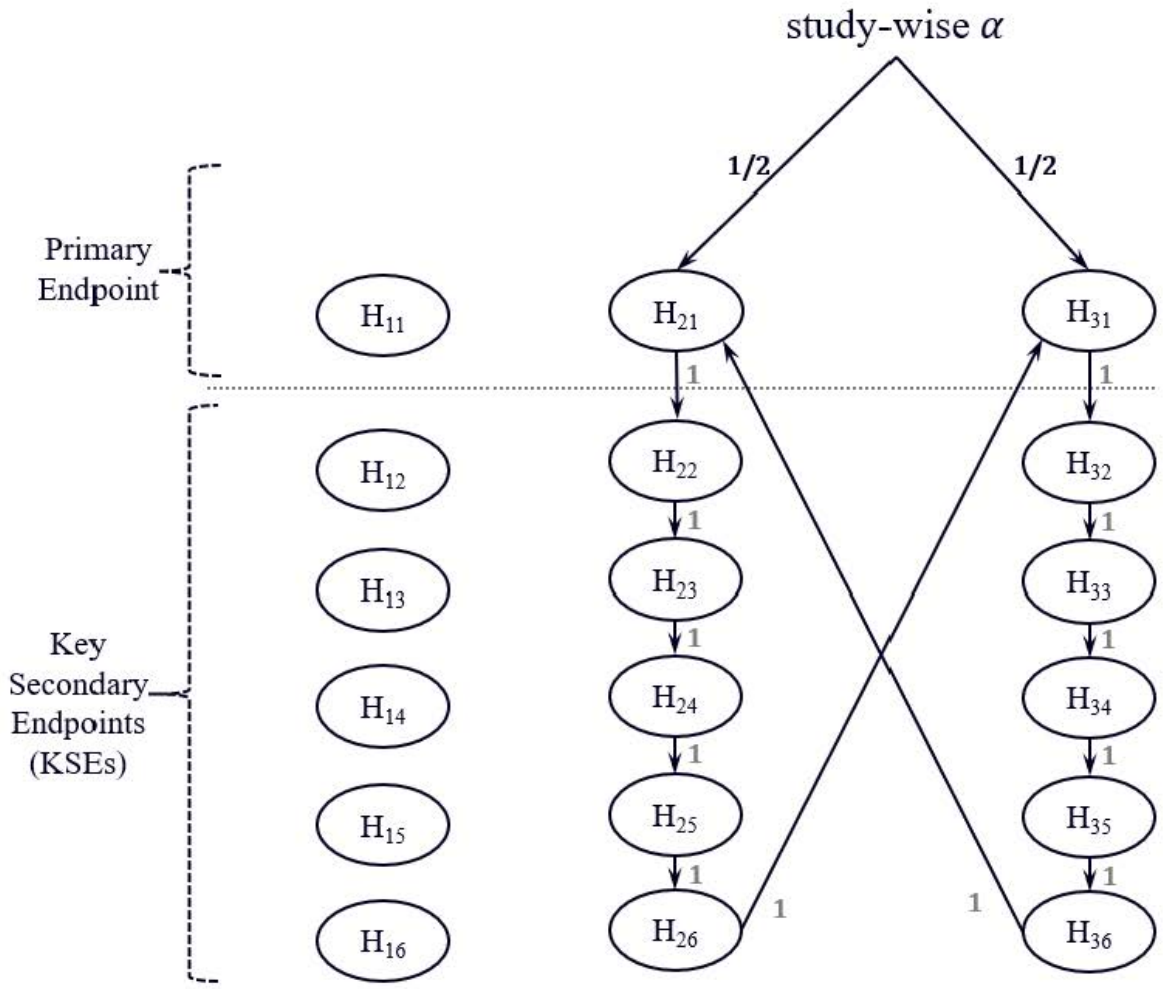
Table 4. Study Endpoints and Associated Statistical Hypotheses

Endpoint	Hypothesis ID for testing High, Medium, Low Dose
Primary Endpoint: Change of VAS-3 score from pre-treatment to 4 h post-treatment	H_{11}, H_{21}, H_{31}
KSE: Time to onset of symptom relief by a ≥30% reduction in VAS-3 score from the pre-treatment score	H_{12}, H_{22}, H_{32}
KSE: Time to almost complete or complete symptom relief by VAS-3 score	H_{13}, H_{23}, H_{33}
KSE: Time to a ≥50% reduction in VAS-3 score from the pre-treatment score	H_{14}, H_{24}, H_{34}
KSE: Change in MSCS at 4 h post-treatment	H_{15}, H_{25}, H_{35}
KSE: TOS at 4 h post-treatment	H_{16}, H_{26}, H_{36}

The study-wise type I error rate for statistical hypothesis testing of the primary and key secondary endpoints will be controlled at 5% significance level for 2-sided test. The testing strategy is described below and illustrated in Figure 2. The low dose will be included in the analysis for evaluating dose response but will not spend α in the multiplicity control procedure; the nominal p values for testing the 10-mg dose will be provided.

To control the overall type I error rate for hypotheses testing among the primary endpoint and KSEs and across the medium and high doses in this study, a graphical multiple testing procedure (Bretz et al 2011) will be applied. As shown in Figure 2, initially the full α will be equally split and allocated to 2 branches of hypotheses testing for the high and medium doses. Within each branch, the endpoints are ordered according to Table 4 and Figure 2, hypotheses can only be tested in sequential order as indicated by the arrows. In the graphical testing procedure, the nodes are individual hypotheses, the numbers labeled on the edges indicate the weights of α to be propagated to testing the next hypothesis pointed by the arrow if the preceding hypothesis testing is passed. If all the hypotheses are successfully passed within a branch (i.e., a dose level), the remaining α will be allocated to testing the hypotheses of the primary endpoint in the other dose level.

Figure 2. Multiple Testing Procedure Controlling for Study-wise Type I Error Rate



3.1.4 Evaluation of Site Effect

The average number of patients projected to be enrolled in each study site is too small to evaluate site effect. No additional analyses on site effect will be performed.

3.1.5 Handling of Missing Data

For primary and key secondary endpoints, the handling of missing data is detailed in section 3.4 with the details for each respective endpoint.

The electronic PRO device does not allow for individual items within VAS-3 to be skipped. Thus, the VAS-3 composite score will not have any imputed data since all items will be completed.

For concomitant medications/processes, if a medication has incomplete start or stop dates, dates will be imputed to determine whether a medication should be considered prior or concomitant. If a medication start date is incomplete, the first day of the month will be imputed for the missing day and January will be imputed for the missing month. If a medication stop date is incomplete, the last day of the month will be imputed for the missing day and December will be imputed for the missing month. In the listings, incomplete start and stop dates will be listed as collected without imputation.

For rescue medications with complete date but unknown time, if the medication is on the same day as the IMP administration, the rescue medication time will be imputed as the IMP administration time; if the medication is after the date of IMP administration, the rescue medication time will be imputed as the earliest possible time of the day.

When deciding if an adverse event (AE) is a treatment-emergent adverse event (TEAE), the incomplete start date/time will be imputed by the latest possible date/time. When deciding if the TEAE starts within 48 h / 5 days post-dose, for an adverse event with complete start date but unknown time, if the adverse event starts on the same day as the IMP administration, the adverse event start time will be imputed as the IMP administration time; otherwise the incomplete start date/time will be imputed by the earliest possible date/time. In the listings, incomplete start and stop dates will be listed as collected without imputation.

3.2 Analysis Sets

3.2.1 Full Analysis Set (FAS)

The FAS includes all patients enrolled and randomized in the study. In analyses performed on the FAS, patients will be analyzed, based on the intention-to-treat principle, according to their randomized treatment assignment regardless of actual treatment taken.

3.2.2 Modified Intent-to-Treat (mITT) Analysis Set

The mITT Analysis Set is a subset of FAS including all randomized patients who had at least one IMP-treated (blinded PHA-022121 or placebo) HAE attack and who had non-missing VAS results at both pre-treatment and at least 1 post-treatment time point of that attack. In analyses performed on the mITT Analysis Set, patients will be analyzed based on the intention-to-treat principle according to their randomized treatment assignment regardless of actual treatment taken. In analyses performed on the mITT Analysis Set, for each patient, only the attacks satisfying the mITT Analysis Set criteria, namely, only the attacks treated with IMP with non-missing VAS results at both pre-treatment and at least 1 post-treatment time point will be included.

3.2.3 Safety Analysis Set

The Safety Analysis Set is a subset of FAS including all randomized patients who received any dose of IMP. In analyses performed on the Safety Analysis Set, patients will be analyzed according to their actual treatment taken.

3.2.4 Per-Protocol (PP) Analysis Set

The PP Analysis Set is a subset of mITT Analysis Set including all patients who had at least one attack satisfying mITT Analysis Set criteria and also with no major protocol deviations or other non-compliance that may impact the key efficacy assessment. For patients in the PP Analysis set, only such attacks satisfying the above criteria will be included in the analyses performed on the PP Analysis Set. The PP Analysis Set will be a secondary analysis set for analysis of the primary and key secondary efficacy endpoints. Major protocol deviations or other non-compliance that may impact the key efficacy assessment include but are not limited to:

- Failed to meet critical eligibility criteria
- Treatment with IMP is not administered within 6 hours after onset of symptoms or is not administered within 3 hours of the VAS score reaching the threshold of 30

- More than half of VAS-3 scores are missing during the first 4 h
- Missed at least 1 out of 3 capsules of the IMP for the treated attack

A list of subjects with major protocol deviations or other non-compliance leading to exclusion from the PP Analysis Set will be finalized prior to unblinding the treatment information.

3.2.5 Pharmacokinetic (PK) Analysis Set

The PK Analysis Set is defined as all patients who receive at least 1 dose of IMP and have at least 1 measurable concentration of PHA-022121 at non-attack visit.

The PK Analysis Set with full PK profile is defined as subset of patients who had full PK profile during the non-attack visit.

3.3 Patient Data and Study Conduct

3.3.1 Patient Disposition

Patients who were screened (signed informed consent) and discontinued early during screening (screen failures) will be listed with the reason of screen failure and if it is due to coronavirus disease 2019 (COVID-19).

Frequencies and percentages of patients will be summarized by dose cohort and in total based on FAS in at least each of the following disposition categories:

- Patients who completed the non-attack visit
- Patients who completed post-attack 1 visit
- Patients who completed post-attack 2 visit
- Patients who completed post-attack 3 visit
- Patients who completed the study
- Patients with early discontinuation

Reasons for early discontinuation will also be summarized and listed.

All attacks recorded will be listed, with flag of whether they are qualifying attacks.

3.3.2 Protocol Deviations

Protocol deviations will be defined in the Protocol Deviation Plan. Frequencies and percentages of patients with CSR reportable protocol deviations by deviation category will be summarized by dose cohort and in total, grouped by eligibility violations and on-study protocol deviations, based on FAS.

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

3.3.3 Analysis Sets

Frequencies and percentages of patients in each analysis set will be summarized by dose cohort and in total based on FAS. Reasons for exclusions from the analysis sets will be listed.

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years) and age categories (<65 years, ≥65 years)
- Sex
- Childbearing potential
- Race
- Ethnicity
- Country
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2) and BMI categories (<30 kg/m^2, ≥30 kg/m^2)
- Time since HAE diagnosis (year)
    - Time since HAE diagnosis (years) is calculated as (date of informed consent – date of diagnosis + 1)/365.25 if the dates are full; Month difference of (date of informed consent and date of diagnosis)/12 if only day is missing; year difference of (date of informed consent and date of diagnosis) if both month and day are missing;
- HAE Type
- Number of HAE attacks in the last 2 months prior to screening
- Number of HAE attacks in the last 4 months prior to screening
- Number of HAE attacks in the last 1 year prior to screening
- Number of patients with prophylactic HAE treatment history

Demographic and baseline characteristics will be summarized with summary statistics as appropriate by dose cohort and in total for FAS, mITT, safety, PP and PK analysis sets. Demographic and baseline characteristics will be listed.

3.3.5 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 (or later version). Frequencies and percentages of patients with medical history by system organ class and preferred term will be summarized by dose cohort and in total based on Safety Analysis Set. Medical history will also be listed.

3.3.6 Concomitant Medications and Procedures

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and Drug Code of the Preferred Name using the WHO Drug B3 Global, March 2022 (or later version). For summary purposes, medications will be considered prior medications if they stopped prior to the first dose of IMP and concomitant medications if they were taken at any time after the first dose of IMP (i.e. started prior to the first dose of IMP and were ongoing or started after the first dose of IMP). Please refer to Section 3.1.5 about how to handle incomplete dates.

Frequencies and percentages of patients taking prior (HAE/non-HAE) medications by ATC class and preferred term will be summarized by actual dose cohort and in total based on the Safety

Analysis Set. The use of any prior or concomitant medication will be listed. The concomitant HAE/non-HAE medications, and rescue medications will be summarized separately similarly.

Prior or concomitant procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 (or later version) and will be listed.

The concomitant medications will be reviewed by the study team in a blinded fashion to adjudicate which of them are HAE medications and which are rescue medications. This will be recorded in an excel spreadsheet and serve as a source data in the end of study for identifying the HAE medications and rescue medications, which can overwrite the same information collected in the CRF.

3.3.7 IMP Exposure and Compliance

Days in the study will be calculated as date of early discontinuation/end of study/Primary Analysis data cutoff date (if applicable) - date of first dose of IMP + 1. Days in the study will be summarized by cohort based on the Safety Analysis Set with frequencies and percentages of patients with exposure in the following categories:

- Treated with IMP at Non-Attack Visit for Part I
- Treated 1 attack with IMP for Part II
- Treated 2 attacks with IMP for Part II
- Treated 3 attacks with IMP for Part II

Compliance with the IMP regimen will be summarized by treatment based on the Safety Analysis Set at each visit/attack with frequencies and percentages of compliance in the following categories:

- 1 Capsule
- 2 Capsules
- 3 Capsules

3.4 Efficacy Analysis

Efficacy data will be summarized by randomized treatment (for the attack) based on the mITT Analysis Set. Unless otherwise specified, all analyses for efficacy endpoints will be based on assessment results from HAE attacks that have been treated with IMP.

Descriptive summary statistics will be presented for all study endpoints. For continuous endpoints, descriptive summary statistics will generally include number of subjects with data, the mean, standard deviation, median, interquartile range (Q1, Q3) and range (minimum, maximum). For categorical endpoints, this will generally include number and the percent of subjects with data in each category.

All efficacy endpoints will be evaluated primarily on the mITT Analysis Set. All statistical tests are carried out 2-sided (with 5% significance level).

For continuous efficacy endpoints, the evaluation of treatment effect will be based on mixed models for repeated measures (MMRM) allowing modeling for within-patient and between-patient variabilities. Unless otherwise specified, the MMRM will include fixed effects of treatment, time, treatment-by-time interaction, attack, and attack specific pre-treatment covariates as appropriate. The time referred to here is the categorical variable for the protocol specified assessment

timepoints per treated attack. The attack refers to attack period, which is used to specify the data from the period of attack 1, 2, and 3, respectively. The same terms are also used in describing models for time-to-event and binary endpoints. A heterogeneous Toeplitz covariance structure will be assumed to model the within-attack variability. Additionally, subject-specific random effects will be used to account for the within-patient and between attack period correlation. Model convergence will be checked. If the MMRM with heterogeneous Toeplitz covariance fails to converge, the following tests will be used in sequence: heterogeneous autoregressive covariance structure, heterogeneous compound symmetry covariance structure, and compound symmetry covariance structure. Least-squares (LS) adjusted mean and its 95% confidence interval (CI) of each treatment group as well as treatment differences between PHA-022121 and placebo, for each dose of PHA-022121 respectively, will be provided with 95% CI and p-values. For the analysis of an efficacy endpoint using MMRM, the model will be based on the data up to the primary timepoint of interest. For example, for the endpoint of change of VAS-3 from pre-treatment to 4 h post-treatment, all VAS-3 results from assessment timepoints up to 4 h post-treatment will be used to fit the MMRM for the main analysis.

For time-to-event efficacy endpoints, the evaluation of treatment effect will be based on marginal Cox proportional hazards models (CPHM) with a robust variance-covariance estimator to account for the within-patient correlation. Unless otherwise specified, the model will include treatment, attack, and attack specific pre-treatment VAS-3 score as independent variables. Patients who have not had the event of interest at the time of the analysis will be censored, for example, a patient's time to symptom relief defined by VAS-3 will be censored at the last post-treatment assessment of VAS-3 if no symptom relief has occurred. The estimated hazard ratio between PHA-022121 and placebo, for each dose of PHA-022121 respectively, will be provided with 95% CI and p-value.

For the binary efficacy endpoint, i.e., the proportion of attacks requiring HAE rescue medication, the analysis will be based on the generalized estimating equation (GEE) with a logit link. Unless otherwise specified, the model will include treatment, attack, and attack specific pre-treatment VAS-3 score as independent variables, and an identity matrix as the working correlation matrix of the robust empirical estimates of error (Jones and Kenward 2014, Section 6.3). The estimated odds ratio of requiring HAE rescue medication between PHA-022121 and placebo, for each dose of PHA-022121 respectively, will be provided with 95% CI and p-value.

For analysis using MMRM, the timepoint defined in Appendix E will be used. For time-to-event endpoints, the actual time length is used for the analysis. The actual time period is also used for defining the binary endpoint.

Any changes and specific detail will be provided for each endpoint in the following subsections.

3.4.1 Primary Efficacy Endpoint

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

Based on this primary objective, the primary estimand is described as follows according to the framework provided in ICH E9(R1) (FDA 2021). The treatment condition of interest for this study is a single dose of PHA-022121 10 mg (low dose), 20 mg (medium dose), 30 mg (high dose) or placebo in oral capsules as acute treatment for HAE attacks. The primary efficacy estimand on the treatment effect of PHA-022121 considers the patient population as defined through the

study inclusion/exclusion criteria, with the primary efficacy endpoint being the change of VAS-3 score from pre-treatment to 4 h post-treatment. The population-level summary is the least squares means (LS-means) of the difference in VAS-3 score change from pre-treatment to 4 h post-treatment between PHA-022121 and placebo for each dose of PHA-022121, respectively, as estimated from the MMRM as described in Section 3.4.

The MMRM will include fixed effects of treatment, time (every 0.5 h from 0.5 to 4 h post-treatment), treatment-by-time interaction, attack, and attack specific pre-treatment VAS-3 value as covariate.

In addition, summary statistics of the changes from pre-treatment at the different post-treatment time points will be provided, for the different doses of PHA-022121. Frequencies and percentages of attacks in each location will be provided. The duration between treatment in days will be summarized by cohort and in total.

The intercurrent events (ICEs) by category and the corresponding strategies for addressing these ICEs are listed in Table 5.

If both Category 1 ICE and Category 2 ICE occur for the same patient, addressing Category 1 ICE takes precedence over Category 2 ICE. For example, if a patient took rescue medication at 2 h post-treatment, and subsequently dropped out at 3 h with no VAS-3 result after 3 h post-treatment, then VAS-3 results after initiation of rescue medication will all be set to missing with analysis following the specified approach for addressing Category 1 ICE. Note that unless otherwise specified, all HAE on-demand treatments (as confirmed via blinded clinical review) administered within 5 days after treatment of the attack will be used for exclusion of efficacy assessment after ICEs.

The following sensitivity and supplementary analyses will be provided.

- VAS-3 results after the initiation of Category 1 or Category 2 ICE will be set to missing and be multiply imputed using copy reference method which is a control-based multiple imputation (Ratitch and O'Kelly 2011).
- In addition to mITT analysis set, the primary efficacy endpoint analyses will be repeated on the PP analysis set.
- The primary efficacy endpoint analysis may be repeated using the actual treatment taken.

Table 5. ICEs by Category and Strategies for Addressing ICEs in the Primary Estimand

Category 1 ICE: Intake of allowed HAE rescue medication (protocol 5.6.1) or prohibited concomitant medications for treating the attack (protocol 5.6.2) within 4 h post-treatment timepoint	**Category 2 ICE:** Any event (e.g., ePRO device malfunction) causing subsequent VAS-3 results all missing through 4 h post-treatment timepoint
Hypothetical Strategy: VAS-3 results after the initiation of Category 1 ICE will firstly be set to missing, then the data will be analyzed using MMRM, which serves as the main analysis method assuming missing at random (MAR).	**Hypothetical Strategy:** All available VAS-3 results up to 4 h post-treatment timepoint will be analyzed using MMRM with missing results after Category 2 ICE assumed as MAR. Additionally, sensitivity analysis will be performed with missing not at random (MNAR)

Additionally, sensitivity analysis will be performed with missing not at random (MNAR) assumption. VAS-3 results after the initiation of Category 1 ICE will be set to missing and be multiply imputed using copy reference method which is a control-based multiple imputation (Ratitch and O'Kelly 2011). For every imputed data set an MMRM will be fitted. Overall inference will then be obtained by applying Rubin's rules (Rubin 1987) on the estimates obtained from every imputed data set.	assumption. VAS-3 results after the initiation of Category 2 ICE will be set to missing and be multiply imputed using copy reference method which is a control-based multiple imputation (Ratitch and O'Kelly 2011). For every imputed data set an MMRM will be fitted. Overall inference will then be obtained by applying Rubin's rules (Rubin 1987) on the estimates obtained from every imputed data set.

The following supportive analyses will be provided.

- The primary efficacy endpoint analysis will be conducted by excluding data with inconsistency in symptom reports between VAS and MSCS/TOS (defined in Appendix G). Note that if there is inconsistency in symptom reports between pre-treatment VAS and pre-treatment MSCS/TOS then all the post-treatment VAS-3 change scores will be excluded for that attack.
- The primary efficacy endpoint analysis will be repeated using only the data from the 1st treated HAE attack.

The example SAS code is provided in Appendix H.

3.4.2 Secondary Efficacy Endpoints

All secondary efficacy endpoints will be analyzed on the mITT Analysis Set. Analyses for the key secondary endpoints will also be conducted on the PP Analysis Set. For key secondary efficacy endpoints, a multiplicity control procedure will be applied as detailed in section 3.1.3. For other secondary efficacy endpoints, analyses are descriptive in nature and nominal p-values will be provided as applicable.

For KSEs, the estimands' attributes concerning treatment and population are the same as the ones described in Section 3.4.1. The KSEs are listed in Table 6, along with the descriptions in the estimand framework.

The example SAS code is provided in Appendix H.

Time-to-event outcomes

The time-to-event endpoints will be modeled using a marginal Cox proportional hazards model (CPHM) as described in Section 3.4. Patients who have not had the event of interest at the time of the analysis (i.e. 48 h ± 6h time period) will be censored at the last assessment time. Patients will also be censored at the time of the last post-treatment VAS assessment prior to intake of rescue medication (except for the endpoint Time to first HAE rescue medication). Estimated hazard ratio of each PHA-022121 dose versus placebo with 95% CI and p-value will be provided from the CPHM.

Additionally, Kaplan-Meier (KM) analyses will be provided with data from the 3 attack periods pooled together by assigned treatment. For example, the time-to-event data from Sequence 1 in Attack 1 and Attack 2, from Sequence 2 in Attack 1 and Attack 3, and from Sequence 3 in Attack 2 and Attack 3 will be pooled as the data for Low Dose group; the time-to-event data from Sequences 1, 4, 7 in Attack 3, from Sequences 2, 5, 8 in Attack 2, and from Sequences 3,

6, 9 in Attack 1 will be pooled as the data for placebo; and thus the standard KM analyses will be applied to compare the Low Dose group with placebo.

In addition, a supportive analysis only based on data from Attack 1 may be provided. For example, KM analyses will be applied to compare Low Dose with placebo by pooling the time-to-event data from Sequence 1 and 2 in Attack 1 as the data for Low Dose group, and pooling the data from Sequence 3, 6, and 9 in Attack 1 as the data for placebo group.

KM estimates of the survival function for time to symptom relief by VAS and time to complete or almost complete symptom relief by VAS may be graphically displayed for each treatment group. KM estimates of quartiles (median, 25th and 75th percentiles) with 95% CI will be calculated if applicable.

Time-to-event analyses will only be performed if at least one treatment group has a large enough number of events. Treatment groups that have a small number of events will be summarized.

Table 6. Key Secondary Endpoints and Corresponding Estimands

Endpoint	Population-Level Summary	Strategy of Addressing Category 1 ICE - Intake of rescue medication during assessment window	Strategy of Addressing Category 2 ICE - Any event causing subsequent missing result of the variable of interest
Time to onset of symptom relief by VAS-3 [a reduction of ≥30% from pre-treatment for VAS-3, which is the mean of the 3 VAS scores for skin swelling, skin pain, and abdominal pain]. Assessment window for this endpoint is from IMP dose to 48 h post-dose timepoint for each treated attack.	Hazard ratio between PHA-022121 and placebo in time to onset of symptom relief by VAS-3 using marginal CPHM.	**Hypothetical Strategy** – censor the time at the last VAS assessment prior to occurrence of Category 1 ICE; treatment effect of interest concerning the outcomes if rescue medication was not available.	**Hypothetical Strategy** – censor the time at the last VAS assessment prior to occurrence of Category 2 ICE. As results after Category 2 ICE are all missing, this is the standard approach to time-to-event analysis when event status is missing.
Time to complete or almost complete symptom relief by VAS (as defined in Section 3.1.1.6). Assessment window for this endpoint is from IMP dose to 48 h post-dose timepoint for each treated attack.	Hazard ratio between PHA-022121 and placebo in time to onset of almost complete or complete symptom relief by VAS score using marginal CPHM.	**Hypothetical Strategy** – similar to above	**Hypothetical Strategy** – similar to above
Time to a ≥50% reduction in VAS-3 score from pre-treatment Assessment window for this endpoint is from IMP dose to 48 h post-dose timepoint for each treated attack.	Hazard ratio between PHA-022121 and placebo in time to ≥50% reduction in VAS-3 using marginal CPHM.	**Hypothetical Strategy** – similar to above	**Hypothetical Strategy** – similar to above
Change of MSCS at 4 h post-treatment. Assessment window for this endpoint is from IMP dose to 4 h post-dose timepoint for each treated attack.	LS-means of the difference in MSCS change from pre-treatment to 4 h post-treatment between PHA-022121 and placebo estimated from the MMRM.	**Hypothetical Strategy**: MSCS results after the initiation of Category 1 ICE will firstly be set to missing, then the data will be analyzed using MMRM assuming missing MAR.	**Hypothetical Strategy**: All available MSCS results up to 4 h post-treatment timepoint will be analyzed using MMRM with missing results after Category 2 ICE assumed as MAR.
TOS at 4 h post-treatment. Assessment window for this endpoint is from IMP dose to 4 h post-dose timepoint for each treated attack.	LS-means of the difference in TOS at 4 h post-treatment between PHA-022121 and placebo estimated from the MMRM.	**Hypothetical Strategy** – similar to above	**Hypothetical Strategy** – similar to above

Time to onset of symptom relief by VAS-3 score (a reduction of ≥30% from pre-treatment)

The analysis of this endpoint is described above and in Table 6.

Similar analysis for the individual VAS symptom relief may be conducted if applicable. The individual VAS pre-treatment value will be adjusted in the marginal CPHM.

Supportive analysis:

The time to onset of symptom relief by VAS-3 score will be rederived by excluding data on or after the first timepoint with inconsistency in symptom reports between VAS and MSCS/TOS (defined in Appendix G). The KM analysis and marginal CPHM analysis may be conducted.

Time to almost complete or complete symptom relief by VAS

The analysis of this endpoint is described above and in Table 6.

Similar analysis for almost complete or complete relief in individual VAS symptom may be conducted if applicable. The individual VAS pre-treatment value will be adjusted in the marginal CPHM.

Supportive analysis:

The time to almost complete or complete symptom relief by VAS will be rederived by excluding data on or after the first timepoint with inconsistency in symptom reports between VAS and MSCS/TOS (defined in Appendix G). The KM analysis and marginal CPHM analysis may be conducted.

Time to a ≥50% reduction in VAS-3 score from pre-treatment

The analysis of this endpoint is described above and in Table 6.

Similar analysis for ≥50% reduction in individual VAS symptom may be conducted if applicable. The individual VAS pre-treatment value will be adjusted in the marginal CPHM.

Supportive analysis:

The time to ≥50% reduction in VAS-3 score from pre-treatment will be rederived by excluding data on or after the first timepoint with inconsistency in symptom reports between VAS and MSCS/TOS (defined in Appendix G). The KM analysis and marginal CPHM analysis may be conducted.

Time to first HAE rescue medication (if applicable)

The Time to first HAE rescue medication analysis will be performed if we observe enough IMP treated attacks with HAE rescue medication taken. Only the treatment arms with enough events will be included in the analysis.

The analysis is described above. Assessment window for this endpoint is from time of IMP dose to 48 h post-treatment for each treated attack.

Time to onset of primary symptom relief by VAS

The analysis is described above. The primary VAS symptom pre-treatment value will be adjusted in the marginal CPHM. Assessment window for this endpoint is from time of IMP dose to 48 h post-treatment timepoint for each treated attack.

If rescue medication is taken during assessment window, time will be censored at the last corresponding VAS assessment prior to occurrence of the ICE.

If any event causing subsequent missing result of the variable of interest, time will be censored at the last corresponding VAS assessment prior to occurrence of the ICE.

Continuous secondary endpoints

Change of the individual VAS scores and MSCS, actual TOS and TSQM score, may be summarized using descriptive statistics by treatment arm at the specified time points. Analyses based on MMRM will be carried out similarly to the analysis for the primary endpoint if applicable. Note that for the individual VAS scores analysis, only symptom scores with a non-zero pre-treatment value will be considered and the individual VAS pre-treatment value will be adjusted in the MMRM.

Mean symptom complex severity (MSCS)

Scores and change from pre-treatment will be summarized using descriptive statistics by treatment arm at each scheduled time point. An analysis based on MMRM (in Section 3.4) will be carried out similarly to the analysis for the primary efficacy endpoint for change from pre-treatment in MSCS score at 4 h post-treatment. The MMRM will include fixed effects of treatment, time (1, 2, and 4 h post-treatment), treatment-by-time interaction, attack, and attack specific pre-treatment MSCS value as covariate. An unstructured covariance structure will be assumed to model the within-attack variability. If the MMRM with unstructured covariance fails to converge, the following tests will be used in sequence: heterogeneous Toeplitz covariance structure, heterogeneous autoregressive covariance structure, heterogeneous compound symmetry covariance structure, and compound symmetry covariance structure. Additionally, subject-specific random effects will be used to account for the within-patient and between attack period correlation. Please refer to Table 6 for handling of ICEs.

The change from pre-treatment in MSCS score will also be analyzed at 24 h post-treatment as a secondary endpoint. The analysis and method of handling ICEs are the same but the timepoint is changed from 4 h to 24 h, including the data used for analysis. The covariance structure in section 3.4 will be assumed.

An emerging symptom complex(es) is any new symptom complex that develops symptoms after dosing with IMP. Emerging symptoms in MSCS will be reported in a listing.

Supportive Analysis:

MMRM analysis for change in MSCS score may be conducted by excluding data with inconsistency in symptom reports between VAS and MSCS/TOS (defined in Appendix G). Note that if there is inconsistency in symptom reports between pre-treatment VAS and pre-treatment MSCS/TOS then all the post-treatment MSCS change scores will be excluded for that attack.

Treatment outcome score (TOS)

Actual scores will be summarized using descriptive statistics by treatment arm at each scheduled time point. An analysis of TOS at 4 h based on MMRM (in Section 3.4) will be carried out similarly to the analysis for the primary efficacy endpoint. The MMRM will include fixed effects of treatment, time (1, 2, and 4 h post-treatment), treatment-by-time interaction, attack, and attack specific pre-treatment TOS value as covariate. An unstructured covariance structure will be assumed to model the within-attack variability. If the MMRM with unstructured covariance

fails to converge, the following tests will be used in sequence: heterogeneous Toeplitz covariance structure, heterogeneous autoregressive covariance structure, heterogeneous compound symmetry covariance structure, and compound symmetry covariance structure. Additionally, subject-specific random effects will be used to account for the within-patient and between attack period correlation. Please refer to Table 6 for handling of ICEs.

The TOS will also be analyzed at 24 h post-treatment as a secondary endpoint. The analysis and method of handling ICEs are the same but the timepoint is changed from 4 h to 24 h, including the data used for analysis. The covariance structure in section 3.4 will be assumed.

Emerging symptoms in TOS will be reported in a listing.

Supportive Analysis:

MMRM analysis for TOS may be conducted by excluding data with inconsistency in symptom reports between VAS and MSCS/TOS (defined in Appendix G). Note that if there is inconsistency in symptom reports between pre-treatment VAS and pre-treatment MSCS/TOS then all the post-treatment TOS will be excluded for that attack.

Treatment satisfaction questionnaire for medication (TSQM)

Domain scores will be summarized using descriptive statistics by treatment arm at 48 hours post-treatment. An analysis based on MMRM (in Section 3.4) will be carried out if applicable, including the handling of Category 1 and Category 2 ICEs. The MMRM will include fixed effects of treatment, attack, and attack specific pre-treatment VAS-3 value as covariate. An unstructured covariance structure will be assumed to model the within-patient variability. If the MMRM with unstructured covariance fails to converge, the following tests will be used in sequence: heterogeneous Toeplitz covariance structure, heterogeneous autoregressive covariance structure, heterogeneous compound symmetry covariance structure, and compound symmetry covariance structure.

Binary efficacy endpoint

Proportion of IMP-treated attacks requiring HAE rescue medication

A generalized estimating equation (GEE) with a logit link will be used to analyze the proportion of IMP treated attacks requiring HAE rescue medication within 12 h, within 24 h, and within 48 h post-treatment, based on binary outcome data. The model will include treatment, attack, and pre-treatment VAS-3 score as fixed effects. An estimated odds ratio of each PHA-022121 dose versus placebo with its 95% CI and p-value will be provided. Please refer to Table 6 for handling of ICEs.

Additionally, the number of attacks requiring HAE rescue medication (after taking IMP) will be summarized using frequencies and percentages by treatment arm.

3.4.3 Subgroups

The primary efficacy endpoint will be summarized for the mITT Analysis Set by age (<65, ≥65), gender (male, female). The primary efficacy analysis may be repeated for each subgroup if sufficient data is available in each subgroup. Other subgroups may also be explored.

The corresponding subgroup analysis will be performed only if each category has at least 5 patients in each treatment group.

3.5 Pharmacokinetic Analysis

Descriptive summary statistics and listing of actual values will be provided for the PK parameters and concentration data. Detailed pharmacokinetic analysis will be described in a separate document.

3.6 Safety Analysis

Safety data will be summarized by actual dose received (and in total for selected analyses) based on the Safety Analysis Set. The occurrence of an event is counted towards the treatment arm (dose) that the patient has taken prior to the event occurrence. Incidence summary tables will be by the actual dose cohort (L, M, H) during the non-attack period and by the actual dose during the attack periods (L, M, H, P). Selected incidence summary tables will be by the actual dose cohort and by the actual dose during the attack periods (L cohort (L, P), M cohort (M, P), H cohort (H, P), Total active, Total P). Summary tables for lab numeric parameters will be by the actual dose cohort (L, M, H, Total) during the non-attack period and by the actual dose (L, M, H, P) during the attack periods. Unless otherwise specified, percentages will be based on the number of subjects in the Safety analysis set for Part I and will be based on the number of treated attacks for Part II. If patients incorrectly receive placebo for the Non-attack Visit, the corresponding safety data (e.g., adverse event) will be listed separately and will not be summarized under the low dose (10 mg), medium dose (20 mg), high dose (30 mg), or Total column for Part I.

3.6.1 Adverse Events (AEs)

AEs will be captured from the date of the informed consent was signed until the end-of-study visit. All AEs will be coded to system organ class and preferred term using MedDRA version 25.0 (or later version). Treatment emergent adverse events (TEAEs) are defined as AEs that occur during the time window that starts from the first IMP administration through the end-of-study visit. Because of the setting of this study with single IMP administration for treating acute HAE attack and approximately 4 hours half-life for PHA-022121, the TEAEs within 48 hours post-treatment are most relevant in safety evaluation.

An overview of AEs within 48 hours post-treatment (of non-attack or attack period) will be provided including frequencies and percentages of patients (and event frequencies) with the following:

- Any TEAEs (overall and by maximum grade/severity)
- Any IMP-related TEAEs (overall and by maximum grade/severity)
- Any treatment-emergent serious AEs (TESAEs)
- Any IMP-related TESAEs (overall and by maximum grade/severity)
- Any TEAEs leading to discontinuation of IMP
- Any TEAEs leading to discontinuation from study participation
- Any AEs leading to death

Frequencies and percentages of patients (and event frequencies) will also be presented by system organ class and preferred term for each of the categories in the overview. The Incidence summary tables described in Section 3.6 will be used.

Overview and frequencies and percentages of patients (and event frequencies) will be repeated including only those AEs that began (or worsened) within 5 days post-treatment (of non-attack or attack period), summarized by actual dose received (prior to the AEs) and in total.

The TEAE is counted towards the specific dose group (e.g., low dose) only if it started during the time period after the patient was administered IMP of that dose (or placebo) and prior to the administration of another different dose (or placebo), if there was any.

AE severity grade will be evaluated and recorded on the CRF according to the grading described in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on the 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

All AEs will be reported in a listing. Separate listings will be presented specifically for SAEs and TEAEs leading to discontinuation of IMP or discontinuation from the study.

3.6.2 Clinical Laboratory Tests

Blood and/or urine sampling for blood chemistry, hematology, coagulation, urinalysis, and pregnancy test will be done at the Screening visit, the Non-attack visit (pre-dose), and the Post-attack visits. Blood sampling for viral testing will be done at Screening only. Blood and urine samples will be processed by a central laboratory. A list of laboratory tests to be performed along with reference ranges is included in Appendix B.

Observed values will be presented at each scheduled visit and baseline by laboratory test. The post attack visits may be pooled together for simplicity. The incidence of abnormalities (as defined by normal ranges) prior to the first dose of IMP and after the first dose of IMP may be summarized with frequencies and percentages of patients.

The incidence of worst post-attack lab abnormalities may be summarized with frequencies and percentages of patients for selected parameters using the grading scheme in the CTCAE Version 5.0. CTCAE criteria are detailed in Appendix C (CTCAE v5.0).

All laboratory data will be listed. Another list will be provided to show the corresponding values for the patient's laboratory parameters with at least one meeting the CTCAE criteria.

3.6.3 Vital Signs

Vital signs include blood pressure, heart rate, body temperature, and respiratory rate. The measurements will be taken at Screening, Non-attack visit, and Post-attack visits. Observed values and changes from baseline will be summarized. The post attack visits may be pooled together for simplicity.

The incidence of Potentially Clinically Significant Abnormalities (PCSA) will be summarized with frequencies and percentages of patients for selected parameters. PCSA criteria are defined in Appendix D.

Vital signs assessments will be listed. Clinically significant changes in vital signs reported as AEs will be flagged as well as the PCSA. Another list will be provided to show the corresponding values for the patient's vital signs with at least one potential clinically significant abnormality.

3.6.4 Electrocardiograms

A 12-lead Electrocardiogram (ECG) (digital triplicate) will be recorded at Screening and at the Non-attack visit. Clinically significant ECG findings will be reported as AEs. The mean over the triplet will be calculated for each parameter. Mean values will be derived during the statistical analysis. Only means will be reported in the summary tables.

The incidence of PCSA may be summarized with frequencies and percentages of patients. PCSA criteria are defined in Appendix D.

ECG readings and abnormalities will be listed. Another list will be provided to show only the corresponding values for the patient's ECG parameters with at least one PCSA. The ECG Medpace Core Laboratories interpretation may be summarized.

3.6.5 Physical Examinations

A physical examination will be conducted at Screening. Physical examination findings will be listed.

4 DATA MONITORING COMMITTEE

An Independent Data Monitoring Committee (IDMC) has been assembled to review safety data on a regular basis (and ad-hoc in case of unexpected safety issues) throughout the study. The review of safety data will be performed according to the IDMC charter.

5 ANALYSIS TIMING

No interim analysis is planned.

A Primary Analysis (PA) is planned as a formal study analysis to address the objectives of the study. The PA will be performed before all enrolled patients have experienced 3 qualified attacks, because some patients may be unable to complete the assessments for 3 qualified attacks within a reasonable treatment period. The PA will include data collected on or before the PA cutoff date: September 23, 2022.

All the formal statistical tests for the efficacy endpoints as specified in Section 3.1.3 will be performed for the PA. Following the PA, a Final Analysis (FA) will be conducted at the very end of the study once most patients have completed the assessments for 3 qualified attacks or have

been discontinued from the study. The FA will include all data accumulated from the beginning of the study through the end of the entire study. Selected analyses will be conducted at the FA, which will be specified in an updated version of SAP prior to the FA. All statistical analyses at the FA will be regarded as descriptive in nature.

After the database is locked at Primary Analysis and blinded Concomitant Medication Clinical Manual Review and exclusions from analysis sets have been finalized, the randomized treatment assignments will be unblinded to the unblinded Project Biostatistics team and designated sponsor team, and the pre-final analysis will be generated and reviewed only by the unblinded personnel. The details are described in the study Unblinding Plan.

After all comments on the pre-final analysis have been resolved and the study database is declared final, the final TFLs will be generated. Final TFLs will be provided after the study database is declared final. If there were no changes to the pre-final analysis or the study database, the pre-final TFLs may be considered final. The same process will be followed for both PA and FA.

6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

The PK Analysis Set defined in Section 3.2.5 is different from the protocol to include all Pharmacokinetic concentrations in the summary.

7 SUMMARY OF CHANGES FROM THE PREVIOUS VERION OF THE SAP

Section 3.1, clarified the definitions of VAS based time-to-event endpoints. Also clarified that only rescue medication confirmed by medical reviewer will be used for definition of use of rescue medication and time to first use of rescue medication for a treated attack. The method for imputation of rescue medication with missing time but with complete date was added.

Section 3.2.5, added the PK Analysis Set with full PK profile to be consistent with PK SAP.

Section 3.4, added subject-specific random effects to account for the within-patient and between attack period correlation in the MMRM; clarified that for MSCS and TOS, the unstructured covariance structure will be assumed for the within-attack covariance in the MMRM.

Section 3.6, added that for summaries of safety data, percentages will be based on the number of subjects in the Safety analysis set for Part I and will be based on the number of treated attacks for Part II; clarified how data will be handled if a patient incorrectly receives placebo in Part I.

Section 5, clarified that the PA will include data collected on or before September 23, 2022.

8 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. All available data will be presented in patient data listings which will be sorted by patient and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

APPENDIX A: REFRENCES

[1] Longhurst H, Moldovan D, Bygum A, Cicardi M, Huissoon A, Aygoren-Pursun E, et al. Oral Plasma Kallikrein Inhibitor BCX7353 is Safe and Effective as an On-Demand Treatment of Angioedema Attacks in Hereditary Angioedema (HAE) Patients: Results of the ZENITH-1 Trial. J Allergy Clin Immun. 2019;143(2):AB36.

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APPENDIX B: LABORATORY TESTS

Hematology:

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

Coagulation:

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

Urinalysis:

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

Blood chemistry:

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

Pregnancy test (for women of childbearing potential):

- Serum human chorionic gonadotropin (hCG)

Menopause test (for post-menopausal women) **:

- Serum follicle-stimulating hormone (FSH)

Viral testing **:

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

* Non-attack visit only

** At Screening only

APPENDIX C: CTCAE V5.0

Laboratory	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Blood chemistry	Hypoalbuminemia	Albumin <LLN - 3 g/dL; <LLN - 30 g/L	Albumin <3 - 2 g/dL; <30 - 20 g/L	Albumin <2 g/dL; <20 g/L	-
	Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
	Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
	Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
	Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
	Hypoglycemia	Glucose <LLN - 55 mg/dL; <LLN - 3.0 mmol/L	Glucose <55 - 40 mg/dL; <3.0 - 2.2 mmol/L	Glucose <40 - 30 mg/dL; <2.2 - 1.7 mmol/L	Glucose <30 mg/dL; <1.7 mmol/L;
	Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences
	Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences
	Hyperkalemia	Potassium >ULN - 5.5 mmol/L	Potassium >5.5 - 6.0 mmol/L	Potassium >6.0 - 7.0 mmol/L	Potassium >7.0 mmol/L
	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences
	Blood bilirubin increased	Total Bilirubin >ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	Total Bilirubin >1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	Total Bilirubin >3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	Total Bilirubin >10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Hematology	Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hemoglobin (Hgb) <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 – 80 g/L	Hemoglobin (Hgb) <8.0 g/dL; <4.9 mmol/L; <80 g/L	-
	Hemoglobin increased	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL	Increase in >4 g/dL	-

Laboratory	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
	Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L
	White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L
	Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L
	Lymphocyte count decreased	<LLN - 800/mm3; <LLN – 0.8 x 10e9/L	<800 - 500/mm3; <0.8 – 0.5 x 10e9/L	<500 200/mm3; <0.5 – 0.2 x 10e9/L	<200/mm3; <0.2 x 10e9/L
	Lymphocyte count increased	-	<4000 - 20000/mm3	>20000/mm3	-
Coagula-tion	INR increased	>1.2 - 1.5; >1 - 1.5 x baseline if on anticoagulation	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation	>2.5; >2.5 x baseline if on anticoagulation	-

This is for the derived CTCAE from the laboratory data without considering the medical input.

APPENDIX D: LIST OF PCSA CRITERIA

PCSA for Vital Signs parameters:

Parameter	PCSA
BMI (kg/m^2)	<18 or > 30
Heart rate (bpm)	< 50 or >100
Systolic blood pressure (mmHg)	< 90 or >140
Diastolic blood pressure (mmHg)	< 50 or > 90
Temperature (C)	< 36 or > 37.5
Respiratory rate (breaths/min)	<12 or > 20

PCSA for ECG parameters:

Parameter	PCSA
Heart rate (bpm)	< 50 or > 100
PR (msec)	<120 or > 200
QRS (msec)	< 80 or > 120;
QT (msec)	> 500
QTcF (msec)	> 450 for men and > 470 for women
RR (msec)	< 600 or > 1200

APPENDIX E: ANALYSIS TIMEPOINT WINDOWING PER TREATED ATTACK

For VAS-3, MSCS and TOS, the entry timing will be calculated as

"entry time" – "corresponding treatment time".

According to the calculated entry timing, the entries will be assigned to the following timepoints based on the timing window. Entries labeled as prior to the corresponding treatment in the data will not be used for post-treatment timepoint. Entries labeled as after the corresponding treatment will not be used for pre-treatment timepoint. If multiple entries fall into the same timing window, the one that is the closest to the target hour will be used for analysis. The later one will be used if two records are the closest to the target hour.

All VAS-3, MSCS and TOS data will be listed.

VAS-3 Timepoint	**Target hour**	**Timing Window**
Pre-treatment	0	[-30, 5] min
0.5	0.5	0.5 h ± 10 min
1	1	1 h ± 10 min
1.5	1.5	1.5 h ± 10 min
2	2	2 h ± 10 min
2.5	2.5	2.5 h ± 10 min
3	3	3 h ± 10 min
3.5	3.5	3.5 h ± 10 min
4	4	4 h ± 10 min
5	5	5 ± 0.5 h (excluding 5.5 h)
6	6	6 ± 0.5 h (including 5.5 h)
8	8	8 ± 1 h
24	24	24 ± 4 h
48	48	48 ± 6 h
MSCS/TOS Timepoint		
Pre-treatment	0	[-30, 10] min
1	1	1 ± 0.25 h
2	2	2 ± 0.25 h
4	4	4 ± 0.25 h
6	6	6 ± 1 h (excluding 7 h)
8	8	8 ± 1 h (including 7 h)
24	24	24 ± 4 h
48	48	48 ± 6 h

APPENDIX F. TREATMENT SATISFACTION QUESTIONNAIRE FOR MEDICATION (TSQM)

Item #1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat the condition?

Item #2. How satisfied or dissatisfied are you with the way the medication relieves symptoms?

Item #3. As a result of taking this medication, do you experience any side effects at all?

Item #4. How dissatisfied are you by side effects that interfere with your physical health and ability to function (e.g., strength, energy levels)?

Item #5. How dissatisfied are you by side effects that interfere with your mental function (e.g., ability to think clearly, stay awake)?

Item #6. How dissatisfied are you by side effects that interfere with your mood or emotions (e.g., anxiety/fear, sadness, irritation/anger)?

Item #7. How satisfied or dissatisfied are you with how easy the medication is to use?

Item #8. How satisfied or dissatisfied are you with how easy it is to plan when you will use the medication each time?

Item #9. How satisfied or dissatisfied are you by how often you are expected to use/take the medication?

Item #10. How satisfied are you that the good things about this medication outweigh the bad things?

Item #11. Taking all things into account, how satisfied or dissatisfied are you with this medication?

For Item #1, #2, #7, #8, #9, #10, #11, the response options include 1 = Extremely dissatisfied, 2 = Very dissatisfied, 3 = Dissatisfied, 4 = Somewhat satisfied, 5 = Satisfied, 6 = Very satisfied, 7 = Extremely satisfied.

For item #3, the response options include Yes and No.

For Item #4, #5, #6, the response options include 1 = Extremely dissatisfied, 2 = Very dissatisfied, 3 = Somewhat dissatisfied, 4 = Slightly dissatisfied, 5 = Not at all dissatisfied.

APPENDIX G. DISCREPANCY BETWEEN VAS AND MSCS/TOS AT THE SAME TIMEPOINT

- VAS skin pain > 5, but none of the following in MSCS/TOS: External Head/Neck, Cutaneous, Stomach/GI, or Genital/Buttocks is "Yes".
- VAS skin swelling > 5, but none of the following in MSCS/TOS: External Head/Neck, Cutaneous, Stomach/GI, or Genital/Buttocks in MSCS/TOS is "Yes".
- VAS abdominal pain > 5, but Stomach/GI in MSCS/TOS is "No".
- External Head/Neck= "Yes" in MSCS/TOS with severity Moderate or Severe but VAS skin pain = 0 and skin swelling = 0.
- Genital/Buttocks = "Yes" in MSCS/TOS with severity Moderate or Severe but VAS skin pain = 0 and skin swelling = 0.
- Stomach/GI = "Yes" in MSCS/TOS with severity Moderate or Severe but VAS Abdominal pain = 0.
- Cutaneous = "Yes" in MSCS/TOS with severity Moderate or Severe but VAS skin pain = 0 and skin swelling = 0.

APPENDIX H: SAS CODE

D1. Example SAS Code for MMRM

```
/*************************************************************************/
/* CHG: Change from baseline                                             */
/* AVALB: Pre-treatment value                                            */
/* TRTPN: Treatment assignment                                           */
/* ATPTN: Analysis timepoint                                             */
/* USUBJID: Unique subject identifier                                    */
/* APERIOD: Treated attack number (1st, 2nd, 3rd)                        */
/*************************************************************************/

PROC MIXED DATA=MMRM;
      CLASS USUBJID TRTPN(REF="0") ATPTN APERIOD;
      MODEL CHG = TRTPN ATPTN TRTPN*ATPTN APERIOD AVALB/
            SOLUTION RESIDUAL CL DDFM=KR OUTP = RES;
      REPEATED ATPTN / SUB=USUBJID*APERIOD TYPE=TOEPH;
      RANDOM INT/SUB= USUBJID;
      LSMEANS TRTPN*ATPTN / PDIFF CL;
      ODS OUTPUT LSMEANS=LSMEANS
                 DIFFS=DIFFS(WHERE = ( ATPTN =_ATPTN & _TRTPN = 0));
RUN;
```

D2. Example SAS Code for CPHM

```
/*************************************************************************/
/* PREVAS: Pre-treatment VAS-3 score                                     */
/* AVAL: Time to event/censoring                                         */
/* TRTPN: Treatment assignment                                           */
/* CNSR: Censor                                                          */
/* USUBJID: Unique subject identifier                                    */
/* APERIOD: Treated attack number (1st, 2nd, 3rd)                        */
/*************************************************************************/

PROC PHREG DATA = COX COVS(AGGREGATE) ;
      CLASS USUBJID TRTPN(REF="0") APERIOD;
      MODEL AVAL*CNSR(1)=TRTPN APERIOD PREVAS /RL;
      ID USUBJID;
      HAZARDRATIO TRTPN/DIFF=REF;
      ODS OUTPUT  PARAMETERESTIMATES =PE95;
RUN;
```

D3. Example SAS Code for GEE

```
/*************************************************************************/
/* PREVAS: Pre-treatment VAS-3 score                                     */
/* AVAL: Binary outcome                                                  */
/* TRTPN: Treatment assignment                                           */
/* USUBJID: Unique subject identifier                                    */
/* APERIOD: Treated attack number (1st, 2nd, 3rd)                        */
/*************************************************************************/

PROC GENMOD DATA=GEE DESCENDING;
      CLASS USUBJID TRTPN(REF="0") APERIOD;
      MODEL AVAL = TRTPN APERIOD PREVAS /DIST=BIN LINK=LOGIT;
      REPEATED SUBJECT=USUBJID/ TYPE=IND ECOVB MCOVB CORRW;
      LSMEANS TRTPN /DIFF EXP ILINK CL;
      ODS OUTPUT  LSMEANS=LSMEANS
                  DIFFS=DIFFS(WHERE = (  _TRTPN = 0));
RUN;
```