



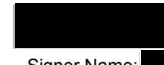
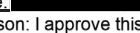
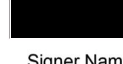
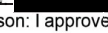
Statistical Analysis Plan
for Final Analysis of Clinical Study Protocol: PHA022121-C301
(Final Analysis SAP)

Study Title:	A Phase II, Double-blind, Placebo-controlled, Randomized, Dose-ranging, Parallel Group Study to Evaluate the Safety and Efficacy of PHA-022121 Administered Orally for Long-term Prophylaxis Against Angioedema Attacks in Patients with Hereditary Angioedema due to C1-Inhibitor Deficiency (Type I or Type II)
Acronym:	CHAPTER-1
Study Number:	PHA022121-C301
SAP Version:	V1.0
Date:	October 30, 2023
Author:	

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APPROVAL

This document has been reviewed and approved by:		
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VERSION HISTORY

SAP Version	Date	Primary Reasons for Amendment
1.0	27-Oct-2023	Initial Version

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LIST OF ABBREVIATIONS

AECT-4wk	angioedema control test 4-week
AE	adverse event
AE-QoL	angioedema quality of life (questionnaire)
BQL	below quantification limit
C1-INH	C1-esterase inhibitor
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
OLE	open-label extension
PGA-change	patient global assessment of change (question)
PGA-QoL	patient global assessment of quality of life (question)
PK	pharmacokinetic(s)
PPS	Per Protocol Analysis Set (PPS)
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TSQM	treatment satisfaction questionnaire for medication
US	United States
WAO	World Allergy Organization

1 INTRODUCTION

The study Primary Analysis (PA) is planned at the end of the double-blind treatment period of the study (study Part 1) when all participants have completed Part 1 of the study or have been early discontinued from the study. The planned analyses for PA using study data from the double-blind treatment period (Part 1 data) are documented in a separated SAP, i.e., Part 1 SAP, version 1.0, dated Oct 27, 2023.

The purpose of this SAP is to provide a description of the statistical methods to be implemented for the Final Analysis (FA), which includes analyses on Part 2 data alone and combined data of Part 1 and Part 2 from protocol PHA022121-C301 version 7 dated 03 May 2023. Any deviations from this SAP after final database lock and release of treatment codes will be documented in the final Clinical Study Report (CSR). For analysis definitions and statistical approaches related to Part 1 data, please refer to the Part 1 data SAP.

2 STUDY OVERVIEW

The study overview and study objectives for Part 1 have been listed in both study protocol and Part 1 SAP. All the definitions for Part 1 data are not changed. This information will not be reiterated in this SAP.

2.1 Study Objectives and Endpoints for Part 2

2.1.1 The study objectives

Primary:

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

Secondary:

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

2.1.2 The Study Endpoints

Safety:

- Treatment-emergent adverse events (TEAEs), treatment-related adverse events (AEs), and treatment-emergent serious adverse events (TESAEs)
- Clinical laboratory tests
- Vital sign parameters
- Electrocardiogram (ECG) data

Efficacy:

- Number of investigator-confirmed angioedema attacks during the treatment period in Part 2
- Number of investigator-confirmed moderate or severe angioedema attacks during the treatment period in Part 2
- Number of investigator-confirmed angioedema attacks requiring acute treatment during the treatment period in Part 2
- Incidence of attacks during the treatment period in Part 2
- Number and proportion of days with angioedema symptoms during the treatment period in Part 2

PK/PD and QoL:

- Pharmacokinetic parameters based on plasma concentration of PHA-022121
- Change from baseline in the AE-QoL questionnaire score
- PGA-QoL and PGA-change questions from Part 1 baseline
- Change from baseline in AECT-4wk scores
- TSQM-II scores

3 DEFINITIONS

3.1 Investigational Medicinal Product (IMP)

In Part 2, IMP refers to open-label PHA-022121.

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

3.2 Dates, Periods, and Points of Reference

3.2.1 Study Baseline

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

3.2.2 Part 2 Baseline

Baseline for Part 2 is defined as the last available observed value of the parameter of interest prior to the first administration of IMP in Part 2 (this includes unscheduled visits). For electrocardiogram (ECG), the baseline is defined as the mean of the last recorded triplicate before the first administration of IMP in Part 2. For AE-QoL, the baseline may be measured within two days of the first dose of Part 2 IMP.

3.2.3 Study Day in Part 2

The first IMP administration date in Part 2 is defined as the date of first open-label extension (OLE) dose as recorded on the CRF.

For any assessments on or after the first IMP administration in Part 2, study day is calculated as: assessment date – date of first IMP administration in Part 2 + 1. As such, the first IMP administration date in Part 2 is study day 1 in Part 2.

3.2.4 Study Day for PHA

For participants in either the 10 mg/day or 20 mg/day actual treatment arm in Part 1, Day 1 is defined as Day 1 of Part 1; for participants in placebo arm who start 20 mg/day treatment in Part 2, Day 1 is defined as Day 1 of Part 2.

3.2.5 Analysis Periods in Part 2

The study period in Part 2 is defined for participants who received at least one IMP in Part 2 and is the period from date and time of the first IMP administration in Part 2 to the end of study (EOS) date or data cut-off, whenever is earlier.

The treatment period in Part 2 is defined as the date and time of first IMP administration in Part 2 to the date and time of last IMP administration in Part 2 +1. The duration of the treatment is calculated as date of the last IMP administration in Part 2 - date of first IMP administration in Part 2+1.

The treatment period without substantial IMP non-compliance in Part 2 is defined as the treatment period excluding all substantial IMP non-compliance periods in Part 2. A participant may have multiple IMP non-compliance periods. An instance of substantial IMP non-compliance occurs when 4 or more consecutive doses of IMP are missing. The substantial IMP non-compliance period then is defined as the time period that starts from 12 hours after the last dose of IMP before the instance of substantial IMP-non-compliance and ends at next available dose or the end of study day which ever earlier. The period is calculated (in days) as the total number of missed doses during non-compliance periods divided by 2.

3.3 Analysis Sets

Intent-to-treat (ITT) Analysis Set in Part 2 will include all participants in the ITT analysis set who received at least one dose of IMP in Part 2 of the study.

Safety Analysis Set in Part 2 will include all participants in the Safety Analysis Set who received at least one dose of IMP in Part 2 of the study. This set will be identical to ITT Analysis Set in Part 2.

PHA Analysis Set

Includes all randomized participants who received at least one dose of PHA-022121. This will include all participants randomized to one of the PHA-022121 arms (10mg/day or 20mg/day) in part 1 and all participants randomized to placebo and received PHA-022121 in Part 2 of the study.

Pharmacokinetic (PK) Analysis Set in Part 1 and Part 2

PK Analysis Set includes all randomized participants who undergo plasma PK sampling and have evaluable concentration data for Part 1 or Part 2.

3.4 Study-Specific Definitions and Key Derived Variables in Part 2

Attack rate related definitions

Unless otherwise specified, “HAE attack” refers to Investigator-confirmed attacks. An attack will be counted as in Part 1 if it occurs after the first IMP administration and within 24 hours after the last administration of IMP in Part 1 or before first IMP administration in Part 2, whichever comes first. An attack will be counted as in Part 2 if it occurs after the first IMP administration in Part 2 and within 24 hours after last IMP administration in Part 2. The attacks occurring in the gap period, i.e., 24 hours after the last dose of Part 1 and before the first dose of Part 2 will not be counted.

Monthly attack rate

The monthly HAE attack rate is calculated for each participant as the number of HAE attacks occurring during the treatment period divided by the number of days the participant contributed to the treatment period multiplied by 28 days.

Attack rate by month-interval

For each month-interval, the attack rate for a participant will be calculated using the number of Investigator-confirmed HAE attacks with onset date within each month-interval during the treatment period in Part 2. Each month interval is defined as 28 days, with the first month interval starting on the first day of the Part 2 study period. For example, if the first open label treatment in Part 2 is on Day 84, the first month period will be from Day 84 to 111 and the second month would be from Day 112 to 139 and so on. Note that for participants whose last monthly period is less than 28 days, the monthly attack rate for the last month-interval will be normalized based on the actual days before early discontinuation within the month-interval multiplied by 28 days.

Percent reduction in attack rate

Percent reduction in attack rate during the treatment period in Part 2 relative to study baseline and Part 1 attack rate will be calculated as follows. A positive reduction from baseline indicates improvement.

Relative to study baseline:

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

Relative to Part 1 attack rate for a participant:

$$\frac{\text{Part 1 attack rate} - \text{Attack rate during treatment period}}{\text{Part 1 attack rate}} \times 100$$

Where both the study baseline attack rate and Part 1 attack rate are defined in Part 1 SAP (section 3.4.1).

AE-QoL and TSQM-II

The angioedema quality of life questionnaire (AE-QoL), the angioedema control test 4-week version (AECT-4wk), patient global assessment of quality of life (PGA-QoL) and patient global assessment of change (PGA-change) questions, and the 11-item treatment satisfaction questionnaire for medication (TSQM-II) are used to assess health-related quality of life and satisfaction with treatment, respectively, and collected throughout the entire study. The derivations for total score and sub-scores remain unchanged. Their definitions and derivations can be found in Part 1 SAP (section 3.4.2).

3.5 Timing and Scope of Milestone Analyses for Part 2

As specified in the Part 1 data SAP, two milestone analyses are planned for this study: Primary Analysis (PA, End of Part 1 Analysis), and Final Analysis (FA, End of Part 2 Analysis). The FA for the study will occur at the end of the entire study when all participants have completed Part 2 of the study or have been early discontinued from the study and the study database final lock is completed. This FA SAP includes the analyses planned for the FA.

4 STATISTICAL METHODS FOR PLANNED ANALYSES

4.1 General Principles

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

In TFLs, the treatment “PHA-022121 10 mg BID” and “PHA-022121 20 mg BID” will be displayed in abbreviations of “PHA 10 mg” and “PHA 20 mg”, respectively. Unless described otherwise in following sections, in TFLs based on Part 1 data, results will be presented by treatment groups: Placebo, PHA 10 mg, and PHA 20 mg; in TFLs based on Part 2 data, and those based combined data from Part 1 and Part 2, results will be presented and grouped by treatment sequence: Placebo / PHA 20 mg, PHA 10 mg / PHA 20 mg, PHA 20 mg / PHA 20 mg

Continuous data will be summarized with the number of participants, mean, standard deviation (SD), median, 25th percentile, 75th percentile, minimum, and maximum. Categorical data will be summarized with the number and percentages of participants in each category.

Data listings will include the data recorded on the CRF or the derived variables for each record. They will be ordered by the treatment group in Part 2 site, participant number, and time of assessment. When expedient, additional levels of ordering hierarchy may reflect subsets of assessments within the participant.

Unless otherwise specified, the ITT Analysis Set will be used for analysis of efficacy and QoL endpoints, and the Safety Analysis Set will be used for analysis of safety endpoints. The PK Analysis set will be used for PK Analysis.

4.1.1 Analysis Visit Windows

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

The analysis visit windows in Appendix A will be applied to all efficacy and safety visits for Part 2 data.

4.1.2 Handling Missing Data and Partial Dates

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

All the missing data in Part 2 will be dealt with the same way as data in Part 1. Refer to Section 4.1.2 of Part 1 Data SAP for more details regarding missing data imputation.

4.2 Disposition

The following categories for disposition will be tabulated on the number of participants enrolled in Part 2.

- Completed the Part 2 treatment
- Part 2 treatment discontinuation
- Study discontinuation in Part 2.
- Participants with Early Study Discontinuation Impacted by COVID

An overall disposition table including both Part 1 disposition information and Part 2 data will be provided.

4.3 Protocol Deviations

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

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

4.4 Demographic Characteristics

Study baseline characteristics for each participant defined below will be presented in summary tables and data listings for participants who enrolled in Part 2 of the study. Percentages will be based on the number of participants in the ITT Analysis Set in Part 2. No formal statistical comparisons will be performed.

Demography

- Age: (years)
- Age group: <65, ≥ 65 years

- Sex
- Race
- Ethnicity
- Country of enrollment

Characteristics

- Height (cm)
- Weight (kg)
- BMI (kg/m²)
- Childbearing potential (Yes, No) for WCBP only
- HAE Type I or II
- HAE Attack Rate (per month)
- HAE Attack Rate Categories (both actual categories and stratification factor in randomization):
- Family History Consistent with HAE Type I or II
- Prophylactic treatment prior randomization (yes or no)

4.5 IMP Exposure and Concomitant Medications in Part 2

Exposure and Compliance

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

- Duration of the treatment period in Part 2
- Total # of capsules Taken in Part 2, calculated as total # of capsules dispensed in Part 2 minus total # of capsules returned in Part 2. If the wallet is not returned, all the capsules contained in that wallet are assumed to be taken.
- Average Daily Dose of IMP in Part 2 (capsules/day), calculated as total # of capsules taken in Part 2 divided by duration of the treatment period in Part 2
- Percent compliance in Part 2, calculated as:
$$\frac{\text{Total \# of Capsules Taken in Part 2}}{\text{Treatment Duration of IMP in Part 2 (days) * 4 - 2}} \times 100$$
- Percent compliance categories, < 80%, 80-110%, >110%

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

Concomitant Medications and Procedures

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) version B3 Global March 2021.

Concomitant medications are defined as medications with a start date/time during the Part 2 treatment period, or medications with a start date/time prior to first IMP administration but ongoing during Part 2 treatment period. If the start or stop dates/times of medications are missing completely, the medication will be deemed as concomitant. If it is partially missing, the missing imputation rules will be applied to determine if it is prior or concomitant medication.

The number and percentage of participants with concomitant medications in Part 2 will be summarized by WHO-DD Anatomical-Therapeutic-Chemical (ATC) classification and PT by treatment groups. For each PT, a participant will only be counted once if he/she has more than one medication. A separate summary of concomitant HAE acute and prophylaxis medications in Part 2 will also be provided.

4.6 Efficacy Endpoints in Part 2

4.6.1 Analysis Methods for Efficacy Endpoints

HAE attack endpoints

The number of investigator-confirmed HAE attacks during the treatment period in Part 2 will be expressed as the normalized number of attacks per month (4 weeks) of exposure. The normalized number of investigator-confirmed HAE attacks during the treatment period in Part 2 will be summarized. Similarly, normalized number of investigator-confirmed moderate or severe HAE attacks during the treatment period in Part 2, normalized number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period in Part 2, and proportion of days with HAE symptoms during the treatment period in Part 2 will be summarized. Summary statistics will be given by treatment groups (20 mg to 20 mg, 10 mg to 20 mg, placebo to 20 mg, all participants in Part 2) and will include the number of events, subject time (in 28-day periods) contribution to the analysis period, monthly event rates and binary endpoints, that include the number and proportion of participants

Days with angioedema symptoms endpoint

Number and proportion of days with investigator-confirmed angioedema symptoms during the treatment period in Part 2 by treatment sequence groups and in total will be summarized using descriptive summary statistics.

Time-to-event endpoint

If more than ten participants reported Investigator-confirmed HAE attacks in Part 2 of the study, the time to first HAE attack during the treatment period in Part 2 will be analyzed using the Kaplan-Meier (KM) Method. For participants with HAE attack(s), this is defined as days from date of the first IMP administration in Part 2 until the onset date of first investigator-confirmed HAE attack. Participants without an Investigator-confirmed HAE

attack during the treatment period in Part 2 will be censored at the date of the last IMP dose +1 in Part 2. As descriptive summary, the time to investigator-confirmed HAE attacks in Part 2 will be provided in a listing.

Supportive binary endpoints

For the following binary endpoints, descriptive summary statistics that include the number and proportion of participants will be provided by treatment groups for participants with at least 4 weeks' of follow up after first dose in Part 2:

- Number of participants achieving $\geq 50\%$ reduction in attack rate relative to baseline during the treatment period in Part 2.
- Number of participants achieving $\geq 70\%$ reduction in attack rate relative to baseline during the treatment period in Part 2.
- Number of participants achieving $\geq 90\%$ reduction in attack rate relative to baseline during the treatment period in Part 2.
- Number of participants that are attack-free during the treatment period in Part 2.

4.6.2 Supportive Analysis

- The efficacy analysis may be repeated using the patient-reported number of attacks in Part 2.
- The efficacy analysis may be repeated using the attacks during the treatment period without substantial IMP non-compliance in Part 2.
- HAE monthly attack rates may be repeated using all the data from Part 1 and Part 2.

4.6.3 Subgroup Analyses

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

Prespecified subgroups are:

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

4.7 QoL Endpoints

AE-QoL

All four domains (functioning, fatigue/mood, fear/shame, nutrition) and total scores as well as their change from study baseline values will be summarized descriptively by treatment sequence groups and by visit in Part 1 and Part 2.

PGA-QoL

PGA-QoL values will be summarized using counts and percentages of participants with responses in each of the four-point response scale (0=not at all, 1=slightly, 2=moderately, 3=highly) by treatment sequence groups and by visit in Part 1 and Part 2.

Similarly, PGA-change will be summarized using counts and percentages of participants with responses in each of the five-point response scale (much better, a little better, no change, a little worse, or much worse) by treatment sequence groups and by visit in Part 1 and Part 2.

AECT-4wk

For AECT-4wk, the total score (ranging from 0 to 16 points) will be computed as the sum of the 4 AECT questions scored on a 0 to 4 scale. Observed values and change from study baseline will be summarized as continuous variables and by treatment sequence groups and by visit in Part 1 and Part 2. In addition, the total score will be categorized as either poorly controlled disease (total scores between 0 to 9 points) or well controlled disease (total scores between 10 to 16 points) and the dichotomized score will be summarized using counts and percentage of participants in each category by treatment sequence groups and by visit in Part 1 and Part 2.

TSQM-II

Each TSQM domain score will be summarized by treatment sequence groups and by visit in Part 1 and Part 2.

4.8 Safety Endpoints

4.8.1 Adverse Events

AEs will be coded using version 24.0 or higher of MedDRA to System Organ Class (SOC) and Preferred Term (PT). Treatment-emergent AEs (TEAEs) in Part 2 are defined as AEs that occur at any point after the first IMP administration in Part 2 or medical conditions that are present prior to the first IMP administration but increase in severity or frequency following the first IMP administration in Part 2. Should there be insufficient data for AE start date, stop date, and time to make this comparison, the AE will be considered treatment-emergent.

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

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

An overall AE summary will be presented and separated TEAE summaries will be produced by SOC and PT with the number and percent of participants by treatment group and overall. Including but not limited to the following AE tables:

- All TEAEs
- Treatment-related TEAEs
- Serious TEAEs
- TEAEs leading to IMP discontinuation
- TEAEs leading to discontinuation from study
- TEAEs leading to death
- TEAEs with CTCAE Grade ≥ 3
- TEAEs by maximum CTCAE Grade
- TEAEs by relationship to the study drug

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

All AEs will be listed by IMP and participant, detailing the verbatim term, the preferred term, system organ class, onset date and time, end date and time, CTCAE grade, outcome, relationship to IMP, seriousness and criteria for seriousness, action taken with IMP, other action taken, and trigger for an HAE attack (Y/N). Related AE listings will be presented with all the data from Part 1 and Part 2. All the analysis will be performed on Safety Analysis Set.

Selected AE analysis will also be presented using PHA analysis set, which will include the data for the participants on PHA-022121 period.

4.8.2 Clinical Laboratory Results

Descriptive analysis for laboratory test results (including hematology, serum chemistry, coagulation, and urinalysis) will be presented. Summaries of observed values at each timepoint and changes from baseline will be presented by the treatment group at each visit. Listings will be presented for all the central and local lab results. Pregnancy test results will be listed.

4.8.3 Vital Signs and Physical Examination

Vital signs will be summarized descriptively using actual values and changes from baseline by treatment group and each visit/at scheduled timepoint. Any abnormal or clinically significant findings will be presented in the listings.

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

4.8.4 12-Lead Electrocardiogram (ECG)

The 12-Lead ECG will be collected in triplicate. The mean over the triplet will be calculated for each parameter. Only means will be summarized in tables.

Potential clinical notable ECG are defined same as of Part 1 SAP (Section 4.8.4). Observed values of PR, QRS, and QTcF as well as change from study baseline values of QTcF will be flagged as potential clinically notable results if criteria met.

ECG parameters (PR, RR, QRS, QT, QTcF and QTcB intervals) will be summarized descriptively using observed values and change from study baseline by treatment sequence groups and scheduled visits in Part 1 and Part 2. In addition, the number and percentage of participants in each potential clinically notable results categories in Part 1 and Part 2 will be included in the summary.

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

4.9 Pharmacokinetic Endpoints

In Part 1, plasma samples for PK evaluation will be collected pre-dose and between 2-3 hours following the participant's morning dose on Day 0 (Visit 1), Day 42 (Visit 4), and Day 84 (Visit 6).

In Part 2, plasma samples for PK evaluation will be collected at Visits 7, 9 (if on-site), and 11. The time of the last dose of IMP and the last meal prior to the PK sampling is to be entered in the eCRF.

Descriptive statistics for plasma concentration data for both Part 1 and Part 2 will include the number of participants (n), mean, SD, coefficient of variation (CV%), median, minimum and maximum. Concentration values below the limit of quantification (BLQ) will be treated as 0 if this is first or last observations, and missing if it is between two measurable concentrations.

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

5 CHANGES FROM PROTOCOL-SPECIFIED ANALYSES

None.

6 SUMMARY OF CHANGES FROM THE PREVIOUS VERSION OF THE SAP

Not applicable.

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APPENDIX A: ANALYSIS VISIT WINDOWS

Outcome	Visit	Week	Target Day	Analysis Window (Days) 1
AE-QoL; AECT-4wk	Visit 7 Day 91	Week 13/Week 1 OLE	1 st OLE dosing day	From 1 st OLE dose to 17 days after 1 st OLE dosing day
	Visit 8 Day 126	Week 18/Week 6 OLE	35 days after 1 st OLE dosing day	From 18 days after 1 st OLE dosing day to 56 days after 1 st OLE dosing day
	Visit 9 Day 168	Week 24/Week 12 OLE	77 days after 1 st OLE dosing day	From 57 days after 1 st OLE dosing day to 98 days after 1 st OLE dosing day
	Visit 10 Day 210	Week 30/Week 18 OLE	119 days after 1 st OLE dosing day	From 99 days after 1 st OLE dosing day to 140 days after 1 st OLE dosing day
	Visit 11 Day 252	Week 36/Week 24 OLE	161 days after 1 st OLE dosing day	From 141 days after 1 st OLE dosing day to 206 days after 1 st OLE dosing day
	Visit 12 Day 343	Week 49/Week 37 OLE	252 days after 1 st OLE dosing day	From 207 days after 1 st OLE dosing day to 297 days after 1 st OLE dosing day
	Visit 13 Day 434	Week 62/Week 50 OLE	343 days after 1 st OLE dosing day	From 298 days after 1 st OLE dosing day to 388 days after 1 st OLE dosing day
	Visit 14 Day 525	Week 75/Week 63 OLE	434 days after 1 st OLE dosing day	From 389 days after 1 st OLE dosing day to 514 days after 1 st OLE dosing day
	Visit 15 Day 686	Week 98/Week 86 OLE	595 days after 1 st OLE dosing day	From 515 days after 1 st OLE dosing day to 640 days after 1 st OLE dosing day
	Visit 16 Day 777	Week 111/Week 99 OLE	686 days after 1 st OLE dosing day	From 641 days after 1 st OLE dosing day to 766 days after 1 st OLE dosing day
	Visit 17 Day 938	Week 134/Week 122 OLE	847 days after 1 st OLE dosing day	>=767 days after 1 st OLE dosing day
TSQM	Visit 7 Day 91	Week 13/Week 1 OLE	1 st OLE dosing day	From 1 st OLE dose to 17 days after 1 st OLE dosing day
	Visit 8 Day 126	Week 18/Week 6 OLE	35 days after 1 st	From 18 days after 1 st OLE dosing day to 56 days after 1 st OLE dosing day

			OLE dosing day	
	Visit 9 Day 168	Week 24/ Week 12 OLE	77 days after 1 st OLE dosing day	From 57 days after 1 st OLE dosing day to 98 days after 1 st OLE dosing day
	Visit 10 Day 210	Week 30/ Week 18 OLE	119 days after 1 st OLE dosing day	From 99 days after 1 st OLE dosing day to 140 days after 1 st OLE dosing day
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	Visit 12 Day 343	Week 49/ Week 37 OLE	252 days after 1 st OLE dosing day	From 207 days after 1 st OLE dosing day to 297 days after 1 st OLE dosing day
	Visit 13 Day 434	Week 62/ Week 50 OLE	343 days after 1 st OLE dosing day	From 298 days after 1 st OLE dosing day to 388 days after 1 st OLE dosing day
	Visit 14 Day 525	Week 75/ Week 63 OLE	434 days after 1 st OLE dosing day	From 389 days after 1 st OLE dosing day to 514 days after 1 st OLE dosing day
	Visit 15 Day 686	Week 98/ Week 86 OLE	595 days after 1 st OLE dosing day	From 515 days after 1 st OLE dosing day to 640 days after 1 st OLE dosing day
	Visit 16 Day 777	Week 111/ Week 99 OLE	686 days after 1 st OLE dosing day	From 641 days after 1 st OLE dosing day to 766 days after 1 st OLE dosing day
	Visit 17 Day 938	Week 134/ Week 122 OLE	847 days after 1 st OLE dosing day	>=767 days after 1 st OLE dosing day
PGA-QoL	Visit 7 Day 91	Week 13/ Week 1 OLE	1 st OLE dosing day	From 1 st OLE dose to 17 days after 1 st OLE dosing day
	Visit 8 Day 126	Week 18/ Week 6 OLE	35 days after 1 st OLE dosing day	From 18 days after 1 st OLE dosing day to 56 days after 1 st OLE dosing day
	Visit 9 Day 168	Week 24/ Week 12 OLE	77 days after 1 st OLE dosing day	From 57 days after 1 st OLE dosing day to 98 days after 1 st OLE dosing day
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	Visit 11 Day 252	Week 36/ Week 24 OLE	161 days after 1 st OLE dosing day	From 141 days after 1 st OLE dosing day to 206 days after 1 st OLE dosing day
	Visit 12 Day 343	Week 49/ Week 37 OLE	252 days after 1 st OLE dosing day	From 207 days after 1 st OLE dosing day to 297 days after 1 st OLE dosing day
	Visit 13 Day 434	Week 62/ Week 50 OLE	343 days after 1 st OLE dosing day	From 298 days after 1 st OLE dosing day to 388 days after 1 st OLE dosing day
	Visit 14 Day 525	Week 75/ Week 63 OLE	434 days after 1 st OLE dosing day	From 389 days after 1 st OLE dosing day to 514 days after 1 st OLE dosing day
	Visit 15 Day 686	Week 98/ Week 86 OLE	595 days after 1 st OLE dosing day	From 515 days after 1 st OLE dosing day to 640 days after 1 st OLE dosing day
	Visit 16 Day 777	Week 111/ Week 99 OLE	686 days after 1 st OLE dosing day	From 641 days after 1 st OLE dosing day to 766 days after 1 st OLE dosing day
	Visit 17 Day 938	Week 134/ Week 122 OLE	847 days after 1 st OLE dosing day	>=767 days after 1 st OLE dosing day
PGA-Change	Visit 7 Day 91	Week 13/Week 1 OLE	1 st OLE dosing day	From 1 st OLE dose to 17 days after 1 st OLE dosing day
	Visit 8 Day 126	Week 18/ Week 6 OLE	35 days after 1 st OLE dosing day	From 18 days after 1 st OLE dosing day to 56 days after 1 st OLE dosing day
	Visit 9 Day 168	Week 24/ Week 12 OLE	77 days after 1 st OLE dosing day	From 57 days after 1 st OLE dosing day to 98 days after 1 st OLE dosing day
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	Visit 13 Day 434	Week 62/ Week 50 OLE	343 days after 1 st OLE dosing day	From 298 days after 1 st OLE dosing day to 388 days after 1 st OLE dosing day
	Visit 14 Day 525	Week 75/ Week 63 OLE	434 days after 1 st OLE dosing day	From 389 days after 1 st OLE dosing day to 514 days after 1 st OLE dosing day
	Visit 15 Day 686	Week 98/ Week 86 OLE	595 days after 1 st OLE dosing day	From 515 days after 1 st OLE dosing day to 640 days after 1 st OLE dosing day
	Visit 16 Day 777	Week 111/ Week 99 OLE	686 days after 1 st OLE dosing day	From 641 days after 1 st OLE dosing day to 766 days after 1 st OLE dosing day
	Visit 17 Day 938	Week 134/ Week 122 OLE	847 days after 1 st OLE dosing day	>=767 days after 1 st OLE dosing day
Vital sign and clinical lab	Visit 7 Day 91	Week 13/ Week 1 OLE	1 st OLE dosing day	From 1 st OLE dose to 38 days after 1 st OLE dosing day
	Visit 9 Day 168	Week 24/ Week 1 OLE	77 days after 1 st OLE dosing day	From 39 days after 1 st OLE dosing day to 119 days after 1 st OLE dosing day
	Visit 11 Day 252	Week 36/ Week 24 OLE	161 days after 1 st OLE dosing day	From 120 days after 1 st OLE dosing day to 206 days after 1 st OLE dosing day
	Visit 12 Day 343	Week 49/ Week 37 OLE	252 days after 1 st OLE dosing day	From 207 days after 1 st OLE dosing day to 297 days after 1 st OLE dosing day
	Visit 13 Day 434	Week 62/ Week 50 OLE	343 days after 1 st OLE dosing day	From 298 days after 1 st OLE dosing day to 388 days after 1 st OLE dosing day
	Visit 14 Day 525	Week 75/ Week 63 OLE	434 days after 1 st OLE dosing day	From 389 days after 1 st OLE dosing day to 514 days after 1 st OLE dosing day
	Visit 15 Day 686	Week 98/ Week 86 OLE	595 days after 1 st OLE dosing day	From 515 days after 1 st OLE dosing day to 640 days after 1 st OLE dosing day
	Visit 16 Day 777	Week 111/ Week 99 OLE	686 days after 1 st OLE dosing day	From 641 days after 1 st OLE dosing day to 766 days after 1 st OLE dosing day

	Visit 17 Day 938	Week 134/ Week 122 OLE	847 days after 1 st OLE dosing day	From 767 days after 1 st OLE dosing day to 861 days after 1 st OLE dosing day
	Visit 18 Day 966	Week 138/ Week 126 OLE	875 days after 1 st OLE dosing day	>=862 days after 1 st OLE dosing day
Pregnancy Test	Visit 7 Day 91	Week 13/ Week 1 OLE	1 st OLE dosing day	From 1 st OLE dose to 38 days after 1 st OLE dosing day
	Visit 9 Day 168	Week 24/ Week 12 OLE	77 days after 1 st OLE dosing day	From 39 days after 1 st OLE dosing day to 119 days after 1 st OLE dosing day
	Visit 11 Day 252	Week 36/ Week 24 OLE	161 days after 1 st OLE dosing day	From 120 days after 1 st OLE dosing day to 206 days after 1 st OLE dosing day
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	Visit 18 Day 966	Week 138/ Week 126 OLE	875 days after 1 st OLE dosing day	>=862 days after 1 st OLE dosing day
ECG, PK	Visit 7 Day 91	Week 13/ Week 1 OLE	1 st OLE dosing day	From 1 st OLE dose to 38 days after 1 st OLE dosing day
	Visit 9 Day 168	Week 24/ Week 12 OLE	77 days after 1 st	From 39 days after 1 st OLE dosing day to 119 days after 1 st OLE dosing day

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