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Statistical Analysis Plan

A Phase 1, Investigator- and Participant-blinded, Placebo-Controlled, Randomized, Crossover Study to Assess the Relative Bioavailability of Two Formulations of AQ280 in Healthy Participants

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LIST OF ABBREVIATIONS

Abbreviations pertain to the SAP only (not the TFLs).

AUC	area under the concentration time curve
AUC ₀₋₂₄	area under the concentration-time curve over the time interval 0 to 24 hours postdose
AUC _{0-∞}	area under the concentration time curve from time 0 extrapolated to infinity
AUC _{0-tlast}	area under the concentration time curve from time 0 to the time of the last quantifiable concentration
ADaM	analysis data model
AE	adverse event
BLQ	below the limit of quantification
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CL/F	apparent total clearance
C _{max}	maximum observed concentration
CSR	clinical study report
CV	coefficient of variation
DAUC ₀₋₂₄	AUC ₀₋₂₄ normalized by dose administered
DAUC _{0-∞}	AUC _{0-∞} normalized by dose administered
DAUC _{0-tlast}	AUC _{0-tlast} normalized by dose administered
DC _{max}	C _{max} normalized by dose administered
DMP	data management plan
ECG	electrocardiogram
eCRF	electronic case report form
F _{rel}	relative bioavailability
F _{rel, AUC0-∞}	relative bioavailability of tablet for solution versus capsule based upon AUC _{0-∞}
F _{rel, Cmax}	relative bioavailability tablet for solution versus capsule based upon C _{max}
GLSM	geometric least squares mean
ICH	International Council for/Conference on Harmonisation
ln	natural log
LSM	least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)

R^2 -adj	adjusted coefficient for determination of exponential fit
SAP	statistical analysis plan
SD	standard deviation
SDV	source document verification
$t_{1/2}$	apparent terminal elimination half life
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
t_{last}	time of the last quantifiable concentration
t_{max}	time of the maximum observed concentration
V_z/F	apparent volume of distribution during the terminal phase
WHODrug	World Health Organization Drug Dictionary
λ_z	apparent terminal elimination rate constant
λ_z Lower	start of exponential fit
λ_z N	number of data points included in the log-linear regression
λ_z Span Ratio	time period over which λ_z was determined as a ratio of $t_{1/2}$
λ_z Upper	end of exponential fit

1. INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version 3 dated 08 May 2025), Letter of Administrative Change dated 15 May 2025 and eCRF.

This SAP describes the planned analysis of the PK, PD, safety, and tolerability data from this study. A detailed description of the planned TFLs to be presented in the CSR is provided in the accompanying TFL shells document.

In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Aqilion AB. A limited amount of information about this study (eg, objectives, study design) is given to help the reader's interpretation.

This SAP must be finalized prior to any unblinding of study data for analysis purposes (interim or final). Additionally, the SAP and TFL shells should be finalized prior to any programming activities commencing.

This SAP supersedes any statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified accordingly in the CSR. Any substantial deviations from this SAP will be agreed with Aqilion AB and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the ICH E3 guideline *Structure and Content of Clinical Study Reports*, ICH E8 guideline *General Considerations for Clinical Trials*, and ICH E9 guideline *Statistical Principles for Clinical Trials*.^{1,2,3}

The document history is presented in [Appendix 1](#).

2. STUDY OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary	
To assess the relative bioavailability of single oral doses of 100 mg AQ280 capsule formulation and 100 mg AQ280 tablet for oral suspension formulation in healthy participants	Primary PK parameters: F_{rel} , $AUC_{0-\infty}$, $AUC_{0-tlast}$, and C_{max} Additional PK parameters: t_{max} , $t_{1/2}$, CL/F , and V_z/F

Objective	Endpoint
Secondary	
To assess the safety and tolerability of single oral doses of 100 mg AQ280 capsule formulation and 100 mg AQ280 tablet for oral suspension formulation in healthy participants	Incidence and severity of adverse events
	Incidence of laboratory abnormalities, based on hematology, clinical chemistry, and urinalysis test results
	12-lead electrocardiogram parameters
	Vital signs measurements
	Physical examinations
Exploratory	
To assess the PD response to AQ280 after single oral doses	CCI

3. STUDY DESIGN

This will be a Phase 1, investigator- and participant-blinded, placebo-controlled, randomized, crossover study.

Up to 8 participants will be randomly assigned to study intervention, for an estimated total of 6 PK-evaluable participants.

Potential participants will be screened to assess their eligibility to enter the study within 35 days prior to first dose administration.

On Day 1 of Treatment Period 1, participants will be randomized to 1 of 4 intervention sequences (Table 1), such that, 2 participants will receive placebo and 6 participants will receive AQ280 and half of participants will receive the capsule formulation in Treatment Period 1 followed by the tablet for oral suspension formulation in Treatment Period 2 whilst the other half of the participants will receive the tablet for oral suspension in Treatment Period 1 followed by the capsule formulation in Treatment Period 2.

Table 1: Intervention Sequences

Intervention Sequence	Number of Participants	Treatment Period 1	Treatment Period 2
1	1	PBO Capsule (A)	PBO Tablet for Oral Suspension (B)
2	1	PBO Tablet for Oral Suspension (B)	PBO Capsule (A)
3	3	AQ280 Capsule (A)	AQ280 Tablet for Oral Suspension (B)

Intervention Sequence	Number of Participants	Treatment Period 1	Treatment Period 2
4	3	AQ280 Tablet for Oral Suspension (B)	AQ280 Capsule (A)

Abbreviations: PBO = placebo

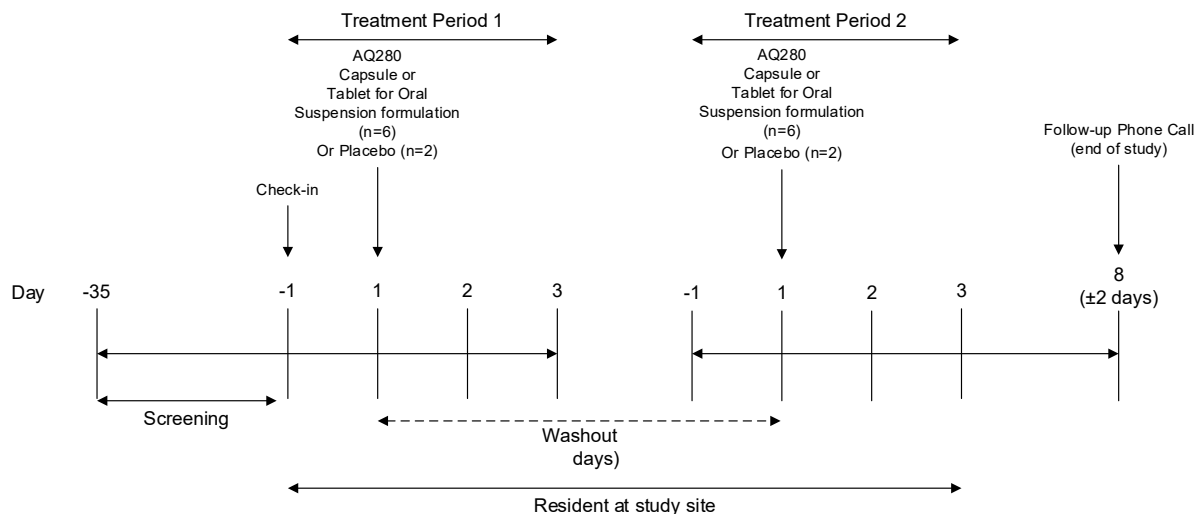
There will be a washout period of at least 5 days between dose administrations.

Participants will reside at the study site from check-in on Day -1 of Treatment Period 1 to Day 3 of Treatment Period 2 and will receive a follow-up (end of study) phone call 7 (± 2) days after their final dose. Participants may be requested to return to the study site for a follow-up visit, if clinically indicated during the follow-up phone call, for the assessment of any new or ongoing adverse events which require further investigation (ie, vital signs, clinical laboratory tests, ECG, physical examination).

The total duration of study participation for each participant (from screening through end of study) is anticipated to be up to approximately 7 weeks.

A schematic of the study design is presented in [Figure 1](#).

Figure 1: Study Schema



4. SAMPLE SIZE JUSTIFICATION

A total of 8 participants will be randomly assigned to study intervention, such that 6 PK evaluable participants will complete the study.

No formal statistical assessment of sample size has been conducted. However, the number of participants is common in early clinical pharmacology studies and is considered sufficient to achieve the objectives of the study.

5. TREATMENTS

The treatment names and ordering to be used in the TFLs are presented in [Table 2](#).

Table 2: Presentation of Treatments in TFLs

Treatment	Order in TFLs
100 mg Placebo	1
100 mg AQ280 Capsule	2
100 mg AQ280 Tablet for Oral Suspension	3

All TFLs will be based on actual treatments (eg, if participant was assigned to receive placebo but was wrongfully dosed with active treatment they would be summarized and listed under active treatment). Placebo will be pooled across participants and periods.

The treatment sequence names and ordering to be used in the TFLs are presented in [Table 3](#).

Table 3: Presentation of Treatment Sequences in TFLs

Treatment Sequence	Order in TFLs
100 mg Placebo Capsule / 100 mg Placebo Tablet for Oral Suspension	1
100 mg Placebo Tablet for Oral Suspension / 100 mg Placebo Capsule	2
100 mg AQ280 Capsule / 100 mg AQ280 Tablet for Oral Suspension	3
100 mg AQ280 Tablet for Oral Suspension / 100 mg AQ280 Capsule	4

The summaries will be based on planned treatment sequences and listings will be based on actual treatment sequences.

Handling of underdosing and/or overdosing cases will be decided on individual basis and with agreement from Aqilion AB.

6. ANALYSIS SETS

Any protocol deviations will be considered prior to database lock for their importance and taken into consideration when assigning participants to analysis sets.

The analysis sets are described in [Table](#) .

Table 4: Analysis Sets

Set	Description
All Participants	All participants who signed the informed consent form and had any study assessments recorded in the database, as per protocol.
Safety	All participants who received at least 1 dose of study intervention (AQ280 or placebo). Participants will be analyzed according to the study intervention they actually received.

Set	Description
Pharmacokinetic	All participants who received at least 1 dose of study intervention (AQ280) and have at least 1 valid pharmacokinetic concentration.
Pharmacodynamic	All participants who received at least 1 dose of study intervention (AQ280 or placebo) and have at least 1 valid postdose pharmacodynamic assessment.

7. STATISTICAL METHODOLOGY

7.1. General

Listings will include all participants assigned to the all participants analysis set and include data up to the point of study completion or discontinuation. Any participant who discontinues the study early will be identified accordingly in the listings. Summaries and statistical analyses will include the participants assigned to the relevant analysis set based on data type.

Data analysis will be performed using the SAS[®] statistical software package Version 9.4 (or higher if a new version is issued during the study).

The ADaM datasets will be prepared using CDISC ADaM Version 2.1 (or higher if a new version is issued during the study) and CDISC ADaM Implementation Guide Version 1.3 (or higher if a new version is issued during the study). Pinnacle 21 Community Validator Version 4.1.0 (or higher if a new version is issued during the study) will be utilized to ensure compliance with CDISC standards.

Where reference is made to ‘valid’ data, this refers to non-missing data which meet the predetermined criteria (eg, are not flagged for exclusion).

Where reference is made to ‘all calculations’, this includes, but is not limited to, summary statistics, statistical analyses, baseline derivation, changes from baseline, and any parameter derivations.

All figures will be produced on linear-linear or discrete-linear scales, as applicable, unless specifically stated otherwise.

7.1.1. Calculation of the Summary Statistics

For continuous data the following rules will be applied:

- Missing values will not be imputed, unless specifically stated otherwise.
- Unrounded data will be used in the calculation of summary statistics.
- If the number of participants with valid observations (n) < 3 , summary statistics will not be calculated, with the exception of n , minimum, and maximum.

- In general, as early termination data are not associated with any scheduled timepoint, they will be excluded from all calculations of summary statistics. Exceptions may be made where justified.

For categorical data the following rules will be applied:

- For ordered categorical data (eg, AE severity), all categories between the possible minimum and maximum categories will be included, even if $n = 0$ for a given category.
- For non-ordered categorical data (eg, race), only those categories for which there is at least 1 participant represented will be included, unless specifically stated otherwise.
- Missing values will not be imputed, unless specifically stated otherwise. A ‘missing’ category will be included for any parameter for which information is missing. This will ensure that the analysis set size totals are consistent across different parameters.

7.1.2. Triplicate Readings

For 12-lead ECG data only, where triplicate readings are taken, the longest value of triplicate readings will replace the separate individual triplicate readings in all calculations.

7.1.3. Repeat and Unscheduled Readings

For vital signs and 12-lead ECG data only, if a value is recorded in addition to the original value, it will be classed as ‘Repeat’ only if it is recorded after the original predose value and before dosing or within 15 minutes of the original postdose value; in all other cases it will be defined as an unscheduled value. For all other data types (eg, laboratory parameters), any value recorded in addition to the original value will be defined as an unscheduled value.

The original value will be replaced by the last associated repeat value in all calculations.

As unscheduled values are not associated with any scheduled timepoint, they will be excluded from all calculations, with the exception of the baseline derivation (see Section 7.1.4). Exceptions may be made where justified.

7.1.4. Definitions of Baseline and Change from Baseline

Baseline will be defined as the last value recorded prior to dosing in each period. If the date/time of the value is incomplete or missing, it will be excluded from the baseline calculation, unless the incomplete date/time indicates the value was recorded prior to dosing in each period.

Individual changes from baseline will be calculated by subtracting the individual participant’s baseline value from the value at the postdose timepoint.

The summary statistics for change from baseline will be derived from individual participants’ values (eg, mean change from baseline will be the mean of the individual changes from

baseline for all participants, rather than difference between the mean value at the postdose timepoint and mean value at baseline).

See Section 7.1.3 for more detail on handling repeat and unscheduled readings in the calculations. See Section 7.1.2 for more detail on handling of triplicate readings in the calculations.

7.2. Participant Disposition and Analysis Set Assignment

Participant disposition and analysis set assignment will be listed.

A summary table by treatment sequence will be provided, based on the safety analysis set.

7.3. Screening Demographics

The screening demographics including age, sex, race, ethnicity, height, body weight, and body mass index will be listed.

A summary table by treatment sequence will be provided, based on the safety analysis set.

7.4. Prior and Concomitant Medication

Prior medication will be defined as medication that ends prior to dosing. Concomitant medication will be defined as medication that starts during or after dosing or starts but does not end prior to dosing.

Prior and concomitant medications will be coded using the WHODrug Global, Format B3, Version March 2025 (or later if a new version is issued during the study; see the DMP for more details). Prior and concomitant medications will be listed.

7.5. Pharmacokinetic Assessments

7.5.1. Pharmacokinetic Analysis

The following PK parameters will be determined where possible from the plasma concentrations of AQ280 using noncompartmental methods in validated software program Phoenix WinNonlin (Certara, Version 8.3.5 or higher):

Parameter	Units ^a	Definition
AUC _{0-t_{last}}	ng*h/mL	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (t _{last}) (Part A and Day 1 of Part B only) ^b
AUC ₀₋₂₄	ng*h/mL	area under the concentration-time curve over the time interval 0 to 24 hours postdose ^b
AUC _{0-∞}	ng*h/mL	area under the concentration-time curve from time 0 extrapolated to infinity ^c (Part A and Day 1 of Part B only)

$\%AUC_{extrap}$	%	percentage of area under the concentration-time curve due to extrapolation from the last quantifiable concentration to infinity (Part A and Day 1 of Part B only)
C_{max}	ng/mL	maximum observed concentration
t_{max}	h	time of the maximum observed concentration
t_{last}	h	time of the last quantifiable concentration
$t_{1/2}$	h	apparent terminal elimination half-life
CL/F	L/h	apparent total clearance (AQ280 only)
V_z/F	L	apparent volume of distribution during the terminal phase (AQ280 only)
$F_{rel, AUC0-\infty}$	%	relative bioavailability of tablet for suspension versus capsule based upon $AUC_{0-\infty}$
$F_{rel, C_{max}}$	%	relative bioavailability tablet for suspension versus capsule based upon C_{max}
$DAUC_{0-t_{last}}$	ng*h/mL/mg	$AUC_{0-t_{last}}$ normalized by dose administered ^d
$DAUC_{0-24}$	ng*h/mL/mg	AUC_{0-24} normalized by dose administered ^d
$DAUC_{0-\infty}$	ng*h/mL/mg	$AUC_{0-\infty}$ normalized by dose administered ^d
DC_{max}	ng/mL/mg	C_{max} normalized by dose administered ^d .

^a Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.

^b The AUC will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations (linear up/log down rule).

^c Based on the last observed quantifiable concentration

^d Calculated by dividing the parameter by the dose (mg)

Additional PK parameters may be determined where appropriate.

Pharmacokinetic analysis will be carried out where possible using actual dose administered (mg) and actual postdose blood sampling times. If an actual time is missing, the sample concentration result will be treated as missing unless there is scientific justification to include the result using the nominal time.

The parameters C_{max} , t_{last} , and t_{max} will be obtained directly from the concentration-time profiles. If C_{max} occurs at more than 1 timepoint, t_{max} will be assigned to the first occurrence of C_{max} .

The parameter $AUC_{0-t_{last}}$ or other common partial area may be used for the determination and statistical analysis of $F_{rel, AUC0-\infty}$ if $AUC_{0-\infty}$ cannot be reliably calculated for the majority of subjects.

7.5.1.1. Criteria for the Calculation of Apparent Terminal Elimination Rate Constant and Half-life

The start of the terminal elimination phase for each subject will be defined by visual inspection. Generally, the first point at which there is no systematic deviation from the log

linear decline in concentrations will be selected as the start time to include only the apparent terminal elimination phase in the slope selection.

The apparent terminal elimination rate constant (λ_z) will only be calculated when a reliable estimate can be obtained using at least 3 data points, preferably not including C_{\max} , and the adjusted coefficient for determination of exponential fit (R^2 -adj) of the regression line is ≥ 0.7 . Parameters requiring λ_z for their calculation (eg, $AUC_{0-\infty}$, $t_{1/2}$, CL/F , V_z/F , and V_{ss}/F) will only be calculated if the R^2 -adj value of the regression line is ≥ 0.7 .

The following regression-related diagnostic PK parameters will be determined, when possible:

Parameter	Units	Definition
λ_z	1/h	apparent terminal elimination rate constant
λ_z Upper	h	end of exponential fit
λ_z Lower	h	start of exponential fit
λ_z N	NA	number of data points included in the log-linear regression
λ_z Span Ratio	NA	time period over which λ_z was determined as a ratio of $t_{1/2}$
R^2 -adj	NA	adjusted coefficient for determination of exponential fit

Where possible, the span of time used in the determination of λ_z (ie, the difference between λ_z Upper and λ_z Lower) should be ≥ 2 half-lives. If the λ_z Span Ratio is < 2 , the robustness of the $t_{1/2}$ values will be discussed in the CSR.

7.5.1.2. Criteria for Calculation and Reporting of Area Under the Concentration-time Curve

The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive concentrations above the lower limit of quantification. If there are only 3 consecutive concentrations, at least 1 should follow C_{\max} .

If the extrapolated area is $> 20\%$, $AUC_{0-\infty}$ (and derived parameters such as $\%AUC_{\text{extrap}}$, CL/F , V_z/F , F_{rel} , $AUC_{0-\infty}$) may be excluded from the summary statistics and statistical analysis at the discretion of the sponsor or pharmacokineticist.

7.5.1.3. Criteria for Handling Concentration Below the Limit of Quantification or Missing Concentrations for Pharmacokinetic Analysis

Plasma concentrations below the limit of quantification (BLQ) will be assigned a value of 0 before the first measurable concentration and thereafter BLQ concentrations will be treated as missing. The following rules apply to the specific situations defined below:

- If an entire concentration-time profile is BLQ, it will be excluded from PK analysis.

- Where 2 or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and any further quantifiable concentrations will be set to missing for the calculation of the PK parameters, unless they are considered to be a true characteristic of the profile of the drug.
- If a predose plasma concentration is missing, it will be set to 0 by default within Phoenix WinNonlin.

7.5.1.4. Treatment of Outliers in Pharmacokinetic Analysis

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude the value from the PK analysis. However, the exclusion of any data must have strong justification and will be documented in the CSR.

Any quantifiable predose concentration value in the first treatment period will be considered anomalous and set to missing for the PK analysis. This will be set to 0 by default in Phoenix WinNonlin.

If the predose concentration is $>5\%$ of C_{\max} in the second treatment period, all PK concentration and parameter data may be excluded from the summary statistics and statistical analysis for that period.

Concentration from the second treatment period may be corrected if the predose concentration is quantifiable, using the method, where t is the elapsed time following the second dose.

$$C_{t,\text{corrected}} = C_{t,\text{observed}} - C_{\text{predose}} e^{-\lambda_z t}$$

7.5.2. Presentation of Pharmacokinetic Data

All PK concentrations and parameters will be listed.

Summary tables, arithmetic mean (+SD) figures, overlaying individual figures, and individual figures by treatment and time postdose will be provided for plasma PK concentrations. All figures will be produced on both linear-linear and linear-logarithmic scales. The +SD bars will only be displayed on the linear-linear scale.

Summary tables by treatment will be provided for all PK parameters, with the exception of diagnostic regression-related PK parameters.

If the actual time of sample collection deviates from the nominal time by more than $\pm 10\%$, the plasma concentration will be flagged and excluded from the summary statistics.

Individual concentrations deemed to be anomalous will be flagged in the listings and excluded from the summary statistics.

For plasma concentration data the following rules will apply:

- Values that are BLQ will be set to 0 for the calculation of summary statistics.
- Arithmetic mean or median values that are BLQ will be presented as 0.

For PK parameters the following rule will apply:

- Geometric mean and coefficient of variation will not be calculated for, t_{last} or t_{max} .

7.5.3. Pharmacokinetic Statistical Methodology

A statistical analysis will be conducted to investigate the relative bioavailability of 100 mg AQ280 Tablet for oral suspension (test treatment) to 100 mg AQ280 Capsule (reference treatment).

The ln-transformed⁴ $AUC_{0-t_{last}}$, $AUC_{0-\infty}$, and C_{max} (for plasma AQ280) will be analyzed using a mixed model.⁵ The model will include planned treatment sequence, period, and actual treatment as fixed effects, and participant within planned treatment sequence as a random effect.

For each PK parameter separately, the LSM for each treatment, difference in LSMs between the test and reference treatments, and corresponding 90% CI will be calculated; these values will then be back-transformed to give the GLSM, ratio of GLSMs, and corresponding 90% CI.

Additionally, the pooled estimate (across treatments) of the within-participant CV will be calculated, and residual plots will be produced to assess the adequacy of the model fitted.

Examples of the SAS code that will be used are as follows:

Mixed Model Analysis

```
proc mixed data = <data in>;  
  by parcatln parcatl paramn param;  
  class trtan aperiod trtseqp usubjid;  
  model lpk = trtan aperiod trtseqp / cl residual ddfm = kr2;  
  lsmeans trtan / cl pdiff = control('1') alpha = 0.1;  
  random intercept / subject = usubjid(trtseqp);  
  ods output lsmeans = <data out>;  
  ods output diffs = <data out>;  
  ods output covparms = <data out>;  
run;
```

7.6. Pharmacodynamic Assessments

7.6.1. Pharmacodynamic Parameters

Pharmacodynamic parameters (CCI [REDACTED]) and relative change from baseline will be listed and summarized. No formal statistical analysis of PD data is planned.

7.6.2. Presentation of Pharmacodynamic Data

All PD parameters and their relative changes from baseline will be listed.

Summary tables and mean figure by treatment and timepoint will be provided for all PD parameters and their relative changes from baseline.

Values recorded as $<x$, $\leq x$, $>x$, or $\geq x$ will be displayed in the listings as recorded. For the derivation of listing flags, all calculations, and presentation in the figures, $<x$ and $\leq x$ values will be set to half of x , whereas $>x$ and $\geq x$ values will be set to x .

7.7. Safety and Tolerability Assessments

7.7.1. Adverse Events

All AEs will be coded using the MedDRA Version 28.0 (or higher if a new version is issued during the study; see the DMP for more details).

A TEAE will be defined as an AE that starts during or after dosing or starts prior to dosing and increases in severity after dosing.

A treatment-related TEAE will be defined as a TEAE with a relationship of possibly related, or related to the treatment, as determined by the investigator.

All AEs will be listed. In addition to the data recorded in the database, the listings will include derived onset time and duration. Onset time will be calculated from the time of dosing for TEAEs only.

The frequency of participants with TEAEs and the number of TEAEs will be summarized for the following categories:

- TEAEs (overall, serious, leading to discontinuation, and leading to death) by treatment
- TEAEs by severity and treatment
- Treatment-related TEAEs (overall, serious, leading to discontinuation, and leading to death) by treatment
- Treatment-related TEAEs by severity and treatment

The frequency of participants will be summarized separately for TEAEs and treatment-related TEAEs by the following:

- System organ class, preferred term, and treatment
- Preferred term and treatment

For the AE data the following rules will apply:

- For the derivation of treatment-emergent status (applicable to all AEs): If the start date/time of an AE is incomplete or missing, an AE will be assumed to be a TEAE, unless the incomplete start date/time or the end date/time indicates an AE started prior to dosing.
- For the derivation of treatment-related status (applicable to TEAEs only): If the treatment relationship for a TEAE is missing, a TEAE will be assumed to be a treatment-related TEAE.
- For the derivation of onset time (applicable to TEAEs only): If the start date/time of a TEAE is missing, onset time will not be calculated. If the start date/time of a TEAE is incomplete, where possible, the minimum possible onset time will be calculated and presented in '≥DD:HH:MM' format (eg, if the date/time of dosing is 01MAY2019/08:00 and recorded start date/time of a TEAE is 03MAY2019, then the minimum possible onset time will be calculated by assuming a TEAE started at the first hour and minute of 03MAY2019 [03MAY2019/00:00], thus will be presented as onset time ≥01:16:00 in the listing). If the start date of a TEAE is the same as the date of dosing but the start time of a TEAE is missing, an onset time will be presented as '≥00:00:01'. If the start date/time of an AE is the same as date/time of dosing, an onset time will be presented as '<00:00:01'. Any clock changes will be accounted for in the derivation.
- For the derivation of duration (applicable to all AEs): If the end date/time of an AE is missing, duration will not be calculated. If the start or end date/time of an AE is incomplete, where possible, the maximum possible duration will be calculated and presented in '≤DD:HH:MM' format (eg, if the start of an AE date/time is 01MAY2019/08:00 and its recorded end date/time is 03MAY2019, then the maximum possible duration will be calculated by assuming an AE ended at the last hour and minute of 03MAY2019 [03MAY2019/23:59], thus will be presented as duration ≤02:15:59 in the listing). If the start date/time of an AE is the same as its end date/time, duration will be presented as '<00:00:01'. Any clock changes will be accounted for in the derivation.
- For the derivation of change in severity flag (applicable to all AEs): If a participant experienced consecutive AEs of different severity with the same preferred term for the same treatment, and end date/time of consecutive event is the same as start date/time of preceding event, they will be assumed to be a single AE that has changed in severity.
- For the calculation of TEAE summary statistics: If the severity of a TEAE is missing, that TEAE will be counted under the 'missing' category.
- For the calculation of TEAE summary statistics: If a participant experienced multiple TEAEs with the same preferred term for the same treatment, this will be counted as 1

TEAE for that treatment under the maximum severity recorded; this will be done separately for TEAEs and treatment-related TEAEs.

7.7.2. Clinical Laboratory Parameters

All clinical laboratory parameters will be listed; any value outside the clinical reference range will be flagged. Separate listings will be provided for any parameter for which there is any individual participant value outside the respective clinical reference range.

All recorded data will be listed, but only protocol-specified parameters will be included in summaries.

Values recorded as $<x$, $\leq x$, $>x$, or $\geq x$ will be displayed in the listings as recorded. For the derivation of listing flags, all calculations, and presentation in the figures, $<x$ and $\leq x$ values will be set to half of x , whereas $>x$ and $\geq x$ values will be set to x .

7.7.3. Vital Signs Parameters

All vital signs parameters and their changes from baseline, will be listed; any value outside the clinical reference range will be flagged.

Summary tables by treatment and timepoint will be provided for all vital signs parameters, their changes from baseline. Summary figures by treatment and timepoint will be provided for changes from baseline.

7.7.4. 12-lead Electrocardiogram Parameters

All 12-lead ECG parameters and their changes from baseline will be listed; any value outside the clinical reference range will be flagged.

Summary tables by treatment and timepoint will be provided for all 12-lead ECG parameters, their changes from baseline. Summary figures by treatment and timepoint will be provided for their changes from baseline of all 12-lead ECG parameters.

7.7.5. Other Assessments

All other assessments not detailed in the above sections will not be listed, except for protocol deviations, participant eligibility, medical history and dose administration information.

7.7.6. Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

8. INTERIM ANALYSES

No formal interim analyses are planned.

9. SIGNIFICANT CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

Protocol didn't define Pharmacodynamic Analysis Set. SAP added definition of Pharmacodynamic Analysis Set in Section 6.

10. REFERENCES

1. ICH. ICH Harmonised Tripartite Guideline: Structure and content of clinical study reports (E3). 30 November 1995.
2. ICH. ICH Harmonised Tripartite Guideline: General considerations for clinical trials (E8). 17 July 1997.
3. ICH. ICH Harmonised Tripartite Guideline: Statistical principles for clinical trials (E9). 5 February 1998.
4. Keene ON. The log transformation is special. *Stat Med*. 1995;14(8):811-819.
5. Brown H, Prescott R. *Applied Mixed Models in Medicine*. Chichester: John Wiley & Sons, 1999.

11. APPENDICES

Appendix 1: Document History

Status and Version	Date of Change	Summary/Reason for Changes
Final Version 1.0	NA	NA; the first version.

NA = not applicable