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Biostatistics & Statistical Programming /
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KAE609

CKAE609X2111 / NCT04321252

A randomized, subject and investigator-blinded, placebo controlled, single and multiple ascending dose study to assess the safety, tolerability, and pharmacokinetics of KAE609 administered intravenously in healthy subjects

Statistical Analysis Plan (SAP)

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1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial **"CKAE609X2111".**

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

1.2 Study reference documentation

Final study protocol (v02) and site operation manual (SOM v01) are available at the time of finalization of the original Statistical Analysis Plan.

1.3 Study objectives

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the safety and tolerability of single and multiple iv doses of KAE609 in healthy subjects	• Adverse events, physical examination findings, vital signs, ECG findings (including QTcF), safety laboratory assessments including chemistry, hematology, and urinalysis results
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the pharmacokinetics (PK) of single and multiple iv doses of KAE609 in healthy subjects	• AUC, Tmax, Cmax, CL, Vz, and T1/2
• To assess local tolerance at infusion site of KAE609 iv administration	• Findings of physical examination of infusion site

1.4 Study design and treatment

This is a randomized, subject and investigator-blinded, placebo-controlled, single and multiple ascending iv dose study in healthy subjects. The study consists of two parts and the study scheme is shown in Figure 1-1:

- Part A is a single ascending dose (SAD) study with 5 cohorts of 8 subjects each
- Part B is a multiple ascending dose (MAD) study with 2 cohorts of 9 subjects each

For both parts of the study, each subject will participate in an up to 28- day screening period during which a full physical examination, medical history, drug screening, vital signs, ECG evaluation and safety laboratory tests evaluation will be performed.

A review of safety and PK data will be conducted at the completion of each cohort prior to dosing of the next subsequent cohort. Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, urinalysis) adverse event and serious adverse event monitoring.

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Part A: Single-ascending dose study

In Part A sequential cohorts of 8 healthy subjects per cohort will be randomized to receive successively higher single iv doses of KAE609 or matching placebo. In each cohort, subjects will be randomized in a 3:1 ratio to KAE609 (6 subjects/cohort) or matching placebo (2 subjects/cohort). Four planned dose cohorts will be included in Part A (A1, A2, A3 and A4).

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Figure 1-2 Study design - SAD

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Part B: Multiple-ascending dose study

In Part B sequential cohorts of 9 healthy subjects per cohort will be randomized to receive successively higher iv doses of KAE609 or matching placebo. Two planned dose cohorts will be included in Part B (B1 and B2). For Cohort B1, healthy subjects will receive a 60 mg dose of KAE609 or matching placebo iv q24h for 5 days. . For Cohort B2, healthy subjects will receive a 120 mg dose of KAE609 or matching placebo iv q24h for 5 days. In each cohort, subjects will be randomized in a 2:1 ratio to KAE609 (6 subjects/cohort) or matching placebo (3 subjects/cohort).

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Figure 1-3 Study design - MAD

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2 First interpretable results (FIR)

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3 Interim analyses

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4 Statistical methods: Analysis sets

For subjects for which the actual treatment received does not match the randomized treatment, the treatment actually received will be used for the analysis.

The safety analysis set will include all subjects who received at least one dose of any study drug.

The PK analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and experienced no protocol deviations with relevant impact on PK data.

The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from PK analysis in case of these PDs:		
TRT01	Incorrect dose administered	Exclude subject from PK analysis set at pharmacokineticist discretion

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

5 Statistical methods for Pharmacokinetic (PK) parameters

The secondary objective is to evaluate the pharmacokinetics of single and multiple ascending iv doses of KAE609 in healthy subjects.

5.1 Variables

The pharmacokinetic parameters are described as follows and will be calculated separately from the KAE609 concentration data:

- Part A (SAD): Cmax, Tmax, AUClast, AUCinf, AUC0-t (AUC0-24), T1/2, Vss and CL
- Part B (MAD): Cmax, Tmax, AUC0-24h, T1/2 Day 1 and Cmax, Tmax, AUCtau (AUC0-24), AUClast, , T1/2, Vss and CL Commercially Confidential Information

5.2 Descriptive analyses

For each part, KAE609 plasma concentration data will be listed by subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, Commercially Confidential Information

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Commercially Confidential Information

PK parameters will be listed by subject. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and

maximum. An exception to this is Tmax where median, minimum and maximum will be presented.

5.3 Statistical model, assumptions and hypotheses

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5.3.1 Model checking procedures

Graphical check will be performed.

5.3.2 Graphical presentation of results

Arithmetic mean (SD) plasma concentration data will be plotted across time, with separate line types for each treatment.

Overlaying individual plasma concentration-time profiles will be generated.

Scatterplots of Cmax and AUC parameters versus dose will be created with the estimated power model curve overlaid.

6 Statistical methods for Pharmacodynamic (PD) parameters

Not applicable.

7 Statistical methods for safety and tolerability data

The primary objective of this study is to assess the safety and tolerability of single and multiple ascending iv doses of KAE609 in healthy subjects.

7.1 Variables

The primary safety and tolerability variables are adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements, as well as subject demographics, baseline characteristics, and treatment information.

7.2 Descriptive analyses

Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by part, treatment group and subject. Summary statistics will be provided by part and treatment group.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by part, treatment group and subject.

Treatment

Data for study drug administration (rescue medication) and concomitant therapies will be listed by part, treatment group and subject.

Vital signs

All vital signs data will be listed by treatment, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by part, treatment and visit/time.

ECG evaluations

All ECG data will be listed by treatment, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by part, treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment, subject, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing is provided presenting all parameters in a subject with any abnormal values. Summary statistics will be provided by part, treatment and visit/time.

Local tolerance at infusion site

Local tolerance at infusion site will be summarized by part and treatment group.

Adverse events

All information obtained on adverse events will be displayed by part, treatment and subject.
The number and percentage of subjects with adverse events will be tabulated by system organ class and preferred term with a breakdown by treatment, and separately by preferred term and treatment. A subject with multiple adverse events within a system organ class is only counted once towards the total of this system organ class and treatment.
The number and percentage of subjects with adverse events by maximum severity of adverse events will be tabulated by system organ class and preferred term with a breakdown by treatment.
The number and percentage of subjects with adverse events classified as related to study drug will be tabulated by system organ class and preferred term with a breakdown by treatment.
For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on all <on-treatment/treatment emergent> adverse events which are not serious adverse events and on all <on-treatment/treatment emergent> serious adverse events and SAE suspected to be related to

study treatment will be provided by system organ class and preferred term on the safety set population.
If for a same subject, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.
The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

Holter ECG data analysis

The relationship between change from baseline in time-matched QTcF and KAE609 plasma concentration will be explored using linear mixed effects modeling. Other ECG parameters (QT, QTcB, HR, PR interval and QRS) will be summarized. Data from the SAD and MAD parts of the study will be pooled for this assessment. The change from baseline in QTcF will be the dependent variable in the model, KAE609 plasma concentration will be a covariate, and time a categorical variable. A random intercept for each subject will be specified. Placebo subjects will be included in the analysis with a plasma concentration of 0. The placebo-corrected change from baseline in QTcF and the two-sided 90% confidence interval will be extracted from the model at the geometric mean maximum plasma concentration for each treatment.
A plot of raw QTcF change vs KAE609 plasma concentration will be presented together with the estimated slope and 90% Confidence Interval (CI) from the statistical model.

The analysis results for categorical outliers and T-wave morphology will be summarized in frequency tables with counts and percentages for both number of subjects and number of timepoints. For categorical outliers, the number of subjects (%) and timepoints will be determined by treatment group for the following:

- increase in QTcF from baseline of > 30 ms and > 60 ms
- absolute QTcF values > 500 ms
- PR change from baseline > 25% increase resulting in PR > 220 ms
- QRS change from baseline > 25% increase resulting in QRS > 120 ms
- heart rate change from baseline > 25% decrease resulting in heart rate < 50 beats per minute
- heart rate change from baseline > 25% increase resulting in a heart rate > 100 beats per minute

For T-wave morphology, the analysis will be focused on the treatment emergent changes.
A cardiac safety report will be prepared separately.

7.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameter) will be created.

8 Statistical methods for biomarker data

Not applicable.

9 Exploratory objectives

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