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Novartis Research and Development

KAE609

Clinical Trial Protocol 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

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study procedures. Note: The SOM will not be a part of the Clinical Study Report.

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List of abbreviations

CCI	Commercially Confidential Information
CCI	Commercially Confidential Information
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	Body Mass Index
BUN	blood urea nitrogen
CFR	U.S. Code of Federal Regulation
CK	creatinine kinase
CMO&PS	Chief Medical Office & Patient Safety
CNS	Central nervous system
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-reactive protein
CTA	Clinical trial application
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
ECG	Electrocardiogram
EDC	Electronic Data Capture
EEA	European economic area
EMA	European Medicines Agency
EOS	End of study
EU	European Union
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
h	hour
CCI	Commercially Confidential Information
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ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International Normalized Ratio

IRB	Institutional Review Board
iv	intravenous
LDH	lactate dehydrogenase
LFT	Liver function test
CCI	Commercially Confidential Information
MAD	Multiple ascending dose
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
PBPK	Physiologically Based Pharmacokinetic
PK	pharmacokinetic(s)
PT	prothrombin time
q24h	Dosing every 24 hours
QMS	Quality Management System
RBC	red blood cell(s)
SAD	Single ascending dose
SAE	serious adverse event
sCR	serum creatinine
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
ULN	upper limit of normal
WBC	white blood cell(s)
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study.
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject.
Cohort	A specific group of subjects fulfilling certain criteria.
Control drug	Any drug(s) (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial.
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day).
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up) which applies across all arms of a study.
Healthy subject	A person with no known significant health problems who volunteers to be a study participant.
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug,” "Investigational Medicinal Product," or “test substance”.
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment.
Screen Failure	A subject who is screened but is not treated or randomized.
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Study treatment	Any drug or combination of drugs administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy.
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date.
Subject	A trial participant (can be a healthy volunteer or a patient).
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.

Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study.
Withdrawal of consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer and does not allow any further collection of personal data.

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Protocol summary

Protocol number	CKAE609X2111
Full Title	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
Brief title	Study to assess safety, tolerability and pharmacokinetics of KAE609 administered intravenously in healthy subjects
Sponsor and Clinical Phase	Novartis Phase I
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to assess the safety and tolerability and pharmacokinetics of single and multiple ascending doses of KAE609 administered by iv infusion in healthy subjects, to support further clinical development of KAE609 in patients with severe malaria and to guide dose selection for future trials.
Primary Objective	The primary objective of this study is to assess the safety and tolerability of single and multiple iv doses of KAE609 in healthy subjects
Secondary Objectives	To assess the pharmacokinetics of single and multiple iv doses of KAE609 in healthy subjects To assess local tolerance at infusion site of KAE609 iv administration
Study design	This is an exploratory, randomized, subject and investigator-blinded, placebo-controlled, single and multiple ascending iv dose study in healthy subjects. The study consists of a single ascending dose part and a multiple ascending dose part. Eligible subjects will be randomized to receive a single or q24h x 5 doses of either KAE609 or placebo. Safety, tolerability and pharmacokinetics will be assessed over the period of 8 days for single dose and 12 days for multiple doses up to end of study visit for each subject.
Population	The study population will be comprised of healthy female and male subjects between the ages of 18 and 55 years inclusive. A total of approximately 58 subjects will be enrolled in the study and randomized to receive KAE609 or placebo treatment.
Key Inclusion criteria	• Healthy male and female subjects 18 to 55 years of age inclusive, and in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests. • Subjects must weigh at least 50 kg to participate in the study, and must have a body mass index (BMI) within the range of 18.0 – 30.0 kg/m^2.

Key Exclusion criteria	• Use of other investigational drugs within 5 half-lives of Screening, or within 30 days of dosing, whichever is longer; or longer if required by local regulations. • Significant illness which has not resolved within two (2) weeks prior to initial dosing. • Pregnant or nursing (lactating) women. • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant. • Sexually active males unwilling to use a condom during intercourse while taking investigational drug and for at least 2 weeks after last dose of investigational drug.
Study treatment	Single or multiple iv doses of: • KAE609 • Placebo
Pharmacokinetic assessments	• KAE609 plasma concentrations
Key safety assessments	• Adverse event monitoring • Physical examinations • Vital signs • Monitoring of laboratory markers in blood and urine • Holter monitoring and ECGs
Other assessments	Commercially Confidential Information
Data analysis	For each part safety and tolerability data will be descriptively summarized. The number and percentage of adverse events will be tabulated by body system and preferred term with a breakdown by treatment group. Separate tables and listings will be prepared presenting adverse event intensity (CTCAE grade) and relationship to study treatment. All data for vital signs, ECG evaluations, hematology, blood chemistry, and urinalysis will be summarized by part, treatment group and visit/time and any abnormalities will be listed by part, treatment group, subject and visit/time. KAE609 concentration data will be listed by part, treatment group, subject and visit/sampling time point. Descriptive summary statistics will be provided by part, treatment group and visit/sampling time point, which will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax for which median, minimum and maximum will be presented. Commercially Confidential Information
Key words	Safety, tolerability, pharmacokinetics, healthy volunteers, phase 1, Malaria, iv KAE609.

1 Introduction

1.1 Background

Malaria is a preventable and curable disease caused mainly by two protozoan parasites, *Plasmodium falciparum* and *Plasmodium vivax*. Globally, 3.3 billion people are at risk of malaria with an estimated 210 million cases and 584,000 deaths each year, mostly children under 5 years of age (World Health Organization 2015). 90% of malaria cases and 91% of malaria deaths occur in Africa, the vast majority in young children.

The majority of deaths occur after infection with *Plasmodium falciparum*. Malaria is an acute febrile illness. In an individual, who is not immune to malaria, symptoms usually appear 10–15 days after the infective mosquito bite. The first symptoms may be mild and difficult to recognize as malaria. They arise because of the blood stage parasitemia with consequent erythrocyte rupture that produces the acute symptoms (spiking fever, rigors, malaise, headache and muscle aches), vascular compromise and organ involvement that can result in complications if not rapidly treated. *P. falciparum* malaria can progress to severe illness and death.

Children with severe malaria frequently develop one or more of the following symptoms: severe anaemia, respiratory distress in relation to metabolic acidosis, or cerebral malaria. Also, in adults, multi-organ involvement is frequent. Thus, it is vital to initiate effective treatment shortly after diagnosis.

The World Health Organization (WHO) recommended treatment of severe malaria is artesunate administered either intravenously (iv) or intramuscularly (im) or quinine administered either iv or im. There are problems with both of these treatments. There are increasing reports of parasite resistance to artemisinins such as artesunate. Resistance has been detected in 5 countries of the Greater Mekong subregion: Cambodia, Lao People's Democratic Republic, Myanmar, Thailand and Vietnam (World Health Organization 2011). Studies have confirmed that artemisinin resistance has emerged independently in many areas of this subregion. Additionally preparation and administration of artesunate injection is complicated. Quinine has to be given by slow infusion because of the risk of cardiovascular side effects. In addition, quinine has lower efficacy than artesunate.

KAE609, a spiroindolone, represents a new class of potent, fast-acting, schizonticidal antimalarial drugs (White et al 2014). It appears to exert its antiplasmodial activity through deregulation of Na+ homeostasis in the parasite cytosol through the inhibition of a P-type non-SERCA ATPase, PfATP4.

KAE609 presents two possible advantages over existing antimalarial drugs for the treatment of severe malaria. Firstly, it is a novel antimalarial agent developed with a different mechanism of action to other marketed antimalarials and it shows activity against existing drug resistant parasites, including artemisinin resistance. Secondly, in early clinical studies, in which KAE609 was given by the oral route to patients with uncomplicated malaria, parasitemia was rapidly reduced Commercially Confidential Information In these studies parasitemia was reduced more rapidly with KAE609 than has been observed with any other marketed agents used to treat malaria (White 2017).

Because of its rapid clearance of parasites and a lack of known resistance, KAE609 is being progressed for the treatment of severe malaria. In severe malaria, reduction of parasite count is one of the top treatment goals and therefore achieving the effective concentration in the systemic circulation is important. In addition, many of the severe malaria patients will not be able tolerate or take oral treatment. Therefore, iv administration is considered most suitable route of administration for KAE609 in severe malaria.

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For more information, please refer to the latest edition of the Investigator's Brochure.

1.2 Purpose

The purpose of this study is to assess the safety and tolerability and pharmacokinetics (PK) of single ascending doses (SAD) and multiple ascending doses (MAD) of KAE609 administered by iv infusion in healthy subjects, to support further clinical development of KAE609 in patients with severe malaria and to guide dose selection for future trials.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

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

3 Study design

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 3-1:

- 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. Please also refer to Section 6.5.1 for more details on dose escalations. 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). Five planned dose cohorts will be included in Part A (A1, A2, A3, A4 and A5). Provisional dose levels are described in Section 6.5.1.2.

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For a detailed outline of safety and other assessments, please refer to Part A Assessment Schedule (Table 8-1). If added, any additional dose cohort will follow the same Part A Assessment Schedule.

Figure 3-2 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). Provisional dose levels are described in Section 6.5.1.2

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For a detailed outline of safety and other assessments, please refer to Part B Assessment Schedule (Table 8-2). Any additional cohort will follow the same Part B Assessment Schedule.

Figure 3-3 Study design - MAD

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4 Rationale

4.1 Rationale for study design

This is the first clinical study for KAE609 administered iv with the purpose of establishing safety, tolerability and pharmacokinetics in healthy subjects. The rationale for key design elements in this study include:

- **Healthy subjects:** Enrolling healthy subjects was chosen to reduce the risk of introducing confounding variables and to minimize the risk and severity of adverse events. This minimizes any underlying disease-related findings that may confound data interpretation that may exist, especially regarding transaminase elevations, which have been seen in patients with uncomplicated malaria treated with KAE609 and can be present in patients with severe malaria.
- **Randomization:** Helps to avoid possible bias in the selection and allocation of subjects.
- **Placebo comparator**: Use of a placebo helps assess if any safety or tolerability findings should be attributed to KAE609 and helps to maintain study blinding.
- **Blinding:** Blinding of subjects with limited un-blinding of investigators and sponsor minimizes bias in the conduct of the study. The Sponsor's clinical trial team will be blinded. Representatives of the Sponsor, such as the Translational Medicine Expert, may be only unblinded to facilitate safety-related decisions. Limited un-blinding of the investigators and sponsor (e.g., at the time of dose-escalation review) will be allowed if needed to help with safety-related decisions. The pharmacist at the CRO who prepares the injections will be unblinded.
- **Sequential cohorts**: This allows for an adequate safety and tolerability assessment prior to the initiation of each ascending dose.
- **Sentinel dosing**: No sentinel dosing is planned for this study. The predicted toxicities are monitorable and reversible. There is no expected effect on QT and no CNS toxicities expected in this study. A QT potential risk was seen in the hERG assay but no effect of oral KAE609 on QTcF has been observed in healthy subject or patient studies so far. Sentinel dosing is not likely to reduce the risk in this study.
- **Domiciliation:** Subjects will be domiciled before and during dosing and after last dosing to allow for close observation of safety and tolerability, and to ensure compliance with instructions for all subjects.

4.2 Rationale for dose/regimen and duration of treatment

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Following completion of each cohort, apart from safety, available PK data will be reviewed to confirm the predictions and to keep the exposure within the AUC and Cmax considered safe

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Starting dose

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Dose escalation

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Highest dose

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4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Placebo is selected as the comparator to strengthen the internal validity of the study, to account for non-specific study effects on read-outs, to allow for blinding of treatment arms, and to better ascertain relation of adverse events to drug treatment.

4.4 Purpose and timing of interim analyses/design adaptations

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4.5 Risks and benefits

This study will be conducted in healthy adult volunteers to demonstrate the safety and tolerability of iv KAE609 at levels beyond projected therapeutic doses. KAE609 has already been investigated by the oral route and as of 5-March-2019, 152 patients have been treated in phase 2 studies in patients with uncomplicated malaria. KAE609 is now being developed for iv administration for the treatment of severe malaria. This is the first study where it is being administered to humans by iv route. By the oral route, KAE609 has been shown to be safe and well tolerated up to single doses of 300 mg and 150 mg daily for 3 days in healthy subjects. In patients dosed up to 75 mg single dose and 50 mg daily up to 3 days oral, KAE609 rapidly cleared malaria parasites and was generally well tolerated. However, there is no clinical experience to date with the iv form.

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There is no benefit expected for subjects participating in this study. The risk to subjects in this trial (listed in Table 7-2 of the IB) will be minimized by adherence to the inclusion/exclusion criteria, stopping rules, close clinical monitoring (including multiple laboratory evaluations as per the Assessment Schedule), the sequential dose escalation and with PK and safety reviews between cohorts.

The COVID-19 pandemic does not impact the benefit/risk assessment for this study. No additional risks related to COVID-19 have been identified.

As is the case with any new compound in clinical development, there are unknown risks to KAE609 that may be serious and unforeseen.

4.5.1 Blood sample volume

A maximum of 200 mL of blood is planned to be collected over a period of 5 (Part A) or 6 weeks (Part B), from each subject as part of the study. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the Assessment Schedules (Table 8-1 and Table 8-2).

A summary blood log is provided in the Site Operations Manual (SOM). Instructions for all sample collection, processing, storage and shipment information is also available in the SOM and/or Instruction Manual.

See the Section 8.5.2.3 on the potential use of residual samples.

5 Population

The study population will be comprised of healthy females of non-child bearing potential and males between the ages of 18 and 55 years inclusive. A total of approximately 58 subjects will be enrolled in the study and randomized to receive KAE609 or placebo treatment. Up to 17 additional subjects in up to 2 additional cohorts may be randomized if additional SAD or MAD cohorts are deemed necessary.

The investigator must ensure that all subjects being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects.

Each inclusion and exclusion criterion specifies if the criterion should be assessed at screening and/or baseline. Pre-dose assessments on Day 1 are not considered for study eligibility. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from **any** entry criterion excludes a subject from enrollment into the study.

Refer to Section 9.1.1.1 for information on replacement subjects.

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

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2. Healthy male and female subjects 18 to 55 years of age inclusive and in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening.

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4. Subjects must weigh at least 50 kg to participate in the study, and must have a body mass index (BMI) within the range of 18.0 – 30.0 kg/m^2at screening [BMI = Body weight (kg) / [Height (m)]^2]

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5.2 Exclusion criteria

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2. Significant illness which has not resolved within two (2) weeks prior to initial dosing.

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19. Pregnant or nursing (lactating) women at screening.
20. Sexually active males, at screening, baseline and during the study, unwilling to use a condom during intercourse while taking investigational drug

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21. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, at screening.

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22. Use of other investigational drugs within 5 half-lives of Screening, or within 30 days of dosing, whichever is longer; or longer if required by local regulations

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6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and taking study treatment are outlined in the SOM and/or Pharmacy Manual.

Refer to the 'dietary restrictions and smoking' Section 6.2.3.1 for subjects' restrictions.

6.1.1 Investigational and control drugs

The investigational drug, KAE609 and the matching placebo will be prepared by Novartis and supplied as open labeled bulk medication to the unblinded site pharmacist (Table 6-1). An unblinded pharmacist or authorized designee is required to dispense the study drug. Drug will be administered at the clinical site by the study personnel in accordance with the specified study procedures.

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration		Sponsor (global or local)
KAE609 15mg/mL (2 mL vial)	Solution for Injection	Intravenous use	Open label bulk supply; vials	Sponsor global
Matching Placebo	Solution for Injection	Intravenous use	Open label bulk supply; vials	Sponsor global

6.1.2 Additional study treatments

No additional treatment beyond investigational drug and control drug are included in this trial.

6.1.3 Treatment arms/group

All dose levels are provisional with the exception of cohort A1 in Part A (SAD).

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6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded in the concomitant medications / significant non-drug therapies or procedures Case Report Forms from screening through the post study safety follow-up call. For further details on potential drug-drug interactions, see Investigator's Brochure.

6.2.2 Prohibited medication

Except for any medication which may be required to treat adverse events, no medication (including vitamins or herbal remedy) other than study treatment will be allowed from the date subject signs the informed consent until the post study safety follow-up call. In case of prior use of concomitant medication with long half-life additional time might be needed (e.g. less than 5 half-life between drug intake and screening or pharmacodynamic effect has not returned to normal). For further details on potential drug-drug interactions, see Investigator's Brochure.

Should a subject have an incidental and limited need for a medication to be taken within the restricted pre-dose timeframe (e.g. paracetamol/acetaminophen for a headache, etc.), the sponsor should be advised, as administration of any concomitant medication *may* require the subject to be withdrawn.

6.2.3 Restriction for study subjects

For the duration of the study, the subjects should be informed and reminded of the restrictions outlined in this section.

6.2.3.1 Dietary restrictions and smoking

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6.2.3.2 Other restrictions

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6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

The subject number assigned to a subject at screening remains the unique identifier for the subject throughout the study. For information on subject numbering, please see 'Subject numbering' section in the SOM.

6.3.2 Treatment assignment, randomization

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A randomization list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio.

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

If only single investigational site, then randomization will be in a sequential fashion using the randomization schedule. Randomization should only occur when all baseline data has been reviewed and eligibility is confirmed.

Follow the details outlined in the SOM regarding the process and timing of treatment assignment and randomization of subjects.

6.4 Treatment blinding

This is a subject and investigator-blinded study. Subjects will remain blinded to study treatment throughout the study, except where indicated below.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Site staff

With the exception of any unblinded site staff identified below, all site staff (including study investigator and study nurse) will be blinded to study treatment during treatment allocation and subject dosing.

Unblinding a single subject at site for safety reasons (necessary for subject management) will occur via an emergency system in place at the site.

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Drug product will be supplied in bulk, so an unblinded pharmacist who is independent of the study team will be required in order to maintain the blind. This unblinded pharmacist will receive a randomization list or treatment allocation cards from GCS with the appropriate treatment allocation numbers. Appropriate measures must be taken by the unblinded pharmacist to ensure that the treatment assignments are concealed from the rest of the site staff.

Trained site staff will be required to administer study treatment. Appropriate measures must be taken by the unblinded site staff to ensure that the treatment assignments are concealed from the rest of the site staff.

Sponsor staff or delegate

The following unblinded sponsor roles are required for this study:

- Unblinded field monitor(s)
- Unblinded clinical staff managing drug re-supply to site
- Unblinded sample analyst(s) (PK)

The unblinded field monitors are required to review drug accountability and allocation at site. The unblinded monitors are not provided with a randomization list directly but will be unblinded through review of source documentation compiled by the unblinded pharmacist, which details treatment allocation to individual subjects. The unblinded monitors will also be able to review the treatment allocation cards/randomization list provided to the unblinded pharmacist. The names of the unblinded monitor(s) are detailed in the monitoring plan.

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under blinded conditions unless otherwise allowed.

The study statistician will be able to access the full randomization list from the start of the study and is allowed to share unblinded information with the rest of the clinical trial team as appropriate for internal decision purposes, as outlined in Table 6-2. For example, unblinded summaries and unblinded individual data can be shared with the team whenever necessary.

The study statistician is also allowed to share treatment assignments with the investigator during dose escalation meetings CCI when knowledge of the treatment assignments could aid decision-making.

Study programmers and other personnel involved in study data analysis CCI are allowed to access treatment assignment information from the start of the study for the purpose of data analysis.

The clinical trial team is allowed to share unblinded results with other sponsor staff (e.g. decision boards) as required for internal decision making on the study or the project while the study is ongoing.

All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure except as described above.

Following final database lock all roles may be considered unblinded.

Table 6-2 Blinding levels

Role	Time or Event			
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	CCI dose escalation
Subjects/Patients	B	B	UI	B
Site staff	B	B	UI	B
Unblinded site staff (see text for details)	B	UI	UI	UI
Drug Supply and Randomization Office	UI	UI	UI	UI
Unblinded sponsor staff (see text for details)	B	UI	UI	UI
Statistician/statistical programmer/data analysts	UI	UI	UI	UI
All other sponsor staff not identified above	B	B	UI	UI

B Remains blinded

UI Allowed to be unblinded on individual patient level

6.5 Dose escalation and dose modification

For Part A (SAD) and Part B (MAD), safety data reviews will be performed after each dose level in order to decide about the progression to the next dose.

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6.5.1.1 Starting dose

Commercially Confidential Information Please see Section 4.2 for rational of dose selection and the pharmacy manual for additional details on the syringes to be used.

6.5.1.2 Provisional dose levels

Table 6-3 describes the starting dose and the dose levels that may be evaluated during this trial.

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6.6 Additional treatment guidance

6.6.1 Treatment compliance

In this study subjects will be dosed at the investigator's center by qualified members of the site staff. Details of each dose of study drug will be recorded in the CRF.

PK parameters (measures of treatment exposure) will be determined in all subjects treated with KAE609, as detailed in the Section 8.5.1.

6.6.2 Recommended treatment of adverse events

At present there is insufficient information to provide specific recommendations regarding treatment of adverse events. Should a subject have an incidental and limited need for a medication to be taken within the restricted pre-dose timeframe (e.g., ibuprofen for a headache, antibiotic prophylaxis prior to dental surgery, etc.), the sponsor should be advised, as administration of any concomitant medication may require the subject to be withdrawn.

Medication used to treat AEs must be recorded on the Concomitant Medications/Significant non-drug therapies CRF.

6.6.3 Emergency breaking of assigned treatment code

Emergency breaking of the assigned treatment code must only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. A complete sets of emergency code break cards is provided to Novartis - to be distributed to the investigators. All code break cards must be retained until the end of the study and returned to Novartis. They must be stored in a secure place but be accessible in case of emergency. The investigator will receive a code break card for each subject, with the details of study treatment covered by a removable, scratch-off cover. In an emergency, the scratch-off cover can be removed to determine the treatment. The scratch-off covers are not to be removed for any reason other than an emergency. When the investigator removes the scratch-off cover he/she must note the date, time, and reason for removing it and retain this information with the case report form documentation. The assigned treatment must not be recorded on the CRF. The investigator must also immediately inform the Novartis local monitor that the code has been broken.

It is the investigator’s responsibility to ensure that there is a dependable procedure in place to allow access to the code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- name
- subject number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

Where possible, subjects should continue with the follow-up visit as per Assessment Schedule (Table 8-1 and Table 8-2) after code break.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under the investigational and control drugs section (Section 6.1.1).

KAE609 will be administered to the subject at the study center via the following route of administration:

- iv bolus administration over approximately 2 min (cohorts A1, A2 and B1)
- iv infusion over approximately 10 min (cohorts A3, A4, A5 and B2)

Depending on emerging data of this study infusion duration might be adapted (for example infusion over 10 min instead of bolus injection).

See the SOM and Pharmacy Manual for further details.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will review the investigators/CRO proposed informed consent form to ensure it complies with the ICH E6 GCP guidelines and regulatory requirements and is considered appropriate for this study. Any further changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between Investigator's Brochure updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

Male subjects must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

Refer to the SOM for a complete list of ICFs included in this study.

8 Visit schedule and assessments

Assessment schedule lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the EOS visit will be performed. At this EOS visit, the adverse event and concomitant medications should be recorded on the CRF.

Specification and timing of each assessment are detailed in the protocol. The methods and recording of each assessment may be outlined in the SOM.

Table 8-1 Assessment Schedule, Part A - SAD

Epoch	Screening		Treatment Period										Post-Treatment Follow-Up					Post Study
Visit Name	Screening	Baseline	Treatment										Follow-up				EOS	Safety Contact
Days	-29 to -2	-1	1										2	3	4	6	8	30
Time (post-dose)	-	-	-1h[1]	0h	2min[2]	10min	30min	1h	3h	4h	6h	12h	24h	48h	72h	120h	-	-
Informed consent	X																	
CCI	CCI																	
Inclusion / Exclusion criteria	S	S																
Demography	X																	
Medical history/current medical conditions	X																	
CCI	CCI	CCI																
CCI	CCI																	
Physical examination	S	S											S				S	
Pregnancy test[3]	X	X															X	
Body height	X																	
Body weight	X	X															X	
Body temperature	X	X															X	

Epoch	Screening		Treatment Period										Post-Treatment Follow-Up					Post Study
Visit Name	Screening	Baseline	Treatment										Follow-up				EOS	Safety Contact
Days	-29 to -2	-1	1										2	3	4	6	8	30
Time (post-dose)	-	-	-1h[1]	0h	2min[2]	10min	30min	1h	3h	4h	6h	12h	24h	48h	72h	120h	-	-
12 lead Holter continuous ECG[8]			X															
ECG evaluation[4]	X	X	X			X	X	X	X		X	X	X				X	
Blood Pressure and Pulse Rate	X	X	X			X	X	X	X				X		X		X	
Drug administration record[7]				X														
Injection/infusion site observation			X		X		X											
Blood chemistry	X	X											X		X		X	
Hematology	X	X											X		X		X	
Urinalysis	X	X											X				X	
PK blood collection			X		X	X	X	X	X		X	X	X	X	X	X	X	
CCI			X															
CCI			X															
Inpatient		X	X															
Concomitant medications	X[10]																	
Adverse events/serious adverse events	X[10]																	

Epoch	Screening		Treatment Period										Post-Treatment Follow-Up					Post Study
Visit Name	Screening	Baseline	Treatment										Follow-up				EOS	Safety Contact
Days	-29 to -2	-1	1										2	3	4	6	8	30
Time (post-dose)	-	-	-1h[1]	0h	2min[2]	10min	30min	1h	3h	4h	6h	12h	24h	48h	72h	120h	-	-
Study completion information																	X	
Safety Follow up Call																		S

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
[1] Pre-dose
[2] Only collected/done in cohorts with bolus injection.
[3] Serum pregnancy test at screening and EOS visit. Urine pregnancy test at baseline. FSH testing at screening.
[4] 12 lead ECG. Triplicate measurements are required at Screening, Baseline and EOS and single ECG measurements at other timepoints.

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[10]AEs and concomitant medications will be captured in the eCRF through post study safety-follow up call

Table 8-2 Assessment Schedule, Part B - MAD

Epoch	Screening			Treatment Period																				Post-Treatment Follow-Up					Post Study
Visit Name	Screening	Baseline		Treatment																				Follow-up				EOS	Safety Contact
Days	-29 to -2	-1		1								2	3	4	5									6	7	8	10	12	35
Time (post-dose)	-	-	-1h[1]	0h	2min[2]	10min	30min	1h	3h	6h	12h	0h[1]	0h[1]	0h[1]	-1h	0h[1]	2min[2]	10min	30min	1h	3h	6h	12h	24h	48h	72h	120h	-	-
Informed consent	X																												
CCI	CCI																												
Inclusion / Exclusion criteria	S	S																											
Demography	X																												
Medical history/current medical conditions	X																												
CCI	CCI	CCI																											
CCI	S																												
Physical examination	S	S										S				S								S				S	
Pregnancy test[3]	X	X																										X	
Body height	X																												
Body weight	X	X																										X	

Epoch	Screening			Treatment Period																				Post-Treatment Follow-Up					Post Study
Visit Name	Screening	Baseline		Treatment																				Follow-up				EOS	Safety Contact
Days	-29 to -2	-1		1								2	3	4	5									6	7	8	10	12	35
Time (post-dose)	-	-	-1h[1]	0h	2min[2]	10min	30min	1h	3h	6h	12h	0h[1]	0h[1]	0h[1]	-1h	0h[1]	2min[2]	10min	30min	1h	3h	6h	12h	24h	48h	72h	120h	-	-
Body temperature	X	X										X				X								X				X	
12 lead Holter continuous ECG[8]			X												X														
ECG evaluation[4]	X	X	X			X	X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X				X	
Blood Pressure and Pulse Rate	X	X	X			X	X		X		X	X	X			X		X	X		X		X	X		X		X	
Drug administration record[7]				X								X	X	X		X													
Injection/infusion site observation			X				X									X			X										
Blood chemistry	X	X										X		X										X		X		X	
Hematology	X	X										X		X										X		X		X	
Urinalysis	X	X										X												X				X	
CCI			X																					X				X	
PK blood collection			X		X[5]	X[5]	X	X	X	X	X	X	X	X		X	X[5]	X[5]	X	X	X	X	X	X	X	X	X	X	X	

Epoch	Screening			Treatment Period																				Post-Treatment Follow-Up					Post Study
Visit Name	Screening	Baseline		Treatment																				Follow-up				EOS	Safety Contact
Days	-29 to -2	-1		1								2	3	4	5									6	7	8	10	12	35
Time (post-dose)	-	-	-1h[1]	0h	2min[2]	10min	30min	1h	3h	6h	12h	0h[1]	0h[1]	0h[1]	-1h	0h[1]	2min[2]	10min	30min	1h	3h	6h	12h	24h	48h	72h	120h	-	-
CCI			X																										
CCI			X																										
Inpatient		X																											
Concomitant medications	X[9]																												
Adverse events/serious adverse events	X[9]																												
Study completion information																												X	
Safety Follow up Call																													S

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Pre-dose
[2] Only collected/done in cohorts with bolus injection.
[3] Serum pregnancy test at screening and EOS visit. Urine pregnancy test at baseline. FSH testing at screening.
[4] 12 lead ECG. Triplicate measurements are required at Screening, Baseline, day 3, day 4 and EOS and single ECG measurements at other timepoints.

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[9] AEs and concomitant medications will be captured in the eCRF through post study safety-follow up call

8.1 Screening

It is permissible to re-screen a subject once if s/he fails the initial screening or was not randomized in the required timeframe. Subjects need to re-consented for re-screening and a new subject number must be assigned.

In the case where a safety laboratory assessment at screening and/or baseline is outside of the range specified in the exclusion criteria, the assessment may be repeated once at screening and once at randomization. If the repeat value remains outside of the specified ranges, the subject must be excluded from the study.

8.1.1 Eligibility screening

Results of below screening measurements will be available as source data at the study site and will not be recorded within the eCRF.

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8.1.2 Information to be collected on screening failures

Information on what data must be collected for screening failures and further information on re-screening is outlined in the SOM.

8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. Subject demographics include date (if permitted) or year of birth, sex, race and predominant ethnicity (if permitted). Relevant medical history/current medical conditions data will also be collected until signature of informed consent. Where possible, the diagnoses and not symptoms should be recorded.

All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented. See the Section 6.2.1 for further details on what information must be recorded on the appropriate page of the eCRF.

8.3 Efficacy

Efficacy / Pharmacodynamics are not measured in this study.

8.3.1 Appropriateness of efficacy assessments

Efficacy / Pharmacodynamics are not measured in this study.

8.4 Safety/Tolerability

Safety assessments are specified in the Assessment Schedule (Table 8-1 and Table 8-2) which details when each assessment is to be performed.

For details on AE collection and reporting, refer to Section 10.1.

Table 8-3 Assessments and Specifications

Assessment	Specification
Physical examination	A complete physical examination at screening will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. At other visits, a shorter physical exam may be performed to include the examination of general appearance. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be included in the Medical History part of the CRF. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the CRF.
Injection/infusion site observation	Injection/infusion site must be examined before and after drug administration for any changes in appearance or pain. Local tolerability at the injection/infusion site will be assessed by the investigator prior and immediately after each infusion on day 1 (Part A and B) and 5 (Part B only). The following parameters will be evaluated by scoring (none, mild, moderate or severe) in each subject: • Pain • Itching • Erythema • Swelling • Inflammation • Phlebitis • Ulceration • Necrosis Infusion reactions also need to be captured as AE according to CTCAE criteria.

Assessment	Specification
Blood pressure and pulse rate	Systolic and diastolic blood pressure will be measured after the subject has been supine for five minutes, using an automated validated device with an appropriately sized cuff. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.
Body temperature	Oral body temperature will be recorded in °C.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

8.4.1 Laboratory evaluations

A local laboratory will be used for analysis of all specimens collected.

All abnormal lab results must be evaluated for criteria defining the inclusion/exclusion criteria, an adverse event and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

Table 8-4 Laboratory Assessments

Test Category	Test Name
Hematology	Hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differentials and platelet count. Coagulation testing including prothrombin time (PT) (also reported as INR), activated partial thromboplastin time (aPTT) and fibrinogen
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Chemistry	Sodium, potassium, creatinine, BUN or urea, uric acid, chloride, albumin, calcium, magnesium, alkaline phosphatase, total bilirubin (direct and indirect), bicarbonate/HCO3, LDH, GGT, AST, ALT, amylase, lipase, CK, glucose, total cholesterol, triglycerides, total protein, C-reactive protein (CRP). Globulin and albumin/globulin ratio
	Commercially Confidential Information
Urinalysis	Dipstick measurements for bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen. If dipstick measurement results are positive (abnormal), results will be captured in the CRF. Microscopy must be assessed following an abnormal dipstick test with results captured in the CRF.
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Pregnancy / FSH Test	Serum / Urine pregnancy test and FSH levels (see Section 8.4.4)
	Commercially Confidential Information

8.4.2 Electrocardiogram (ECG)

For Part A, triplicate ECGs will be collected at screening, baseline, and at Day 8 (EOS). At other times, single ECGs will be collected at all times when PK samples are collected (ECG is not needed at 2 min).

For Part B, triplicate ECGs will be collected at screening, baseline, Days 3, 4, and Day 12 (EOS). At other times, single ECGs will be collected at all times when PK samples are collected (ECG is not needed at 2 min).

All ECGs will be measured after a 10 min rest in the supine position. The following parameters will be reported : PR interval, QRS duration, heart rate, RR interval, QT interval, QTcF.

The Fridericia QT correction formula (QTcF) must be used for clinical decisions.

As applicable, QTcF and QTcB may be calculated at the site. Unless auto-calculated by the ECG machine, the investigator must calculate QTcF at the Screening and/or Baseline visit(s) (as applicable) to assess eligibility and continuation in the study.

Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE eCRF as appropriate.

8.4.3 Holter ECG Monitoring

25-hour Holter monitoring will be conducted on specified days to collect ECG data for QTcF assessment. These data will not immediately be visible to the site investigator and staff. The Holter recordings will be transmitted to the selected ECG core laboratory for analysis. ECG extractions for QTcF analysis will be taken at the same nominal timepoints as the PK draws. All ECGs will be measured after a 10 min rest in the supine position prior to the PK draws.

In Part A, continuous 12 lead ECG Holter monitoring will be performed for 25 hours on Day 1 from 1 hour pre-dose through 24 hours post-dose.

In Part B, continuous 12 lead ECG Holter monitoring will be performed for 24 hours on Days 1 and 5 from 1 hour pre-dose through 24 hours post-dose.

Full details of all procedures relating to the ECG collection are contained in the SOM and/or Holter monitoring manual.

8.4.4 Pregnancy and assessments of fertility

All women will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

At screening and at the end of the study, serum pregnancy test should be performed, while during the study duration urinary pregnancy tests are sufficient. In case the pregnancy urine test is positive, the result needs to be confirmed with serum test.

Assessments of Fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female subject regardless of reported reproductive/menopausal status at screening/baseline.

8.4.5 Appropriateness of safety measurements

The safety assessments selected are standard for this subject population.

8.5 Additional assessments

Additional assessments are specified below with the Assessment Schedule (Table 8-1 and Table 8-2) detailing when each assessment is to be performed.

The methods for each assessment and data recording details are specified in the SOM.

8.5.1 Pharmacokinetics

PK samples will be collected at the visits defined in the Assessment Schedule (Table 8-1 and Table 8-2). Follow instructions outlined in the SOM regarding sample collection, numbering, processing, and shipment. See the potential use of residual samples for more information.

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PK samples will be obtained from all subjects, but only samples from KAE609 treated subjects will be analyzed.

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For standard PK abbreviations and definitions see the list provided at the beginning of this protocol.

The following PK parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 8 or higher): For SAD: C(0), Cmax, Tmax, AUC0-24h, AUClast, AUCinf, T1/2, Vss and CL and for MAD: Cmax, Tmax, AUC0-24h, Ctrough, AUCtau etc. as applicable from the plasma concentration-time data.

The linear trapezoidal rule will be used for AUC calculation. Regression analysis of the terminal plasma elimination phase for the determination of T1/2 will include at least 3 data points after Cmax. If the adjusted R^2 value of the regression analysis of the terminal phase will be less than 0.75, no values will be reported for T1/2, AUCinf, Vss and CL.

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9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

Study treatment must be discontinued under the following circumstances:

- Subject decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment Section 6.2.2
- Any situation in which study participation might result in a safety risk to the subject
- Following emergency unblinding

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- Any laboratory abnormalities (e.g., LFT increase) that in the judgment of the investigator, taking into consideration the subject's overall status, prevent the subject from continuing receiving the study medication
- If a liver or renal event occurs, follow guidelines outlined in Section 16.1 (Appendix 1) and Section 16.2 (Appendix 2) regarding discontinuation of study treatment.
- Deviation from the planned dose regimen for the study drug

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject’s premature discontinuation of study treatment and record this information.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdrawal of informed consent Section 9.1.2). In case only study treatment is discontinued, where possible, they should return for the follow-up visits as per Assessment Schedule. Subjects who prematurely discontinue the study (treatment and visits) for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the EOS visit will be performed.

If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- new / concomitant treatments
- adverse events/Serious Adverse Events

9.1.1.1 Replacement policy

If a subject is considered as non-evaluable for a dose escalation decision, enrollment of a new subject to the current cohort will be considered if there is less than the required number of evaluable subjects. Enrollment of new subjects may be considered until at least the minimum number (6 for SAD and 7 for MAD) or at most the maximum number (for SAD 8 and MAD 9) of evaluable subjects is achieved within the cohort.

9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation (EOS visit) at the time of the subject's study withdrawal should be made as detailed in the Assessment schedule (Table 8-1 and Table 8-2).

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until the time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Study stopping rules

Cohort stopping rules and dose escalation decision points:

Dose escalation, as well as continued dosing within any given cohort, will be paused and may be stopped based on full review of all available clinical safety data and discussion with the Investigator if any of the following occur:

- Any treatment-emergent SAEs, except those that are clearly and incontrovertibly due to extraneous causes
- Two or more subjects in the same cohort experience a similar AE which was assessed as CTCAE grade 3 or greater in intensity, and are considered as potentially related to the study treatment;
- The Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify putting the study on hold
- Two or more subjects experience Grade 2 or higher hypersensitivity reactions
- Two or more subjects experience Grade 3 or higher injection site reactions.
- Two or more subjects with QTcF greater than 500 msec and/or an increase greater than 60 msec, expected to be related to the study treatment

The severity of adverse events will be graded by the study site investigator (or sub-investigator) based on CTCAE and captured in the CRF (see Section 10.1). This information will be used to quantify events that may lead to subject's discontinuation or stopping dose escalation.

Drug administration of subsequent cohorts will only be triggered if an adequate safety and tolerability profile has been confirmed from the preceding cohort.

Safety reviews will be conducted jointly between medically qualified representatives of the Sponsor and Investigator and a joint decision will be made. If a dose level is identified to be intolerable, the preceding dose level will be defined as the maximum tolerated dose.

Overall study stopping rules:

Enrollment in the study will be placed on hold and dosing held if any of the rules for a cohort or dose escalation are met as above.

The study may resume following the safety review, if the investigator and Sponsor agree it is safe to proceed.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to subjects enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible for EOS visit as per Assessment Schedule and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their EOS visit , and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

All randomized and/or treated subjects should have a safety follow-up call conducted 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3 and SOM. Documentation of attempts to contact the subject should be recorded in the source documentation.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The Common Toxicity Criteria (CTC) AE grade (version 5 or higher)

- Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE)
- If CTCAE grading does not exist for an adverse event, use 1=mild; 2=moderate, 3=severe; and 4=life threatening. CTCAE grade 5 (death) is not used, but is collected in other CRFs (e.g., End of Study Visit, Death/Survival).

2. its relationship to the study treatment
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- No treatment given
- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn

6. its outcome
    a. not recovered/not resolved;
    b. recovered/resolved;
    c. recovering/resolving,
    d. recovered/resolved with sequelae;
    e. fatal;
    f. or unknown.

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Any AE that constitutes a dose limiting toxicity should be reported like a grade 3 adverse event.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. Continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in healthy subjects.

Follow the instructions found in the SOM for data capture methodology regarding AE collection for subjects that fail screening.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - elective or pre-planned treatment for a pre-existing condition and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the subject’s general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis/ safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period following the last administration of study treatment should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Only women of non child bearing potential are eligible for this study and no pregnancy in women is expected.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

The newborn will be followed up for a minimum of 1 year after delivery.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the, respective sections above.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Table 16-1 in Appendix 1 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2. Repeat liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

- These liver chemistry repeats will be performed using the local laboratory. Repeated laboratory test results must be reported as appropriate.
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF.

Refer to the SOM for additional details.

10.2.2 Renal safety monitoring

Every renal laboratory trigger or renal event as defined in Table 16-3 (in Appendix 2) should be followed up by the investigator or designated personnel at the trial site as summarized in Section 16.2 (in Appendix 2).

Refer to the SOM for additional details.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

eSource is a data collection system allowing electronic capture of source data and study data, as required per protocol. eSource is intended to be used for this study. If it is not possible to use eSource for source data capture due to exceptional circumstances, data capture and data management will revert to paper and other electronic methods as appropriate.

This study will incorporate electronic technology (eSource DDE) to capture source documents and source data electronically, consistent with final (CDER 2013) FDA guidance regarding electronic source and regulations related to the maintenance of adequate subject case histories (21 CFR 312.62 [b]). All electronic source documentation and data collected in this study will "meet the same fundamental elements of data quality (e.g. attributable, legible, contemporaneous, original, and accurate) that are expected of paper records" into a system that is fully validated and conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the system(s) until they have been appropriately trained.

Study sites using eSource DDE will be supplied with a tablet PC to directly record subject data and clinical observations on electronic forms with a similar look, feel, and behavior to paper forms. The system will permit the collection of both structured and unstructured information including ad-hoc comments, drawings, and relevant clinical notes the investigative site deems important. Information to be originally captured and reviewed electronically shall include details of the subject visit and the protocol required assessments performed as a part of these visits, medical history, and concomitant medications.

Certain data may be captured via other source documentation (such as safety laboratory data report, imaging) and then transcribed, uploaded or transferred into the eSource DDE system. This, and any additional data treated in this manner, will be source data verified by the study field monitor per the monitoring plan and the location of source data (i.e. source, paper or a local electronic system) will be documented prior to study start. The eSource system has the ability to illustrate when a document has been entered from another source. When using an electronic source record as the original point of data capture, there is no additional data entry step for the site for data collected directly into the application. Rather, the electronic source record directly populates the study database.

Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the vendor working on behalf of Novartis.

Remote monitoring of the original electronic source records will take place, however on-site monitoring inspections will continue to take place in order to review data entry of source documentation directly captured on paper and transcribed into the system, to ensure protocol adherence, to assess site operational capabilities, and to perform other monitoring activities that cannot be performed remotely.

The investigator must certify that the data entered into eSource are complete and accurate. After database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused supplies to Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis or delegated CRO representative will review the protocol and data capture requirements (i.e. eSource or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/delegated CRO/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

The analysis will be conducted on all subject data at the time the trial ends, under the direction of Novartis personnel in compliance with internal documents and standards.

12.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment received, where treatment received is defined as the randomized/assigned treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received.

The safety analysis set includes all subjects who received at least one dose of any study treatment.

The PK analysis set will include all subjects with at least one valid (i.e. not flagged for exclusion) KAE609 concentration data, who received study drug and had no protocol deviations with relevant impact on the interpretability of the PK data.

Within a study part, all placebo subjects from all cohorts will be pooled.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data will be listed by part, treatment group and subject. Summary statistics will be provided by part and treatment group for the safety set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be listed by part, treatment group and subject.

12.3 Treatments

The safety set will be used for the analyses below.

Data for study treatment administration, concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by part, treatment group and subject.

12.4 Analysis of the primary endpoint(s)

The primary aim of the study is to determine the safety and tolerability of KAE609 after single and multiple iv doses in healthy subjects. All safety analyses will be performed on the safety analysis set.

12.4.1 Definition of primary endpoint(s)

The primary endpoints are safety and tolerability assessments including adverse events, vital signs, ECG findings (including QTcF), safety laboratory assessments including chemistry, hematology, and urinalysis results assessed at baseline up to Day 8 in Part A and up to Day 12 in Part B (EOS).

12.4.2 Statistical model, hypothesis, and method of analysis

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group. Graphical representations of the safety data may be produced.

Adverse events

All information obtained on adverse events will be displayed by part, treatment group and subject. The number and percent of patients with adverse events will be tabulated by system organ class and preferred term with a breakdown by treatment group. A subject with multiple adverse events within a system organ class is only counted once towards the total of the system organ class. Separate tables and listings will present adverse event severity (CTCAE grade) and relationship to study treatment.

The number (and percent) of subjects with adverse events of infusion site reaction may be summarized by treatment group.

Vital signs

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

ECG evaluations

Abnormal ECG data will be flagged and will be listed by part, treatment group, subject and visit/time. Summary statistics may be provided by part, treatment group and visit/time.

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 msec and > 60 msec
- absolute QTcF values > 500 msec
- PR change from baseline > 25% increase resulting in PR > 220 msec
- QRS change from baseline > 25% increase resulting in QRS > 120 msec
- 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.

Clinical laboratory evaluations

If normal ranges are available, laboratory data abnormalities will be flagged and will be listed by part, treatment group, subject and visit/time. Summary statistics may be provided by part, treatment group and visit/time.

Individual profile plots of laboratory data (e.g. sodium, potassium, calcium, AST and ALT) will be provided. Graphical summary of these laboratory parameters will also be provided by part and treatment group.

12.4.3 Handling of missing values/censoring/discontinuations

No imputation of missing data will be considered for safety and tolerability analysis.

12.4.4 Sensitivity and Supportive analyses

Not applicable.

12.5 Analysis of secondary endpoints

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

12.5.1 Pharmacokinetics

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.

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PK concentration data from this study may be used for population PK modeling. If performed, the results will be reported separately.

Table 12-1 Non-compartmental pharmacokinetic parameters

AUC0-t	The AUC from time zero to time t (e.g. 24h) (mass x time x volume-1)
AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
AUCinf	The AUC from time zero to infinity (mass x time x volume-1)
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
T1/2	The elimination half-life associated with the terminal slope (lz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
CL	The total body clearance of drug from the plasma (volume x time-1)
Vss	The apparent volume of distribution at steady state from an intravenously administered dose (volume)

12.6 Analysis of exploratory endpoints

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12.7 Interim analyses

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12.8 Sample size calculation

12.8.1 Primary endpoint(s)

In Part A, 8 subjects will be enrolled into each dose level cohort. Six of the subjects in each cohort will receive KAE609 and 2 subjects will receive placebo. In Part B, 9 subjects will be enrolled in each dose level cohort with 6 subjects receiving KAE609 and 3 subjects receiving placebo.

With 6 subjects receiving KAE609 in each iv cohort in Part A and Part B, it is highly probable that adverse events will be observed if the underlying adverse event rate is medium to high. For instance, if the underlying adverse event rate is 1 in every 5 subjects then there is a 74% chance that this adverse event will be detected in at least 1 subject on active treatment. Conversely, adverse events with low event rates are unlikely to be detected in this part of the study. For instance, if the underlying adverse event rate is 1 in every 100 subjects then the probability of observing this adverse event in at least 1 subject on active treatment is only 6%.

Table 12-2 Probability of observing events given a range of underlying event rates in Part A and Part B

Underlying event rate	Probability of observing no subjects* with adverse event	Probability of observing at least 1 subject* with adverse event	Probability of observing at least 2 subjects* with adverse event
1 in 100	94%	6%	< 1%
1 in 20	74%	26%	3%
1 in 10	53%	47%	11%
1 in 5	26%	74%	34%
1 in 2	2%	98%	89%

* Out of 6 subjects on active treatment

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

This study only involves healthy subjects and as such Novartis will register the protocol as required to databases specified by local regulations (e.g. EudraCT during CTA filing for studies in EU/EEA). After study completion (defined as last patient last EOS visit) and finalization of the study report, results of this trial may be submitted for publication (e.g. peer-reviewed journal) or registered to databases where required by local regulations.

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the site initiation visit.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

14.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request.

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World Health Organization (2015). World Malaria Report 2014. Geneva: 2015.

16 Appendices

16.1 Appendix 1: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 16-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN · 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal

Table 16-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)

Criteria	Actions required	Follow-up monitoring
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

16.2 Appendix 2: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-3 Specific Renal Alert Criteria and Actions

Serum Event	
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ³ 50% compared to baseline	Follow up within 24-48h if possible Consider study treatment interruption Consider patient hospitalization /specialized treatment
Urine Event	
New dipstick proteinuria ≥1+ Albumin- or Protein-creatinine ratio increase ≥2-fold Albumin-creatinine ratio (ACR) ≥30 mg/g or ≥3 mg/mmol; Protein-creatinine ratio (PCR)≥150 mg/g or >15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider study treatment interruption / or discontinuation
New dipstick glycosuria ≥1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria ≥1+ not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed	
Monitor patient regularly (frequency at investigator's discretion) until either:	
Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or	
Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.	