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Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

CMK389

CCMK389B12201 / NCT04836858

A randomized, subject and investigator blinded, placebo-controlled multicenter study to assess the efficacy and safety of CMK389 in patients with moderate to severe atopic dermatitis

Statistical Analysis Plan (SAP)

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1 Introduction

1.1 Scope of document

The Reporting and Analysis Plan (RAP) documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial **"*CCMK389B12201".***

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

1.2 Study reference documentation

Study Protocol v02 is available at the time of finalization of SAP.

1.3 Study objectives

1.3.1. Primary objective

Primary objective	***Endpoint for primary objective***
• To assess the efficacy of CMK389 in participants with moderate to severe atopic dermatitis (AD)	• Investigator Global Assessment (IGA) response (defined as clear or almost clear and at least 2-point reduction from baseline) at Week 16

1.3.2. Secondary objective

Secondary objective	***Endpoint for secondary objective***
• To assess the safety and tolerability of CMK389 in participants with AD	• Number, seriousness and frequency of adverse events over time.

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1.4 Study design and treatment

This is a randomized, placebo-controlled, parallel-group, non-confirmatory, investigator and participant blinded study in adult participants with moderate to severe AD. The study will randomize approximately 64 participants to the following four treatment arms in a ratio of 4:1:2:1 as follows:

- Arm 1: 32 participants treated intravenously (i.v.) with 10 mg/kg CMK389
- Arm 2: 8 participants treated i.v. with placebo
- Arm 3: 16 participants treated subcutaneously (s.c.) with 300 mg CMK389
- Arm 4: 8 participants treated s.c. with placebo

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4 Statistical methods: Analysis sets

For all analysis sets, participants will be analyzed according to the study treatment received. For participants for which the actual treatment received does not match the randomized treatment, the treatment actually received will be used for the analysis.

The safety analysis set will include all participants who received any study drug.

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The PD analysis set will include all participants who received any study drug and had no protocol deviations with relevant impact on PD data.

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

Table 4-1 Subject classification rules

Analysis set	PD codes that cause a subject to be excluded	Non-PD criteria that cause a subject to be excluded
Safety set	None	No treatment taken

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PD analysis set	None	No treatment taken, no valid PD data

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

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6 Statistical methods for Pharmacodynamic (PD) parameters

6.1 Primary objective

The primary objective of this study is to assess efficacy of CMK389 in participants with moderate to severe AD. This analysis will be performed on the safety analysis set.

6.1.1 Variables

The primary variable is the IGA response at Week 16, defined as clear or almost clear at Week 16 with at least 2-point reduction from baseline.

The IGA rating scale is a Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD™) and it describes the overall disease severity for the whole body on a 5-point scale: clear (0), almost clear (1), mild (2), moderate (3), and severe (4).

For the descriptive analysis (Section 6.1.2) the placebo groups (i.e. placebo i.v. and placebo s.c.) will be presented both separately and pooled. For the inferential analysis (Section 6.1.3), the two placebo groups (placebo s.c. and i.v.) will be only presented pooled.

Baseline is considered to be the last assessment (including those from unscheduled visits) obtained before the first dose of study treatment.

The primary clinical question of interest is: What is the effect of CMK389 versus placebo on IGA response after 16 weeks of treatment in patients with moderate or severe atopic dermatitis without any relevant use of prohibited medication or use of rescue medication taken after first 6 weeks.

Prohibited or rescue medication are relevant when their use may have a potential confounding effect on the efficacy assessment.

This estimand will enable assessment of the effect of CMK389 for the full duration in the absence of relevant use of prohibited medication or use of rescue medication taken after the first 6 weeks.

The primary estimand is described by the following attributes:

Population: Adult participants with moderate to severe atopic dermatitis is the target population for biologics (Beck et al 2014, Simpson et al 2016) and is defined by an IGA score of moderate to severe (3 or 4) and an EASI score of at least 12 as defined by the study inclusion and exclusion criteria who were randomized to treatment. Further details about the population are provided in Section 5 of the protocol. This implies that analyses will be based on the safety analysis set.

Endpoint: IGA response at week 16, where IGA response is defined as clear or almost and with at least a 2-point reduction compared to baseline and no use of confounding therapy before the assessment time point.

Treatment of interest: the treatment (the investigational treatment CMK389 or placebo) actually taken for the entire study duration without any use of prohibited medications or use of rescue medication taken after the first 6 weeks.

Handling of remaining intercurrent events:

1. Relevant use of rescue therapy (after first 6 weeks of treatment)
2. Relevant use of prohibited medication to treat AD symptoms or with impact on efficacy
3. Study treatment discontinuation due to lack of efficacy
4. Study treatment discontinuation due to AE related to AD, e.g. worsening of AD
5. Study treatment discontinuation due to AE not related to AD or due to lack of tolerability
6. Study treatment discontinuation due to other reasons (e.g. administrative if participant relocates to a region where the trial is not offered, or withdrawal of informed consent)

For the intercurrent events 1 to 4, a composite strategy will be used: use of any therapy (prohibited or rescue medication taken after the first 6 weeks) as well as any study treatment discontinuation due to lack of efficacy or due to AE related to AD are considered as unfavorable outcome, i.e. the participant will be treated as a non-responder.

For the intercurrent events 5 to 6, a treatment policy strategy will be used and the intercurrent event will be ignored (set data after discontinuation to be missing)

The summary measure: treatment difference of the CMK389 and placebo in absolute responder rates.

6.1.2 Descriptive analyses

The IGA response will be listed by treatment group, participant and visit and summarized by categorical frequency tables by treatment group and all visits available.

Graphical methods may be used to present the IGA response rates by treatment over time.

6.1.3 Statistical model, assumptions and hypotheses

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6.1.3.1 Handling of remaining intercurrent events of primary estimand

Relevant use of any therapy (prohibited or rescue medication taken after the first 6 weeks) as well as any study treatment discontinuation due to lack of efficacy or due to an adverse event (AE) related to AD are considered as unfavorable outcomes. In that case, the composite strategy will be followed, i.e. the participants will be treated as non-responders.

The data on relevant use of rescue or prohibited medication taken after the first 6 weeks was provided by TME under blinded medical review,

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Study treatment discontinuation due to other reasons and AEs not related to AD or due to lack of tolerability will be handled with a treatment policy strategy, i.e. they will be ignored (no carry-forward data will be needed).

Frequency of patients with intercurrent events will be summarized by treatment arm. A patient may experience the same intercurrent event more than once during the trial and will be counted only one time for that intercurrent event.

6.1.3.2 Handling of missing values not related to intercurrent event

For the primary endpoint analysis, there will be no planned imputation of missing data.

6.2 Exploratory objectives

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7 Statistical methods for safety and tolerability data

All participants within the Safety analysis set will be included in the safety data analysis.

7.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements, as well as participant demographics, baseline characteristics, and treatment information.

7.2 Descriptive analyses

For the below analyses, results will be displayed for both pooled and separated placebo groups (i.e. placebo i.v. and placebo s.c.).

Participant demographics and other baseline characteristics

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

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term by treatment group.

Treatment

The duration of exposure to study treatment will be summarized by treatment group.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

Additionally, rescue therapy as well as concomitant anti-histamines will be summarized by treatment group.

Vital signs

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

ECG evaluations

All single 12-lead ECG data (included but not limited to PR, QRS, QT, QTcF and RR intervals) will be listed by treatment, participant and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Categorical analysis of QT/QTcF interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT/QTcF intervals or changes from baseline will be presented.

A listing of these participants by treatment group will be presented.

Clinical laboratory evaluations

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

Summary statistics will be provided by treatment and visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Adverse events

All information obtained on adverse events will be displayed by treatment group and participant.

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication (up to 112 days after the date of the last actual administration of any study treatment) or events present prior to the start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term
- by treatment, primary system organ class, preferred term and maximum severity

A participant with multiple adverse events within a body system is only counted once towards the total of the primary system organ class.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, and other significant adverse events leading to discontinuation.

The number and percentage of participants with adverse events of special interest (hypersensitivity reactions such as serum sickness and anaphylaxis) will be summarized by treatment group.

Additionally, since part of the study was conducted during the COVID-19 pandemic, a listing of patients with suspected or confirmed SARS-COV-2 infection will be produced.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment-emergent adverse events which are not serious adverse events with an incidence greater than 5% and on treatment-emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

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

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

7.3 Graphical presentation

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

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9 Consideration due to COVID-19

Due to the COVID-19 pandemic, it may not be possible to perform some procedures as per protocol. All deviations due to COVID-19 will be listed separately to other deviations and may also be tabulated.

Observations that were impacted due to COVID-19, may be excluded from the primary analyses, for example including (but not limited to) observations taken at participant's house instead of site, and separately explored to identify if there is an impact of them on the analyses.

10 References

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11 Appendix

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