NOVARTIS

Biostatistics & Statistical Programming /
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CMK389

CCMK389X2201 / NCT04064242

A subject and investigator blinded, randomized, placebo-controlled, repeat-dose, multicenter study to investigate efficacy, safety, and tolerability of CMK389 in patients with chronic pulmonary sarcoidosis

Statistical Analysis Plan (SAP)

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1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial ***"CCM389X2201".***

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

Tables, Figures, Listings (TFL) details the presentation of the data, including shells of summary tables, figures and listings, and Programming Datasets Specification **(**PDS) contains programming specifications e.g. for derived variables and derived datasets, to support the creation of CSR outputs.

1.2 Study reference documentation

This Statistical Analysis plan is based on the Amendment 8 of the study protocol (dated: 23Jun2022).

1.3 Study objectives

1.3.1. Primary objective(s)

Primary objective(s)	***Endpoints related to primary objectives***
• To assess the efficacy of CMK389 in subjects with chronic pulmonary sarcoidosis	• Change in forced vital capacity, % of predicted, (FVC%) between baseline and Week 16, between CMK389 and placebo.

1.3.2. Secondary objective(s)

Secondary objective(s)	***Endpoints related to secondary objective(s)***
• To assess the impact of CMK389 on steroid use (mg days)	• Difference in steroid usage for each arm of the study between baseline and end of treatment.
• To assess the impact of CMK389 on a composite index of pulmonary physiology and exercise capacity	• Proportion of patients who deteriorate from baseline to Week 16, defined as: relative reduction in FVC $\geq$ 10% or relative reduction if FEV1 $\geq$ 10% or relative reduction of DLCO $\geq$ 15% or relative reduction of 6MWD $\geq$ 50 m.
• To explore the impact of CMK389 observed with [^{18}F]-fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F]FDG-PET/CT) imaging	• Change in [^{18}F]FDG-PET/CT parameters (SUVmax and SUVmean) between baseline and Week 16.

• To assess the pharmacokinetics of CMK389	• Pharmacokinetic parameters (Cmax/End of infusion, Ctrough) of CMK389.
• To assess the safety and tolerability of CMK389	• Adverse events, vital signs and routine safety laboratory results.
• To assess the impact of CMK389 on pulmonary physiology	• Change in forced expiratory volume in one second (FEV1) and diffusion capacity for carbon monoxide (DLCO) between baseline and Week 16.
• To assess the impact of CMK389 on exercise capacity	• Change in 6-minute walk distance (6MWD) between baseline and Week 16.

1.3.3. Exploratory objective(s)

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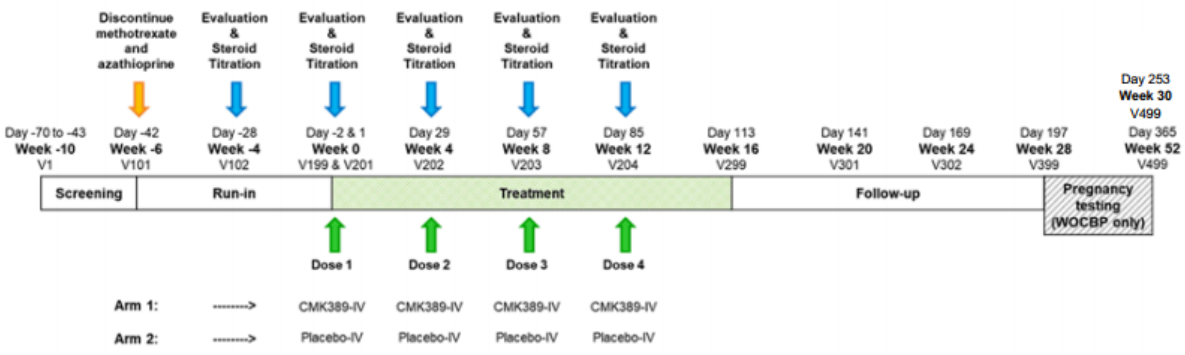
1.4 Study design and treatment

This is a subject and investigator-blinded, randomized, placebo-controlled, parallel group, repeat-dose, multicenter, non-confirmatory study of the safety and efficacy of CMK389 administered intravenously every 4 weeks for a total of 4 doses in chronic pulmonary sarcoidosis patients.
Approximately 66 patients will be randomized in a 1:1 ratio to receive either CMK389 or placebo. Randomization will be stratified by prior sarcoidosis immunosuppressant therapy (azathioprine or methotrexate).The expected total duration of participation for men and women of non-child bearing potential is approximately 38 weeks. For women of childbearing potential, the expected duration of participation is approximately 62 weeks.

Figure 1-1: Study design scheme



2 First interpretable results (FIR)

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3 Interim analyses

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4 Statistical methods: Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received. In case(s) of miss-stratification, the real stratum will be used in the analysis.

The safety analysis set will include all subjects that received any study drug.

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

The PD analysis set will include all subjects with available PD data and no protocol deviations with relevant impact on PD data. Also, data collected after a change of the background therapy not based on the CSE algorithm (see Section 3.1 of protocol) will be excluded from the analysis set if assessed as having a potentially relevant impact on PD data.

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from all *(safety)* analysis in case of these PDs:		Exclude subject completely from all ***(safety)*** analysis sets
INCL01	Deviation from inclusion criteria: Written informed consent was not obtained before any study assessment was performed	Yes
Subjects are excluded from PK analysis in case of these PDs:		Exclude subject from PK analysis set
INCL01	Deviation from inclusion criteria: Written informed consent was not obtained before any study assessment was performed	*Yes*
Subjects are excluded from PD analysis in case of these PDs:		Exclude subject from PD analysis set
INCL01	Deviation from inclusion criteria: Written informed consent was not obtained before any study assessment was performed	Yes
TRT01	Treatment deviation with impact on PD data	Yes
TRT02	Treatment deviation with impact on PD data from a timepoint onwards	Yes from a timepoint onwards
OTH01	Other deviation with impact on PD data	Yes
OTH02	Other deviation with impact on PD data from a timepoint onwards	Yes, from a timepoint onwards

Category Deviation code	Text description of deviation	Data exclusion
OTH04	Impact on spirometry and DLCO at a specific time point	Yes, at a specific timepoint only.
OTH12	Impact on spirometry at a specific time point	Yes, at a specific timepoint only.
OTH13	Impact on DLCO at a specific time point	Yes, at a specific timepoint only.
CMD02	Prohibited concomitant medication used with a relevant impact on efficacy endpoint	Yes, from a timepoint onwards
INCL04	Deviation from inclusion criteria: No biopsy proven pulmonary sarcoidosis diagnosed > 1 year prior to screening	Yes
INCL06	Deviation from inclusion criteria: HRCT <= 15% reticular volume at screening	Yes
EXCL05	Deviation from exclusion criteria: FVC < 50% at screening	Yes
EXCL06	Deviation from exclusion criteria: mMRC dyspnea scale >= 3 at screening	Yes
EXCL27	Deviation from exclusion criteria: deteriorated during Run-in	Yes

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.
All DLCO related parameters will be excluded at specific visit only if the condition below is encountered: DLCO % change (absolute value) vs previous assessment > 35% or % change in alveolar volume vs previous assessment > 20%.
DLCO related parameters are: DLCO (absolute value and % predicted), ALVVOL (alveolar volume), DLCOHCCP (corrected by Hg), DLCOVA (/ volume), CPID (CPI = it includes DLCO).

5 Statistical methods for Pharmacokinetic (PK) parameters

All subjects within the PK analysis set will be included in the PK data analysis.

5.1 Variables

The following pharmacokinetic parameters will be determined:

- CMK389 plasma concentration.
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5.2 Descriptive analyses

CMK989 plasma concentration data will be listed by subject and visit/sampling time point. Descriptive summary statistics will be provided by visit/sampling time point. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Commercially Confidential Information

The geometric mean will not be reported if the dataset includes zero values.

Graphical methods will be employed to show mean and individual concentration-time profiles.

6 Statistical methods for Pharmacodynamic (PD) parameters

All subjects within the PD analysis set will be included in the PD data analysis.

6.1 Primary objective

To assess the efficacy of CMK389 in subjects with chronic pulmonary sarcoidosis.

It will be estimated in the PD analysis set and considering the FVC (% of predicted) change from baseline at week 16, irrespective of the role played by the steroid dose ('treatment policy' approach) and managing missing values according to an hypothetical approach. Therefore, the primary analysis will estimate the treatment effect if everyone would have been able to finish the treatment period. The difference in the model based mean in the CMK389 vs placebo arm will be used to estimate the effect.

6.1.1 Variables

The primary variable will be the change from baseline in percent predicted FVC at Week 16. The FVC is measured at screening, day 1, week 4, week 8, week 12, and week 16. Baseline is defined as day 1.

For the primary analysis, the only data quality condition affecting data inclusion to the analysis will be that the number of accepted tests is greater than zero. No other flags related to quality

will lead to an exclusion of records Also, the main efficacy analysis will exclude all the data collected after a steroid dose increase NOT driven by the algorithm.

These cases will be detected programmatically and will be reconciled by manual checks. Should it become not feasible to detect all cases programmatically, then the team will release an excel file with the list of events and dates. According to each case, efficacy data will be excluded at a specific visit, or will be excluded from a timepoint onwards.

6.1.2 Descriptive analyses

The raw percent predicted FVC values and other spirometric endpoints will be listed by treatment, subject and visit/time. Descriptive statistics of both the raw and change in percent predicted FVC will be provided by treatment and visit/time. Summary statistics will include arithmetic mean, SD, CV (arithmetic), median, minimum and maximum.

Boxplots to visualize trends in spirometry endpoints will be created.

6.1.3 Statistical model, assumptions and hypotheses

The change from baseline in percent predicted FVC will be analyzed using a Bayesian model for repeated measurements including data collected at weeks 4, 8, 12 and 16. The model will investigate effects for treatment by time (included as a class variable) interaction, baseline percent predicted FVC by time interaction and will include the covariates prior sarcoidosis immunosuppressant therapy (stratification factor) and baseline prednisone dose. Uninformative priors for all the parameters will be utilized to obtain the posterior estimates. The correlation among the repeated measures collected on the same subject will be assessed via unstructured covariance matrix. The stratification factor may be removed in case of strata with low sample sizes impacting on the model fit. Baseline FVC and prednisone will be centered and standardized before used in the model.

6.1.3.1 Handling of missing values/censoring/discontinuations

The primary analysis will include all available information in terms of measurements at all times. If missing measurements are missing at random (MAR), an analysis of the available data provides consistent estimates of model parameters. Alternative assumptions may be explored to investigate the robustness of the results under plausible non-missing at random situations.

6.1.3.2 Graphical presentation of results

Posterior means with error bars (SD of the posterior) by treatment and time will be used to visualize the results over time.

6.1.4 Supportive analyses

If data permits, a subgroup analysis will be performed on the primary endpoint for the following two subgroups: subjects with a final prednisolone dose of 2.5 mg, subjects with a final prednisolone dose > 2.5 mg. The same analysis as defined in Section 6.1.3 will be performed, for each group.

Summary tables will be provided by subgroup.

6.1.5 Sensitivity/Supplementary analyses

Supplementary analyses may be conducted including also FVC values collected after a change of the background therapy driven by the algorithm or not.

Finally the analysis may be repeated excluding the observations with flags related to data quality (REIRESFL='Y').

A scatterplot will be produced to investigate the relationship between week 16 FVC changes from baseline and SUV max % changes

6.2 Secondary objectives

6.2.1 Variables

Secondary variables for this study are:

- Steroid use (mg days): Change from baseline in steroid usage as determined by the investigator's decision (for any reason - algorithm mediated or just related to an investigator's decision) .
- .

  Dose for subjects dosed with Methylprednisolone steroid doses of 4, 6, 8, 10 mg will be multiplied by 1.25 to become Prednisolone equivalent.
- Composite index of pulmonary physiology and exercise capacity: Subject who deteriorates from baseline to each visit/Week 16, is defined as a subject with:
  - relative reduction if FVC ≥ 10%, or
  - relative reduction if FEV1 ≥ 10%, or

- relative reduction of DLCO ≥ 15%, or
- relative reduction of 6MWD ≥ 50 m.

- [^{18}F]FDG-PET/CT: Percent change from baseline in SUVmax and SUVmean
- Pulmonary function tests: Change from baseline in FVC (L), FEV1 (L and % predicted), FEV1/FVC, PEF and DLCO (absolute values and % predicted). DLCO expressed as % predicted and adjusted for Hemoglobin will be derived by the vendor as described in: Graham et others 2017. A composite physiological index (CPI) will be derived too following this formula: CPI = 91 – 0.65*DLCO(%) – 0.53*FVC(%) + 0.34*FEV1(%)
- 6MWD: Change from baseline in distance walked and for the distance saturation product. The latter will be derived as the product between the distance walked and lowest oxygen saturation (SpO2%) value observed during the test, that is to say the lowest of the values taken after 1,2,3,4,5,6 Minutes from the start of the test (Lettieri 2006).
- IL-18 and IL-18bp concentrations

The direction of benefit is as follows

- an increase in values is beneficial for: absolute FVC, FEV1, PEF , DLCO and 6MWD.
- A decrease in values is beneficial for: [^{18}F]FDG-PET/CT (SUVmax and SUVmean).

[^{18}F]FDG-PET/CT

The [^{18}F]FDG-PET/CT imaging data will be analyzed by the vendor to identify the standardized uptake values in the following categories:

- A maximum of 10 focal nodal uptake regions (mediastinal, hilar)
- A maximum of 10 focal regions of uptake in lung parenchyma
- A maximum of 10 extra-thoracic focal uptake regions on the whole body scan

[^{18}F]FDG-PET/CT mean uptake in the reference tissue:

- Lung parenchyma, unaffected by focal lesion uptake
- Ascending aorta blood pool

During the statistical analysis, for each category, a mean of the SUVmax values over the different regions from baseline and Week 16 scans will be derived. For each region a percent change at week 16 vs the initial scan, will be derived and averaged within each category too. The mean percent change represents the main endpoint for this analysis.

SUVmean values will be managed in the same way.

6.2.2 Descriptive analyses

All secondary variables will be listed by treatment, subject and visit/time. Descriptive statistics will be provided by treatment and visit/time for all continuous variables. Summary statistics will include arithmetic mean, SD, CV (arithmetic), median, minimum and maximum. Summary statistics for ancillary data (oxygen saturation, and vital signs data) collected during the 6 minute walking test will be provided too.

Il-18 and IL-18bp concentrations will be listed and summarized by treatment producing outputs mirroring the ones provided for the PK analysis of CMK389 concentrations but including the results observed in the placebo group.

Clinical status evaluation data (see section 3.1 of the study protocol) will be listed and summarized by treatment and visit. The summary table will report for each component (6MWT distance, FVC, FEV1, MMRC dyspnea score) the corresponding evaluation (Better, Same, Worse) and the overall evaluation.

Subjects who deteriorate at Weeks 4, 8, 12 and 16 and subjects with any increase in steroids for any reason (algorithm driven or not) during the treatment epoch will be summarized, separately, by treatment group using frequency tables.

The correlation between percent changes from baseline [^{18}F]-FDG-PET/CT scan in SUVmax and changes from baseline in FVC, FEV1 and 6MWT distance will be assessed with scatterplot grids. As we may not be able to assume normality of the data, Kendall's tau-b coefficients and its corresponding p-values will be displayed to assess correlation.

Data on new lesions from [^{18}F]-FDG-PET/CT will be only listed.

6.2.3 Statistical model, assumptions and hypotheses

[^{18}F]-FDG-PET/CT

The mean percent change from baseline in SUVmax in the nodules and lung parenchyma at week 16 will be analyzed using ANCOVA with baseline SUVmax and baseline steroid doses as covariates and treatment and prior sarcoidosis immunosuppressant therapy as factors.

The same analysis as for the percent change from baseline in mean SUVmax in the nodules and lung parenchyma will be performed for the percent change from baseline in SUVmax in extra-thoracic regions, where available, at week 16. It will also be repeated for SUVmean in the three categories.

The same sensitivity and subgroup analyses as the primary may also be performed, if deemed necessary.

A bar chart plot of the percent change from baseline with the corresponding SE will be provided.

Composite index of pulmonary physiology and exercise capacity /steroid dose

A logistic regression model with baseline steroid doses as a covariate and treatment and prior sarcoidosis immunosuppressant therapy as factors, will be applied to patients showing at least a deterioration (as determined by Composite index of pulmonary physiology and exercise

capacity- section 6.2.1) during the treatment period and to patients with at least one steroid dose increase (for any reason - algorithm mediated or just related to an investigator's decision).

Bar chart plots representing the percentage of patients with at least a deterioration during the course of the trial/ with at least one steroid increase during the course of the trial will be provided by treatment.

Key Pulmonary function tests and 6MWD

FVC (in litres), FEV1, FEV1/FVC, PEF, DLCO, DLCO adjusted for hemoglobin, CPI, 6MWD and distance saturation product changes from baseline will be analyzed using the same analysis as defined in Section 6.1.3 but under a frequentist approach (no prior will be applied). The same sensitivity and subgroup analyses as the primary may also be performed, if deemed necessary.

Model based means with corresponding standard errors (SE) by treatment and time will be used to visualize the results over time. A change from baseline of 0 will be assumed at baseline.

6.3 Exploratory objectives

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7 Statistical methods for safety and tolerability data

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

7.1.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements, immunogenicity, as well as subject demographics, baseline characteristics (including but not limited to prior sarcoidosis immunosuppressant therapy (stratification factor), baseline prednisone dose and mMRC dyspnea scale), and treatment information.

For each women of child bearing potential (WOCBP) the duration (in days) of the total follow-up period will be derived as:

Date of the last assessment - date of the last dosing + 1.

7.1.2 Descriptive analyses

Subject demographics and other baseline characteristics

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

Relevant medical history and current medical conditions, results of laboratory screens, will be listed by treatment group and subject.

Treatment

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

For each WOCP subject the duration (in days) of the total follow-up period will be listed.

A summary of the steroid dose (prednisone) assigned at the start of the treatment phase and of the prior immunosuppressant therapy will be provided too.

Vital signs

If ranges are available abnormalities will be listed by treatment, subject and visit/time. Summary statistics will be provided by treatment and visit/time. Vital signs collected during the 6MWT will be reported separately.

ECG evaluations

Abnormalities will be listed by treatment, subject and visit/time. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

Abnormalities will be listed by treatment, subject and visit/time. A fasting lipid panel will be performed, measuring cholesterol, direct LDL, HDL cholesterol, LDL cholesterol, and triglycerides. Lipid panel parameters and glucose will be summarized only under fasting conditions. For all other lab parameters, the fasting status will be ignored for summary statistics and graphical presentations. Summary statistics will be provided by treatment and visit/time. All data will be included in the listings and the fasting status will be distinguished by a fasting status flag.

Adverse events

Adverse events collected before the start of the study drug and during the pregnancy testing epoch will be listed separately, while treatment emergent adverse events (events with an onset day >= date of the first dosing and <= date of the end of the follow-up phase) will be listed and summarized as described below.

All information obtained on adverse events will be displayed by treatment and subject. The number and percentage of subjects with adverse events will be tabulated by body system and

preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system and treatment.

The number and percentage of subjects with adverse events of special interest will be summarized by treatment.

AEs of Special Interest comprise hypersensitivity reactions such as serum sickness and anaphylaxis (as defined by Sampson criterion #1; Sampson et al 2006).

Criteria #1	Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
	AND AT LEAST ONE OF THE FOLLOWING
a.	Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
b.	Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

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7.1.3 Graphical presentation

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

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9 Reference list

Graham BL, Brusasco V, Burgos F, et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. Eur Respir J 2017; 49: 1600016

Lettieri C, Nathan S, Browing R, et al. 2006 The distance-saturation product predicts mortality in idiopathic pulmonary fibrosis. Respiratory Medicine (2006) 100, 1734–1741

Sampson HA, Munoz-Furlong A, Campbell RL, et al (2006) Second symposium on the definition and management of anaphylaxis: Summary Report- Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol 2006;117(2):391-97.

10 Appendices 1

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