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Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

ACZ885

CACZ885X2205

A multiple-dose, subject- and investigator-blinded, placebo-controlled, parallel design study to assess the efficacy, safety, and tolerability of ACZ885 (canakinumamb) in patients with 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 ***"CACZ885X2205".***

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

Final study protocol is available at the time of finalization of Statistical Analysis Plan.

1.3 Study objectives

1.3.1. Primary objective(s)

Primary objective(s)	***Endpoints related to primary objectives***
• To compare the effect of ACZ885 versus placebo on the clinical disease activity of sarcoidosis patients as measured by the change from baseline in the percent predicted forced vital capacity (FVC) at week 24	• Change from baseline in percent predicted FVC at week 24.

1.3.2. Secondary objective(s)

Secondary objective(s)	***Endpoints related to secondary objective(s)***
• To determine the effect of ACZ885 on decreasing the maximum standardized uptake value (SUVmax) [F-18]FDGPET in nodules (nodular uptake regions) after 12 weeks of treatment, compared to placebo	• Percent change from initial scan in [F-18]FDG-PET SUVmax at week 12
• To determine the effect of ACZ885 versus placebo on other parameters of pulmonary function testing (i.e., absolute FVC, FEV1, FEV1/FVC, FEV3, FEV6, FEF25-75, FEV3/FVC, 1- (FEV3/FVC), TLC, RV, RV/TLC, DLco and postbronchodilator FEV1/reversibility) in patients with	• Lung function testing results at 24 weeks compared to baseline

sarcoidosis at 24 weeks compared to baseline	
• To determine the effect of ACZ885 versus placebo on HRCT of patients with sarcoidosis at 24 weeks compared to initial HRCT scan as measured by side-by-side comparison by blinded reviewers and HRCT scoring	• HRCT results at 24 weeks compared to HRCT initial scan measured by blinded reviewers and HRCT scoring
• To determine the effect of ACZ885 versus placebo on the 6-minute walk test (6MWT) distance of patients with sarcoidosis at 12 and 24 weeks compared to baseline	• 6MWT results at week 12 and 24 compared to baseline
• To determine the effect of ACZ885 on additional [F-18]FDG-PET outcomes (i.e., SUVmean, SUVpeak and volume of the lesions) after 12 weeks of treatment compared to placebo	• Percent change from initial scan in additional [F-18]FDG PET outcomes at week 12
• To assess the safety and tolerability of ACZ885 in patients with sarcoidosis as measured by adverse events (AEs)	• Adverse events in patients taking ACZ885 compared to placebo

1.3.3. Exploratory objective(s)

1.4 Study design and treatment

This is a subject- and investigator-blinded, randomized, placebo-controlled, parallel group, non-confirmatory study to assess the clinical efficacy of ACZ885 administered subcutaneously (s.c.) every four weeks for a total of 24 weeks.

The study will randomize approximately 38 patients with evidence of parenchymal involvement determined by HRCT and histologically proven, chronic pulmonary sarcoidosis of ≥1 year duration with persisting activity at baseline despite background therapy.

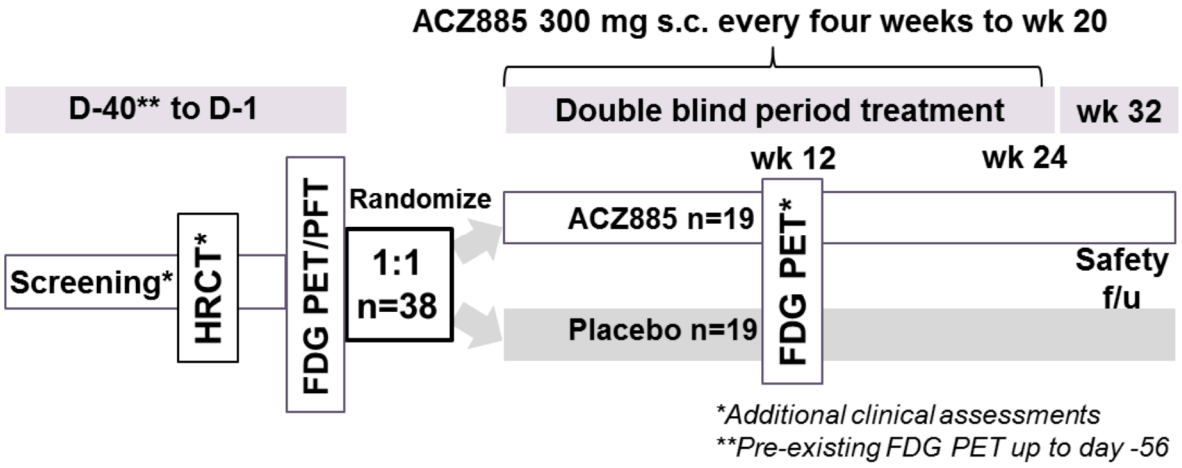

Figure 1-1: Study design scheme

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 available PK data and no protocol deviations with relevant impact on PK data.

The PD analysis set will include all subjects that received any study drug and that have no protocol deviations with relevant impact on PD data.

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

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*

Category Deviation code	Text description of deviation	Data exclusion
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*
Subjects are excluded from PD analysis after the PD date in case of these PDs:		Exclude subject from PD analysis set after the date of the event
COMD01	Prohibited medication used	*Yes*
Subjects are excluded from PK and PD analysis in case of these PDs:		Exclude subject from PK and PD analysis sets
INCL01	Deviation from inclusion criteria: Written informed consent was not obtained before any study assessment was performed	*Yes*

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

5 Statistical methods for Pharmacokinetic (PK) parameters

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

5.1 Variables

The following pharmacokinetic parameter will be determined: ACZ885 serum concentration.

5.2 Descriptive analyses

ACZ885 serum concentration data will be listed by subject and visit/sampling time point.

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 compare the effect of ACZ885 versus placebo on the clinical disease activity of sarcoidosis patients as measured by the change from baseline in the percent predicted forced vital capacity (FVC) at week 24.

6.1.1 Variables

The primary variable will be the change from baseline in percent predicted FVC after 24 weeks of treatment. The FVC is measured at screening, day 1, week 4, week 8, week 12, week 16, week 20 and week 24. Baseline is defined as day 1. At the visits (day 1 and week 24) where pre- and post-bronchodilation assessments are done, the pre-bronchodilation values are used.

6.1.2 Descriptive analyses

The raw percent predicted FVC values will be listed by treatment, subject and visit/time and 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.

Graphical methods will be employed to show mean (SD) figures for change in percent predicted FVC.

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. The model will investigate effects for treatment by time (included as a class variable) interaction, baseline by time interaction. Uninformative priors will be utilized to obtain the posterior estimates.

The posterior probability that ACZ885 is better than placebo in terms of change from baseline in percent predicted FVC at 24 weeks will be derived. If it is at least 90%, it will be considered a sign of efficacy of ACZ885 in increasing FVC after 24 weeks of treatment in this patient population.

The primary analysis will include all available information in terms of measurements at all times. If missing measurements are missing at random, 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.

6.1.3.1 Graphical presentation of results

Model estimated means with 90% credibility intervals will be used to present the results over time.

6.1.4 Supportive analyses

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6.1.5 Sensitivity analyses

A sensitivity analysis will be performed on the primary endpoint adding PET positivity (yes/not) prior to randomization a factor. The same analysis as defined in Section 6.1.3 will be performed, and adding PET positivity as a covariate in the model.

A further sensitivity analysis may be performed using an LOCF imputation for missing values. The main purpose of this analysis will be the investigation of potential bias, caused by subjects excluded from the analysis due to prohibited concomitant medication use (as concomitant medication increase is primarily due to poor response). However, the analysis will not be restricted to these subjects. A summary of prohibited medication incidence (as defined by the Protocol Deviations database), will be produced which will present the number of subjects with COMD01 deviations and time to first COMD01 deviation by treatment group, this summary will serve to decide whether the LOCF analysis will be performed.

6.2 Secondary objectives

6.2.1 Variables

Secondary variables for this study are:

- [F-18]FDG-PET/CT
- HRCT
- Pulmonary function tests: Change from baseline in absolute and % predicted FVC, FEV1, FEF25-75, FEV1/FVC, FEV3, FEV3/FVC, FEV6, TLC, RV, RV/TLC, DLCO, and post-bronchodilator FEV1/reversibility and other parameters as needed
- 6MWT outcomes: Change from baseline in distance, oxygen saturation, hearth rate and Borg Questionnaire score

For the pulmonary function test parameters the direction of benefit is as follows

- an increase in values is beneficial: absolute and % predicted FVC, FEV1, FEF25-75, FEV1/FVC, FEV3, FEV6, FEV3/FVC, DLCO
- a decrease in values is beneficial: RV, TCL, RV/TCL.

[F-18]FDG-PET/CT

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

- A maximum of 5 focal nodal uptake regions (mediastinal, hilar)
- A maximum of 5 focal regions of uptake in lung parenchyma
- A maximum of 5 extra-thoracic focal uptake regions on the whole body scan [F-18]FDG-PET/CT mean
- Reference regions
    - Lung parenchyma, unaffected by focal lesion uptake
    - Ascending aorta blood pool

The mean of the SUVmax values (resp. SUVmean) for each category will be taken to obtain one SUVmax value (resp. SUVmean) per patient / time point / category. The percent change from initial scan mean SUVmax values (resp. SUVmean) will be used for all analysis.

Also the change in the individual lung nodules will be examined, using a discretized scale of complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) as in the oncology European Organization for Research and Treatment of Cancer criteria for [F-18]FDG-PET/CT (Young et al, 1999).

High resolution computed tomography

The HRCT scans will be evaluated using the following HRCT scoring systems:

- Parameters provided by Paraxel*:
    - total parameter score
    - total sarcoidosis score
    - and HRCT results evaluated for worsening, improvement, or stable outcome by independent reviewer(s)
- Parameters provided by MedQIA read-out:
    - Key: Percentage air trapping in the whole lung
    - Secondary: Percentage air trapping at the lobar level (i.e. by location)

and HRCT results evaluated for worsening, improvement, or stable outcome by two independent assessors consolidated into one reading by MedQIA.Change in HRCT total score from initial scan will be used for analysis.

Details on the derivations of these scores are provided in the study's independent imaging charter and they will be included in the source database.

*Where multiple reviewers have assessed the Paraxel HRCT, the worse results will be selected for categorical summaries and the mean will be used for the continuous.

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. Graphical methods will be employed to show mean (SD) figures for raw or derived value (such as change from baseline or percent change from baseline) for each endpoint.

Incidences of patients with complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) will be summarized by treatment group over time, patients who discontinue for lack of efficacy will be treated as a separate category in this summary. The best response by subject will also be summarized by treatment group; CR is the best possible response and will supersede any previous response of PR or SD. PR will supersede SD. If a subject has a response of PD this is the only best response they can have.

The correlation between changes from initial FDG-PET scan in SUVmax and changes from baseline in FVC, FEV1, PROs, 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.

Summary stats by PET positivity will be provided for the analyses on:

- PET data
- HRCT total scores
- 6MWT
- FEV1,FEV3,FEV6 (L as well as % of predicted)

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

6.2.3 Statistical model, assumptions and hypotheses

[F-18]FDG-PET/CT

The mean percent change from baseline in SUVmax in the nodules at week 12 will be analyzed using ANCOVA with baseline SUVmax as a covariate and treatment as factor.

The same analysis as for the percent change from baseline in mean SUVmax in the nodules will be performed for the percent change from baseline in SUVmax in the lung parenchyma and the extra-thoracic regions, where available, at week 12. It will also be repeated for SUVmean in the parenchyma.

The percentage of patients with at least 50% reduction of SUVmax in nodules will be analyzed via logistic regression with baseline SUVmax as a covariate and treatment and PET positivity (yes/no) prior to randomization as factors.

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

High resolution computed tomography

Change in total HRCT score and total parameter scores from initial scan to 24 weeks will be analyzed, using an ANCOVA model with baseline HRCT score as a covariate and treatment at screening as factors.

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

Key Pulmonary function tests (FEV1, FEV3 and FEV6)

FEV1, FEV3 and FEV6 (both in liters and percent as units) 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.

6.3 Exploratory objectives

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 PET disease assessment and MMRC dyspnea scale), and treatment information.

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, current medical conditions, results of laboratory screens, drug tests and any other relevant information 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.

Vital signs

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

ECG evaluations

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

Clinical laboratory evaluations

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

Adverse events

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.

Immunogenicity

All immunogenicity results will be listed by subject and visit/time.

7.1.3 Graphical presentation

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

8 Statistical methods for Biomarker data

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9 Reference list

Young H, Baum R, Cremerius U, et al (1999) Measurement of clinical and subclinical tumour response using [^{18}F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. Eur J Cancer; 35:1773-1782.