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Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

CJM112

CCJM112X2203

A randomized, subject and investigator blinded, placebo-controlled, multi-center study in parallel groups to assess the efficacy and safety of CJM112 in patients with moderate to severe inflammatory acne

Statistical Analysis Plan (SAP)

Personal Data

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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 ***"CCJM112X2203".***

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 (v02) is available at the time of finalization of this Statistical Analysis Plan amendment v01.

1.3 Study objectives

1.3.1. Primary objective(s)

Primary objective(s)	***Endpoints related to primary objectives***
• To assess the efficacy of CJM112 versus placebo on facial inflammatory lesion counts in patients with moderate to severe inflammatory acne.	• Total inflammatory facial lesion count at week 12.

1.3.2. Secondary objective(s)

Secondary objective(s)	***Endpoints related to secondary objective(s)***
• To assess the safety and tolerability of CJM112 in patients with moderate to severe inflammatory acne.	• Number and severity of AEs • Safety and tolerability assessments including general safety parameters (laboratory parameters, physical examination, vital signs, ECG assessed at baseline and repeatedly until study completion visit.
• To assess the PK of CJM112 in patients with moderate to severe acne.	• Cmin,ss (multiple doses) from serum concentration data (non-compartmental analysis).

1.4 Study design and treatment

This is a randomized, placebo controlled, subject and investigator blinded, multi-center, non-confirmatory, parallel group, proof of concept study in patients with moderate to severe inflammatory acne. After an initial screening period (up to 4 weeks), the study is conducted in 2 consecutive treatment periods, each of 12 weeks, to show clinical efficacy (in treatment period 1) and potential sustainability of response (in extension period 2). At the beginning of treatment period 1, patients will be randomized to one of 3 treatment groups for the first 12 weeks only:

1. CJM112 at monthly intervals,
2. CJM112 at monthly intervals,
3. Placebo s.c. at monthly intervals.

At the end of treatment period 1, all patients will be offered to the opportunity to remain in the study for the extension period 2. Patients who enter extension period 2 will receive the following treatments:

- Treatment Period 1, . Extension Period 2,
- Treatment Period 1, Extension Period 2,
- Treatment Period 1, Placebo. Extension Period 2, via re-randomization with a randomization ratio of 1:1.

Therefore, exposure to placebo will be limited to a maximum of 12 weeks (treatment period 1). To keep the blinding at each time point, 3 injections will be given.

Whether patients continue or do not continue into extension period 2, all patients will be followed up for safety and potential sustainability of efficacy, for an additional 13 weeks without any treatment.

Figure 1-1: Study design

2 First interpretable results (FIR)

First interpretable results (FIR) will be provided for this trial.

4 Statistical methods: Analysis sets

For all analysis sets, patients will be analyzed according to the study treatment(s) received. This implies that for patients for whom the actual treatment received does not match the randomized treatment, the treatment actually received will be used for the analysis.

All patients who received at least one dose of any study drug will be included in the safety data analysis "safety population".

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

All patients with evaluable PD parameter data and no major protocol deviations impacting PD data will be included in the PD data analysis "PD population".

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

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Patients are excluded from all *(safety)* analysis in case of these PDs:		Exclude patient completely from all ***(safety)*** analysis sets
Patients are excluded from PK analysis in case of these PDs:		Exclude patient from PK analysis set
Patients are excluded from PD analysis in case of these PDs:		Exclude patient from PD analysis set

Category Deviation code	Text description of deviation	Data exclusion
Patients are excluded from PK and PD analysis in case of these PDs:		Exclude patient from PK and PD analysis sets

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

5 Statistical methods: Group presentations

For the analysis plan here onwards, treatment groups are defined as below and these groups will be followed for most summary tables by period and treatment group, unless otherwise stated.

- Period 1 (P1, up to and including Visit 201): Treatment group for Period 1 i.e.:
  - CJM112
  - CJM112
  - and Placebo.
- Extension Period 2 (P2, from Visit 201 onwards) and post-treatment follow-up: Treatment sequence for the people participating in the extension i.e.:
  - CJM112 CJM112
  - CJM112 CJM112
  - Placebo/ CJM112
  - Placebo/CJM112

For the summary statistics when performed by period and summary plots (such as mean plots and boxplots), unless otherwise stated, Visit 201 will be included in both P1 and P2; the "Post-treatment Follow-up" epoch will be summarized together with P2.

Patients not entering P2 and proceeding directly to follow-up, unless stated otherwise, will also be summarized for alone (without patients entering Period 2) in a table including all their P1 assessments and follow-up assessments. Respective summary plots are not planned but may be provided, if deemed necessary by the team.

Individual (Spaghetti) plots over time will be performed, unless otherwise stated, by sequence and will include the whole duration of the study.

6 Statistical methods for Pharmacokinetic (PK) parameters

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

6.1 Variables

The following pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher): Cmin,ss from the serum concentration-time data.

6.2 Descriptive analyses

CJM112 serum concentrations (µg/mL) will be listed by treatment group, patient, and visit/sampling time point. Descriptive summary statistics will be provided by treatment group and visit/sampling time point. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, maximum, and the frequency (n, %) of concentrations below the LLOQ. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values.

Pharmacokinetic parameters will be listed by treatment group and patient, and summarized by treatment with descriptive statistics as listed above. Graphical methods will be employed to show mean and individual concentration-time profiles over the whole study by treatment sequence, with time defined as visit and actual day respectively.

7 Statistical methods for Pharmacodynamic (PD) parameters

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

7.1 Primary objectives

The primary aim of this study is to assess the efficacy of CJM112 versus placebo on inflammatory facial lesion counts in patients with moderate to severe inflammatory acne in Period 1.

7.1.1 Variables

The primary variable is the natural log transformed total inflammatory facial lesion counts. Baseline is defined as the Visit 101 assessment.

7.1.2 Descriptive analyses

The primary variable will be listed by treatment sequence, patient, period and visit/time, and descriptive statistics will be provided, for raw, change from baseline and percentage change from baseline, by period, treatment group and visit/time. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, maximum; geometric mean and its CV will only be provided for the raw values.

Graphical methods will be employed to show geometric mean and individual (Spaghetti) plots over time.

7.1.3 Statistical model, assumptions and hypotheses

The log transformed inflammatory facial lesion count will be analyzed using a Bayesian model for repeated measurements. The model will include effects including log transformed baseline inflammatory facial lesion count, treatment group, visit, treatment group by visit interaction and

log transformed baseline inflammatory facial lesion count by visit interaction. A non-informative prior will be utilized to obtain the posterior estimates and an unstructured covariance will be assumed. Other factors such as gender and race may also be explored if the distribution per factor is reasonably balanced. The log transformed baseline will be centered and standardized before used in the model.

The posterior estimates of the treatment effect and the treatment difference (along with its 90% credibility interval) at each visit (with Week 12 being of primary interest) will also be provided. The results will be reported in terms of ratio of geometric means by back transforming the estimates from the log-scale.

7.1.4 Model checking procedures

All patients with available data after baseline and until Week 12 will be included in the primary analysis. The primary analysis model is known to give unbiased results under the assumption that missing data are at random (MAR), i.e. given observed data the missingness does not depend on unobserved data. If a patient drops out of the study according to the predefined discontinuation criteria (Protocol Section 7.2), this MAR assumption remains valid. Besides, last observation carried forward (LOCF) method will be used in a sensitivity analysis to handle missing data.

7.1.5 Sensitivity analyses

As a sensitivity analysis, the facial inflammatory lesion count at Week 12 will be analyzed via a generalized linear model with a Poisson or negative binomial distribution, depending on the dispersion. Baseline lesion count will be used as a covariate (or offset variable) and treatment group as a factor.

The primary analysis may be repeated with Baseline defined as the mean of Screening and Visit 101.

7.1.6 Supportive analyses

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Due to the nature of the primary endpoint, heterogeneity may also be observed due to different assessors and sites, hence as a supportive analysis site and/or assessor may also be included in the primary analysis model as fixed effects to investigate site/assessor impact.

Further, supportive analyses may be performed adding other covariates in the model such as baseline IGA and other baseline characteristics in the model.

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8 Statistical methods for safety and tolerability data

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

8.1.1 Variables

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

8.1.2 Descriptive analyses

Patient demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment sequence and patient and summarized by period, treatment group. Baseline background data include but are not limited to absolute neutrophil count and neutrophil count percentage of peripheral white blood cell (WBC) count.

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

Treatment

Use of concomitant medications and data on administration of study drug will be listed by treatment sequence, and patient.

Vital signs

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

ECG evaluations

QTcF will be listed by treatment sequence, patient and visit/time, and abnormalities will be flagged. Summary statistics will be provided by period, treatment group and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment sequence, patient, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by period, treatment group and visit/time.

Adverse events

All information obtained on adverse events will be displayed by treatment sequence and patient.

Adverse events tabulations will be done separately for the following time windows:

- Period 1:
    - Including all data until before Week 12 visit for all patients. A pooled CJM112 group will be added in the summary for P1.
    - Including all data (including follow-up data) for patients not continuing to Period 2. A pooled CJM112 group will be added in the summary for P1.
- Period 2 plus post-treatment follow-up: Including all data from the Week 12 till EoS. A pooled CJM112 and pooled CJM112 groups will be added in the summary for this period.

The number and percentage of patients with adverse events will be tabulated by body system and preferred term with a breakdown by period and treatment. A patient with multiple adverse events within a body system is only counted once towards the total of this body system and treatment. Separate tables and listings will be presented indicating event severity and study drug relationship.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on <on-treatment/treatment emergent> adverse events which are not serious adverse events with an incidence greater than X% and on <on-treatment/treatment emergent> serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population. The value of the cutoff value X will be decided with the team when disclosure tables are prepared.

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.

Immunogenicity

All immunogenicity results will be listed by sequence, patient and visit/time.

Other safety evaluations

Pregnancy test results will be listed by treatment sequence, patient and visit/time.

8.1.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameter) will be created. Mean and overlaying individual figures will be presented for selected parameters from vital signs, ECG and lab.

10 References

Fleischer AB, Dinehart S, Stough D, et al (2006) Safety and efficacy of a new extended-release formulation of minocycline. Cutis;78 (Suppl.4):21-31.
Fisch R, Jones I, Jones J, et al (2015) Bayesian Design of Proof-of-Concept Trials. Therapeutic Innovation & Regulatory Science; 49: 155-162.