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Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

CJM112

CCJM112X2204

A randomized, subject- and investigator-blinded, placebo controlled, multi-center, multiple dose study to assess the efficacy and safety of CJM112 in patients with inadequately controlled moderate to severe asthma

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 **"CJM112X2204".**

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 and IA outputs.

1.2 Study reference documentation

Final study protocol (version v01) is available at the time of finalization of the original Statistical Analysis Plan and the version v02 of the study protocol is available at the finalization of SAP Amendment 3.

1.3 Study objectives

1.3.1 Primary objective

Primary objective	**Endpoints related to primary objectives**
• To determine whether treatment with CJM112 in patients with inadequately controlled moderate to severe asthma leads to an improvement in airflow obstruction.	• Change from baseline FEV1 in L.

1.3.2 Secondary objective(s)

Secondary objective(s)	**Endpoints related to secondary objectives**
• To determine whether treatment with CJM112 in patients with inadequately controlled moderate to severe asthma leads to an improvement in FEV1% of predicted.	• Change from baseline FEV % of predicted.
• To determine whether treatment with CJM112 in patients with inadequately controlled moderate to severe asthma leads to an improvement in asthma control.	• Change from baseline in ACQ score, % of patients with ≥ 0.5 decrease in ACQ score.
• To assess the safety and tolerability of CJM112 in patients with inadequately controlled moderate to severe asthma.	• Study treatment discontinuations and adverse events.

1.3.3 Exploratory objective(s)

1.4 Study design and treatment

This is a non-confirmatory, randomized, subject- and investigator-blinded, placebo-controlled, multi-center, parallel-arm study evaluating the efficacy of CJM112 on top of standard of care in patients with inadequately controlled moderate to severe asthma.

This study will enroll approximately 110 male and female patients between 18 and 75 years old with uncontrolled symptoms of moderate or severe asthma (defined by ACQ score of ≥1.5) who are compliant on standard of care medications.

After an initial screening visit and run-in period of 4 weeks, subjects eligible per inclusion and exclusion criteria at the baseline visit will be randomized (3:2) to receive Company Confidential Information CJM112 or matching placebo subcutaneously over 3 months during visits at the clinical study site. All baseline safety evaluation results must be available prior to the first dose. After the end of the treatment period, subjects will be followed for an additional Site visits to administer dose and assess safety and efficacy will be scheduled as depicted in the figure below.

At least two interim analyses (IA) will be conducted, as further described below.

Figure 1-1 Study design

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2 First interpretable results (FIR)

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3 Interim analyses

4 Statistical methods: Analysis sets

For subjects 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 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 experienced no protocol deviations with relevant impact on PK data.

The PD analysis set will include all subjects with any available PD data and experienced no protocol deviations with relevant impact on PD or efficacy data. If a subject has an asthma exacerbation adverse event during the study, all subsequent efficacy assessments will be excluded from the PD analysis set.

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
Subjects are excluded from PD analysis in case of these PDs:		Exclude subject from PD analysis set
INCL05	Deviation from inclusion criterion 5	Yes
INCL07	Deviation from inclusion criterion 7	Yes
EXCL01	Deviation from exclusion criterion 1	Yes

Category Deviation code	Text description of deviation	Data exclusion
EXCL02	Deviation from exclusion criterion 2	Yes
EXCL03	Deviation from exclusion criterion 3	Yes
EXCL07	Deviation from exclusion criterion 7	Yes
EXCL20	Deviation from exclusion criterion 20	Yes
EXCL21	Deviation from exclusion criterion 21	Yes
EXCL22	Deviation from exclusion criterion 22	Yes
COMD01	Use of prohibited medication during the study	Yes (from this visit onwards)
WITHO1	Patient who met withdrawal criteria but were not withdrawn	Yes (from the visit subjects met withdrawal criteria onwards)

If updates to this table are needed, an amendment to the SAP will 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

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5.2 Descriptive analyses

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6 Statistical methods for Efficacy /Pharmacodynamic (PD) parameters

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6.1 Primary objective

To determine whether treatment with CJM112 in patients with inadequately controlled moderate to severe asthma leads to an improvement in airflow obstruction.

6.1.1 Variables

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6.1.2 Descriptive analyses

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6.1.2.1 Graphical presentation of results

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6.1.3 Statistical model, assumptions and hypotheses

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6.2 Handling of missing values/censoring/discontinuations

The repeated measures analysis includes all available information in terms of measurements at all times. If missing measurements are assumed missing at random, an analysis of the available

data provides consistent estimates of model parameters, i.e. given observed data the missingness does not depend on unobserved data. Alternative assumptions may be explored to investigate the robustness of the results under plausible non-missing at random situations. Reasons for dropouts will be explored.

A Kaplan Meier plot of time to dropout (any reason) will be produced to assess dropouts.

The inclusion of the data of subjects who miss at least one dose will be determined on a case-by-case basis, and will be decided during the Protocol Deviation assignment in a blinded fashion.

For spirometry assessments, a pre- and post-bronchodilator assessment should be conducted during baseline and at visits 105, 107, 201, and 299. Both short and long acting bronchodilators must be withheld prior to the study visits as described in the SOM, patients must be instructed to withhold bronchodilators (both short and long acting) prior to performing spirometry at applicable visits, as follows:

- Short-acting β2-agonists (SABAs) ≥ 6 h
- SAMA ≥ 8 h
- Long-acting bronchodilators (LABAs and LAMAs) given twice daily ≥ 24 h
- Long-acting bronchodilators (LABAs and LAMAs) given once daily ≥ 48 h

When bronchodilators are given combined with ICS, the ICS component will have to be withheld as well. When such situation arises, and rescheduling of the visit is not possible, the spirometry test results and other parameters that involves Spirometry results, e.g. ACQ7, will be omitted from analysis for that visit.

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6.3 Secondary objectives

To determine whether treatment with CJM112 in patients with inadequately controlled moderate to severe asthma leads to an improvement in

- FEV1% of predicted.
- asthma control

6.3.1 Variables

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6.3.2 Descriptive analyses

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6.3.3 Statistical model, hypothesis, and method of analysis

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6.4 Exploratory objectives

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6.4.2 Descriptive analyses

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6.4.3 Statistical model, assumptions and hypotheses

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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 Variables

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

7.2 Descriptive analyses

Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and patient. 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 patient.

Treatment

Data for study drug administration, rescue medication and concomitant therapies will be listed by treatment group and patient.

Vital signs

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

ECG evaluations

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

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, patient, 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 group and visit/time.

Boxplots of laboratory data will also be provided.

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.

The number and percentage of subjects with adverse events by maximum severity of adverse events will be tabulated by body system and preferred term with a breakdown by treatment.

The number and percentage of subjects with adverse events classified as related to study drug will be tabulated by body system and preferred term with a breakdown by treatment.

<u>Asthma exacerbation AE</u>

Adverse events related to asthma will also be analyzed separately using safety analysis set as detailed below.

The number and percentage of subjects with any one AE preferred term corresponding to exacerbation of asthma will be summarized for each treatment group.

In addition the 'Time to first exacerbation' in days, will be presented graphically by treatment group using a Kaplan-Meier plot. A summary table the number and percentage who had exacerbations treated with antibiotics without steroids by treatment group will be presented together with the Kaplan-Meier plot. Descriptive statistics will also be summarized in a tabular format. Time to first exacerbation is defined as:

Start date of the AE – Date of first treatment dose + 1

A Cox proportional hazard model with previous exacerbations and baseline IgE will be performed to compare the time to first exacerbation between CJM112 and placebo.

Patients that have completed the study but did not experience any event during the study will be right censored at their EOS.

Patients that discontinued from the study but did not experience any event during the study will be right censored at the day of discontinuation.

Patients that are still ongoing in the study but did not experience any event by the time of data cut date then these subjects will be right censored at this date.

ClinicalTrials.gov and EudraCT

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 2 % 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 $\leq$ 1-day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number and percent of deaths will be provided by treatment group.

Other safety evaluations

Immunogenicity

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

Pregnancy

Pregnancy test results will be listed by treatment group, subject and visit/time.

7.3 Graphical presentation

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8 Statistical methods for biomarker data

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9 Reference list

Fisch R, Jones I, Jones J, et al (2015) Bayesian Design of Proof-of-Concept Trials. Therapeutic Innovation & Regulatory Science; 49: 155-162.

Busse W, Holgate S, Kerwin E, et al (2013) Randomized, Double-Blind, Placebo-controlled Study of Brodalumab, a Human Anti–IL-17 Receptor Monoclonal Antibody, in Moderate to Severe Asthma.

Wenzel S, Castro M, Corren J, et al (2016) Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomized double-blind placebo-controlled pivotal phase 2b dose-ranging trial.

10 Appendix 1: Historical clinical trials use in meta-analyses of informative prior of FEV1.

Table 10-1 Mean change from baseline of FEV1 (L) at Week 12 in the placebo group of the selected six studies

Selected study	Selected population	n	FEV1 change from baseline (L)	SE
AIN457D2204	IgE < 100 IU/ml	7	0.007	0.098
QBX258X2201	IgE <400 IU/ml	9	0.015	0.116
QAW029A2206	overall	136	0.038	0.039
QAW039A2214	non-atopic	93	0.03	0.029
Dupilumab (Wenzel et al, 2016)	eos count < 300	71	0.1	0.040
Brodalumab (Busse et al, 2013)	overall	76	0.056	0.036