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Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

CDZ173

CCDZ173X2203

A randomized, double-blind, placebo-controlled, parallel group study to assess the safety, tolerability, pharmacokinetics and preliminary efficacy of CDZ173 in patients with primary Sjögren's syndrome

Statistical Analysis Plan (SAP)

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Document type: SAP Documentation – NIBR

Document status: Final Version 2

Release date: 30-June-2017

Number of pages: 16

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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 "*CCDZ173X2203*".

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

1.2 Study reference documentation

This SAP has been developed using Clinical Trial Protocol version v00 (original protocol) dated 26 January 2016.

1.3 Study objectives

1.3.1 Primary objectives

- To assess the safety and tolerability of CDZ173 in patients with primary Sjögren's syndrome (pSS).
- To compare the effect of CDZ173 versus placebo on the patient reported outcome (ESSPRI) of pSS patients after 12 weeks of treatment (study week 13).

1.3.2 Secondary objectives

- To assess the pharmacokinetics of CDZ173 in pSS patients.
- To evaluate the effect of CDZ173 versus placebo on clinical disease outcomes (ESSDAI, SF-36, MFI) in pSS patients after 12 weeks of treatment (study week 13).
- To evaluate the changes in the physician global assessment of the patient's overall disease activity after 12 weeks of treatment (study week 13).
- To evaluate the changes in the patients' self-reported global assessment of their disease activity after 12 weeks treatment (study week 13).

1.3.3 Exploratory objectives

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1.4 Study design and treatment

This is a double-blind, randomized, placebo-controlled, parallel design, non-confirmatory study to assess the safety, tolerability, pharmacokinetics and preliminary clinical efficacy of multiple oral doses of CDZ173 (70 mg b.i.d.) in patients with pSS.

The study will consist of a 4-week screening period, a baseline period prior to randomization, a 12-week treatment period and a 4-week follow-up period (no study drug or study visits) before the End of Study visit. The total duration for each patient in the study will be approximately 21 weeks.

Approximately 27 patients will be randomized (2:1) to a 12 week treatment receiving either CDZ173 or placebo. Randomization will be stratified according to baseline glucocorticoid intake (yes/no).

For the entire duration of the treatment period (12 weeks), patients will receive a b.i.d. dosing regimen to be administered at approximately 12 h intervals.

Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, biochemistry and urinalysis) as well as adverse event and serious adverse event monitoring.

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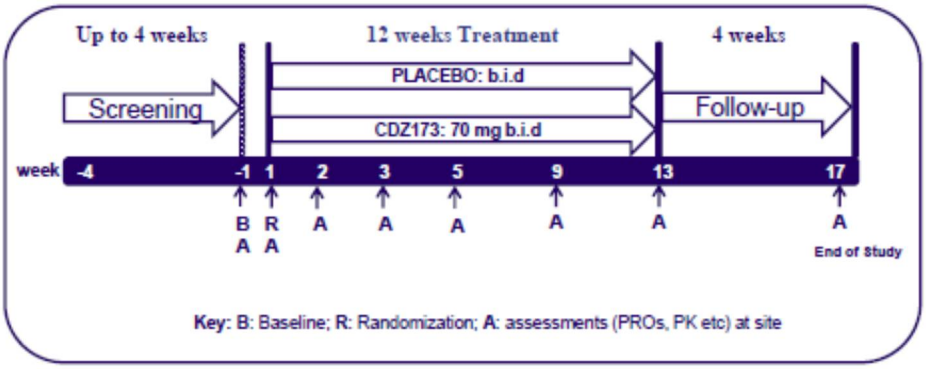
Other assessments to be completed are outlined in the Assessment schedule in the protocol.

The study design is summarized in Figure 1-1 below:

Figure 1-1 Study Design



2 First interpretable results (FIR)

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3 Interim analyses

4 Statistical methods: Analysis sets

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

All subjects that received study drug and with no protocol deviations with relevant impact on safety will be included in the safety analysis set.

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 baseline and post-dose PD data, who received any study drug and experienced no protocol deviations with relevant impact on PD data.

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 all *(safety)* analysis in case of these Protocol deviations:		Exclude subject completely from all ***(safety)*** analysis sets
I1	ICF not obtained	
I2	ICF was signed after the other screening procedures; ICF wrong version was obtained.	
S1	If Patient did not take the drug ever	

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from PK analysis in case of these Protocol deviations:		Exclude subject from PK analysis set
I1	ICF not obtained	
I2	ICF was signed after the other screening procedures; ICF wrong version was obtained.	
S1	If Patient did not take the drug ever	
Subjects are excluded from PD analysis in case of these Protocol deviations:		Exclude subject from PD analysis set
S1	If Patient did not take the drug ever	
E1	Secondary Sjögren's syndrome	
I1	ICF not obtained	
I2	ICF was signed after the other screening procedures; ICF wrong version was obtained.	
I3	Diagnosis of primary Sjögren's syndrome	
I4	ESSDAI at screening/baseline ≥6	
I5	ESSPRI at screening/baseline ≥5	

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

5.1 Variables

The following plasma pharmacokinetic parameters will be determined using the actual recorded sampling times on Day 1 and non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher): Cmax, Tmax, AUC0-7h and AUClast. Other PK parameters may be added as appropriate. After multiple doses, PK will be summarized in terms of trough concentration (Ctrough).

PK parameters will be calculated as per Novartis Guidance on Standardization of Pharmacokinetic Parameters. The linear trapezoidal rule will be used for AUC calculation. Regression analysis of the terminal plasma elimination phase for the determination of T1/2 will include at least 3 data points after Cmax. If the adjusted R^2 value of the regression analysis of the terminal phase will be less than 0.75, no values will be reported for T1/2, AUCinf and CL/F. The extrapolated part of the AUCinf will not contribute to more than 20% of total AUC.

5.2 Descriptive analyses

The pharmacokinetics of CDZ173 will be evaluated in patients in the PK analysis set. CDZ173 plasma concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented. 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 and subject.

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5.2.1 Graphical presentation of results

Arithmetic mean (SD) and geometric mean (95% CI) plasma concentration data will be plotted over time.

Overlaying individual plasma concentration-time profiles will be generated along with concentration versus time profiles for individual subjects.

Relationships between exposure (average Ctrough over time) and selected PD variables, Corporate Confidential Information will be explored by a graphical approach and descriptive statistics of exposure and PD variables will be provided.

6 Statistical methods for pharmacodynamic (PD) parameters

6.1 Primary objective

6.1.1 Variables

The primary aims of this study are to assess safety in patients with pSS and to investigate the effect of CDZ173 on efficacy (as measured by the ESSPRI) at study week 13. The statistical analysis model will include ESSPRI data from all time points up to study week 13. The

primary efficacy variable is the ESSPRI change from baseline (based on the mean of the below first 3 questions from the questionnaire):

- How severe has your dryness been during the last 2 weeks?
- How severe has your fatigue been during the last 2 weeks?
- How severe has your pain been during the last 2 weeks?

The other questions will be listed but not summarized. The safety and tolerability, as described in Section 7, will be summarized.

6.1.2 Descriptive analyses

Summary statistics will be provided for baseline, as well as for absolute and percent change from baseline in ESSPRI, by treatment and timepoint.

6.1.3 Statistical model, assumptions and hypotheses

It is assumed that the ESSPRI will follow an approximately normal distribution.

A positive sign of therapeutic effects will be considered to be a reduction of at least 1 point in the change from baseline between CDZ173 and placebo with a moderate level of evidence. Additionally there should be a high level of evidence that is a difference between CDZ173 and placebo. These criteria will be evaluated by calculating Bayesian posterior probabilities as follows:

$Pr(\theta_{CDZ173,13w}-\theta_{placebo,13w} < 0 \mid data) > 90\%$ and
$Pr(\theta_{CDZ173,13w}-\theta_{placebo,13w} < -1 \mid data) > 50\%$
where θ means change from baseline in ESSPRI at 13 weeks.

It is assumed that Y_{ijt}, the observed change from baseline in ESSPRI for subject i receiving treatment j (CDZ173 or placebo) at time t, follows a normal distribution $N(\theta_{jt}, \sigma^2)$, It is further assumed that θ_{jt} follows a standard non-informative prior Normal distribution, $p(\theta_{jt}, \sigma^2) = 1/\sigma^2$.

The statistical model will be a repeated measures model fitting terms for treatment by timepoint and baseline by timepoint using the SAS procedure PROC MCMC. Estimates of the difference between CDZ173 and placebo at each timepoint will be derived from this model and presented together with 95% credible intervals. The estimates of the posterior probabilities of the efficacy criteria being met will be provided.

Patients with missing ESSPRI at baseline will not be included in the analysis. Patients with missing data at one or more timepoints post baseline will be included in the analysis. The planned model assumes that missing values are missing at random. The reasonableness of this assumption will be checked during the blinded review of the data and if necessary further methods may be applied.

6.1.3.1 Model checking procedures

Diagnostic output from the PROC MCMC model will be reviewed.

6.1.3.2 Handling of missing values/censoring/discontinuations

All subjects with a baseline ESSPRI and at least one post-baseline ESSPRI will be included in the primary analysis. The primary analysis method provides unbiased estimates of the treatment effect under the assumption that data are missing at random (MAR). Guidelines for subject discontinuation should ensure that this assumption is reasonable. If a substantial proportion (e.g. more than 15%) of subjects discontinue before week 13 visit, alternative methods to account for missing data may be considered.

Follow up visits from subjects who discontinued will not be included in the analysis.

For patients where treatment was withdrawn PD summary statistics and all the analysis using the PD analysis set will only include data that was measured <= 7 days after the treatment was stopped, i.e. data longer than 7 days after treatment discontinuation will be excluded. For individual figures using the PD analysis set all the data will be displayed but the lines will be solid up to the treatment discontinuation + 7 days and for subsequent time points the line should be dotted, i.e. the data that is excluded from the summary stats/analysis should be presented dotted.

If a subject took a prohibited medication then a footnote will be added to detail this in all PD outputs to explain that data after the usage make be affected by the medication.

6.1.3.3 Supportive analyses

The supportive analysis will be based on a longitudinal mixed model of change from baseline in ESSPRI as a function of baseline ESSPRI, baseline intake of steroids (yes/no, which is a stratification factor for the randomization), treatment, time (days from first treatment) as a continuous variable (linear and quadratic terms), interaction between treatment and time, as well as a random intercept, random slope and random quadratic effects by subject to account for within-subject correlations.

An unstructured covariance matrix for the random effects will be fitted along with an independent error matrix. The difference between active treatment and placebo in change from baseline in ESSPRI at study week 13 will be estimated from the model and presented with 80% and 95% confidence intervals (estimates will also be provided corresponding to the other visits where ESSPRI was assessed). Simpler models will also be considered in case the pre-specified model does not fit the data well.

Simpler models may be considered, including simpler covariance structures. If the time course does not appear to be quadratic, time may be modelled as a categorical variable.

The following criteria will be considered indicative of treatment efficacy:

- Statistically significant decrease in ESSPRI at week 13 visit on treatment compared to placebo (at one-sided 10% level)
- Estimated mean reduction in ESSPRI at week 13 visit for CDZ173 of 1 point or more than for placebo

6.1.3.4 Graphical presentation of results

Lsmean (SE) and individual profiles will be produced by treatment and time.

6.2 Secondary objectives

6.2.1 Variables

Secondary efficacy variables supporting the secondary objectives are:

- Change from baseline in ESSDAI
- Change from baseline in SF-36 for both physical and mental component
- Change from baseline in MFI
- Change from baseline in Physician and Patient VAS of global disease activity

There was a scaling problem with the printed batch for the CRF sheets for the VAS scale in Hungary. The line that is printed and which is marked by either the patient or the phy sician should be 100mm long, but in the Hungarian site both VAS scales only measured 95mm therefore both VAS scales for the Hungarian site will be transformed by multiplying by 1.053 to get comparable results to the German site.

In the listings both the actual measurement and the value based on a length of 100mm will be presented with the transformed results based on a length of 100mm used in all other VAS outputs.

The key timepoint is the week 13 visit.

6.3 Exploratory objectives

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7 Statistical methods for safety and tolerability data

7.1.1 Variables

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

Baseline concomitant medication related to pSS will be summarized by treatment group.

Summaries and listings of cumulative exposure to study drug (cumulative dose received over the treatment period) will be provided.

Heatmaps of exposure will be provided.

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.

In the protocol it was stated to use a longitudinal PK-QT model to check for concentration-dependent increase in QT. If this pooled analysis is done it will be presented in a separate report.

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.

Heatmaps of neutropenia and rashes will be presented.

Liver and renal events will be listed and summarized using frequency tables.

Other safety evaluations

Immunogenicity

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

Infections

The frequency of infections will be tabulated.

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

Biomarker data (except for hypothesis-free platforms), change from baseline and percentage changes from baseline will be listed by treatment, subject, and visit/time.

Summary statistics will be provided by treatment and visit/time. In the summary tables, the frequency (n, %) of values below the LLOQ and above the ULOQ, respectively, will be included.