

Clinical Development

CFZ533

CCFZ533X2203

**A multi-center, randomized, double-blind, placebo-controlled, parallel group study to assess the safety, tolerability, pharmacokinetics and preliminary efficacy of CFZ533 in patients with primary Sjögren's syndrome**

**TSc RAP Module 3: Detailed Statistical Methodology**

Personal Data

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## 1 Introduction to RAP documentation

### 1.1 Scope

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial “**CCFZ533X2203**”.

**Module 3 (M3) provides the description of the statistical methodology** used to analyze the data, **Module 7 (M7)** details the presentation of the data, including shells of summary tables, figures and listings, and **Module 8 (M8)** contains programming specifications e.g. for derived variables and derived datasets, to support the creation of CSR outputs.

### 1.2 Changes to RAP documentation (M3)

Refer to corresponding guidances and Translational Sciences (TSc) RAP Addendum template for detailed information on the requirements of documenting changes to RAP documentation.

**For the statistical methodology (M3)**, any major changes occurring before database lock to the statistical methodology should be reflected in the RAP M3 documentation via version control (new document version to be approved by the trial team as the original module).

Major changes include, but are not limited to, changes in protocol that affect study design and statistical methodology.

Minor changes to the RAP M3 documentation can be captured e.g. by a study note to file / note in RAP Addendum or within the CSR itself. Minor changes include, but are not limited to, change in statistical model. Corrections of typographical errors or modification of spelling (from English to American, for example) do not need to be incorporated into the RAP M3 documentation.

## **2 Study objectives and design**

### **2.1 Study objectives**

#### **2.1.1 Primary objectives**

- To assess the safety and tolerability of multiple subcutaneous doses and multiple intravenous infusion of CFZ533 in patients with primary Sjögren's syndrome (pSS) as measured by adverse events (AEs).
- To compare the effect of multiple intravenous infusion of CFZ533 versus placebo on the clinical disease activity of pSS patients as measured by the change of an EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) after 12 weeks treatment.

#### **2.1.2 Secondary objectives**

- To assess the safety and tolerability of multiple subcutaneous doses of CFZ533 in patients with pSS as measured by AEs.
- To compare the effect of multiple subcutaneous doses of CFZ533 versus placebo on the clinical disease activity of pSS patients as measured by the change of an ESSDAI after 12 weeks treatment.
- To assess the pharmacokinetics of multiple subcutaneous doses and multiple intravenous infusion of CFZ533 in pSS patients.
- To evaluate the effect of multiple subcutaneous doses and multiple intravenous infusions of CFZ533 versus placebo on self-reported outcomes in pSS patients after 12 weeks treatment as measured by the EULAR Sjögren's Syndrome Patient Reported Intensity (ESSPRI), the Short Form (36) Health Survey (SF-36) and the Multidimensional Fatigue Inventory (MFI) Questionnaire.
- To evaluate the changes in the physician global assessment of the patient's overall disease activity as recorded by a visual analog scale (VAS) after 12 weeks treatment.
- To evaluate the changes in the patients global assessment of their disease activity as recorded by a VAS after 12 weeks treatment.

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## 2.2 Study design and treatment

This is a double-blind followed by open-label, randomized, placebo-controlled, parallel-group, non-confirmatory study to assess the safety, tolerability, pharmacokinetics, and preliminary clinical efficacy of multiple doses of CFZ533 in the following Cohorts 1 and 2:

- Cohort 1: CFZ533 administered subcutaneously in patients with pSS, in a doubleblind and placebo-controlled fashion, followed by open-label treatment;
- Cohort 2: CFZ533 administered by intravenous infusion in patients with pSS, in a double-blind and placebo-controlled fashion, followed by open label treatment.

These cohorts will be followed by an open label, randomized, parallel group, non-confirmatory part of Cohort 3:

- Cohort 3 (patients with pSS):  
In treatment arm 1 CFZ533 will be given at [redacted] s.c. weekly on 4 occasions (loading regimen), followed by [redacted] s.c. weekly on 9 occasions (maintenance regimen starting on study day 29). In treatment arm 2, the loading regimen will consist of a single i.v. dose of [redacted] CFZ533 (on study day 1), followed by [redacted] s.c. weekly on 12 occasions (maintenance regimen starting on study day 8).

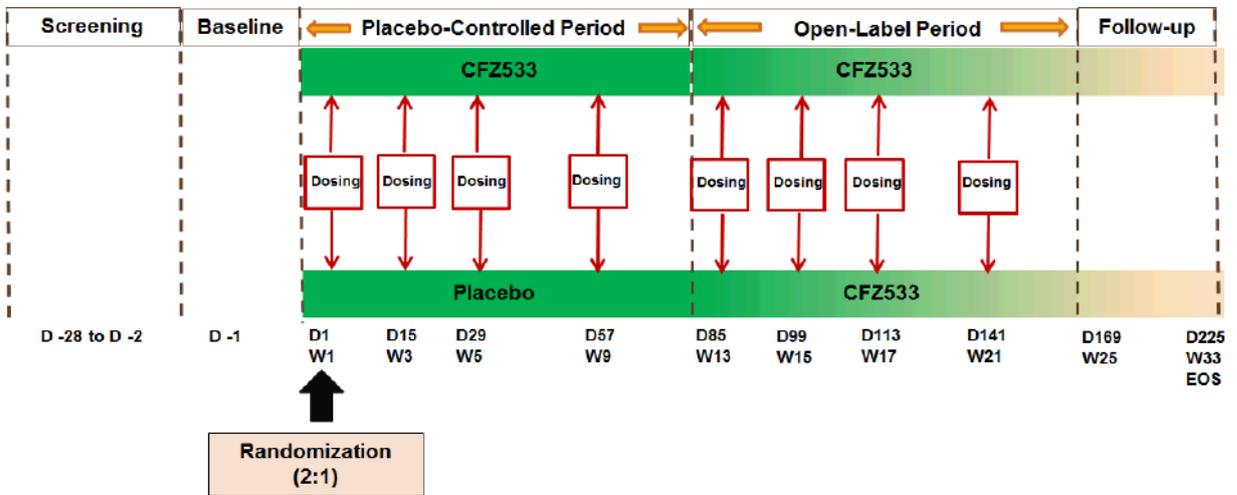
The study will randomize approximately 68 patients with primary Sjögren's syndrome. In Cohorts 1 and 2, the randomization will be stratified by baseline intake of oral corticosteroids (yes/no). There will be no stratification in Cohort 3.

The study comprises three periods for Cohort 1 and Cohort 2:

- 1) placebo-controlled period (from Day 1, Week 1 to completion of pre-dose assessments on Day 85, Week 13), during which 4 doses of CFZ533 or placebo will be administered on top of the standard of care therapy, (e.g., low dose corticosteroid) that is necessary to treat pSS;
- 2) open-label period (from dosing on Day 85, Week 13 to completion of assessments on Day 169, Week 25), when all patients will receive 4 doses of open-label CFZ533 treatment, and
- 3) follow-up period (Weeks 25 – 32), when patients will be followed up without study medication.

An illustration of the study design for Cohorts 1 and 2 is provided in Figure 2-1.

**Figure 2-1 Study design Cohort 1 and Cohort 2**



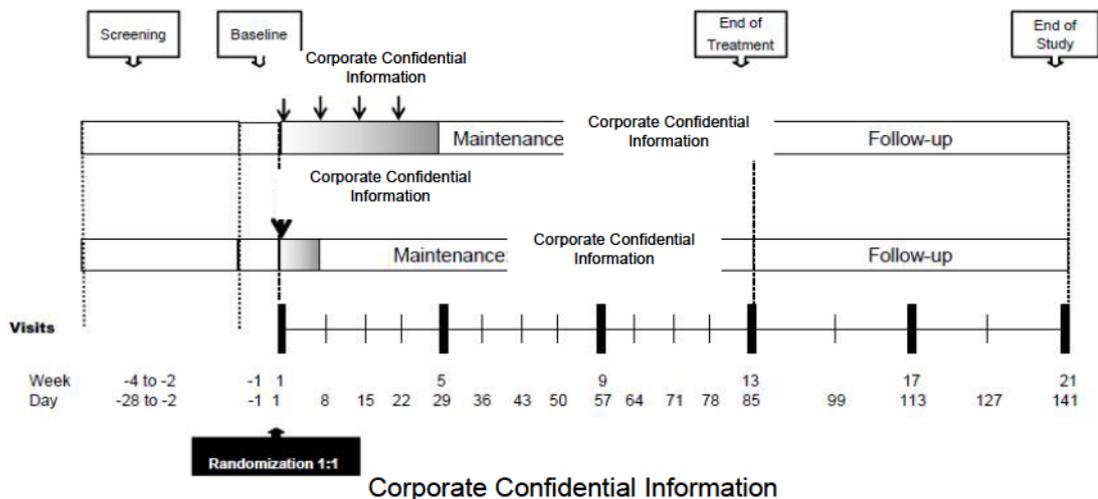
Cohort 3, comprises two periods, namely:

1. open-label treatment period (from dosing on Day 1, Week 1 to last dose and completion of assessments on Day 85, Week 13),
2. follow-up period (from Week 13 to Day 141/Week 21), when patients will be followed up for 8 weeks without study medication.

In the open label period, treatment arm 1 dosing starts with CFZ533 s.c. q1w for 4 weeks, whereas in treatment arm 2, dosing starts with CFZ533 i.v. on Day 1. In both arms maintenance dosing then continues with CFZ533 s.c. q1w for 4 weeks (treatment arm 1) or 9 weeks (treatment arm 2).

An illustration of the study design for Cohort 3 is provided in Figure 2-2.

**Figure 2-2 Study design Cohort 3**



### **3 First interpretable results (FIR)**

First interpretable results (FIR) will be provided for this trial but not as fully as usual due to interim analyses that have already occurred. Corporate Confidential Information

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The template shows the analysis / results to be presented in the FIR. Study outputs required to be created at the time of the FIR will be marked as “Key” in the Tracking sheet output list.

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## 5 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.

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 available PK data and 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.

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

**Table 5-1 Protocol deviation severity codes and analysis sets**

Protocol deviation severity code		Safety analysis set	PK analysis set	PD analysis set
Code	Text			
5	Exclude subject from all safety analysis	-	-	-
8	<i>Exclude from all analyses</i>	-	-	-
20	Exclude subject from PK analysis set	+	-	+
22	Exclude subject from PD analysis set	+	+	-
23	Exclude subject from PK and PD analysis set	+	-	-
49	Report relevant protocol deviation – include subject in all analysis sets	+	+	+

+ = include in analysis set, - = exclude from analysis set, NA = not applicable

## 6 Statistical methods for Pharmacokinetic (PK) parameters

### 6.1 Pharmacokinetic parameters

If data permits, the following pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental analysis: C<sub>max</sub>, C<sub>max,ss</sub>, C<sub>trough</sub>, C<sub>trough,ss</sub> and AUC's from the CFZ533 plasma concentration-time data. Concentrations below the LLOQ will be treated as zero for PK parameter calculations. The linear trapezoidal rule will be used for AUC calculation. Regression analysis of the terminal plasma elimination phase for the determination of T<sub>1/2</sub> will include at least 3 data points after C<sub>max</sub> (but not including C<sub>max</sub>). If the adjusted R<sup>2</sup> value of the regression analysis of the terminal phase is less than 0.75, T<sub>1/2</sub>, AUC<sub>inf</sub>, V<sub>z</sub>/F and CL/F will be excluded and indicated as missing values.

### 6.2 Analysis of pharmacokinetics

Plasma CFZ533 concentration data will be listed by cohort, treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by cohort, 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. Concentrations below LLOQ will be treated as zero in summary statistics. A geometric mean will not be reported if the dataset includes zero values.

Pharmacokinetic parameters will be listed by cohort, treatment and subject. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented.

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. During any modeling of PK data, the broad principles outlined in the FDA Guidance for Industry: Population Pharmacokinetics, will be followed.

## **7 Statistical methods for Pharmacodynamic (PD) parameters**

### **7.1 Analysis of the primary variable**

#### **7.1.1 Statistical model, hypothesis, and method of analysis**

The primary efficacy variable is the ESSDAI change from baseline.

It is assumed that the ESSDAI will follow an approximate normal distribution. If this assumption appears to not be met, alternative statistical methods may be applied. For example, data may be log transformed with changes from baseline in the log transformed data being analyzed.

The analysis of the data for the primary variable from Cohorts 1 and 2 differs from that proposed in the protocol in that it will not be conducted combining placebo data from those two cohorts. Being in two separate consecutive cohorts, one s.c. and the other i.v., they are not now considered similar enough to combine. As a result, the active treatments under consideration, Corporate Confidential Information are each compared to their respective matching placebo treatments within each cohort. Cohort 3 simply compares two alternative loading regimes.

For each of cohorts 1 and 2, a longitudinal model describing ESSDAI change from baseline over time will be fitted up to Week 13 with the following fixed effect terms: baseline ESSDAI, treatment group, visit, and interaction between treatment group and visit. In the first instance an unstructured variance-covariance matrix will be fitted; if there are issues with convergence then other variance-covariance matrices will be investigated. The change from baseline in ESSDAI at Week 13 (end of placebo-controlled period) will be estimated from the model. Inference will be done in the frequentist framework.

For Cohorts 1 and 2 the results from the primary analysis will be assessed against the following efficacy criteria:

- a statistically significant reduction in ESSDAI at Week 13 in the CFZ533 i.v. group compared to placebo, at the one-sided 10% significance level, and
- an estimated mean reduction in ESSDAI in the CFZ533 i.v. group to be 5 points or greater than placebo.

The decrease of 5 points was chosen because it is in the range of what was observed at week 12 in a small open-label study with rituximab ([Meiners et al 2012](#)). A positive sign of efficacy will be considered if both criteria are met.

In Cohorts 1 and 2, ESSDAI data after Week 13, where there is no longer a placebo treatment, will be examined similarly. It will also be summarized using descriptive statistics of both absolute values and changes from baseline and the raw data displayed graphically for individual patients and for visit treatment means. Graphs will also be used to display modelled treatment effects over time.

ESSDAI data from Cohort 3 up to Week 13 and then to Week 21 will also be analyzed in a similar way to the data from each of Cohorts 1 and 2, but with two active treatment groups instead of comparison with control. It will also be summarized with descriptive statistics and plots similarly.

### **Handling of missing values/censoring/discontinuations**

All subjects with a baseline ESSDAI and at least one post-baseline ESSDAI will be included in the primary analysis. The planned models assume that missing values are missing at random. The guidelines for subject discontinuation provided in the protocol should ensure that the missingness mechanism is as close as possible to missing at random. The reasonableness of this assumption will be checked and if necessary further methods may be applied.

### **Supportive analysis**

The Bayesian analyses proposed in the protocol for the interim analysis of Cohort 1 will serve as supportive to the main frequentist analysis above when applied in a similar manner to Cohorts 1 and 2.

Two Bayesian posterior probabilities as follows will be calculated for Cohorts 1 and 2:

$$\Pr(\theta_{CFZ533,13w} - \theta_{\text{placebo},13w} < 0 \mid \text{data})$$

$$\Pr(\theta_{CFZ533,13w} - \theta_{\text{placebo},13w} < -5 \mid \text{data})$$

where  $\theta$  means change from baseline in ESSDAI at Week 13.

It is assumed that  $Y_{ijt}$ , the observed change from baseline in ESSDAI for subject  $i$  receiving treatment  $j$  (CFZ533 or placebo) at time  $t$ , follows a normal distribution  $N(\theta_{jt}, \sigma^2)$ . It is further assumed that  $\theta_{jt}$  follows a standard non-informative prior Normal distribution,  $p(\theta_{jt}, \sigma^2) = 1/\sigma^2$ .

This statistical model will be a repeated measures Bayesian analysis with baseline as a covariate using PROC MCMC. Example SAS code is provided in the RAP Module 8. Estimates of the difference between CFZ533 and placebo at each timepoint will be derived from this model and presented together with 95% credible intervals.

If required, further frequentist supportive analyses will attempt to model the time effect to better describe changes over time. If so, the model may include the following covariates: baseline, treatment, time, treatment by time interaction, treatment by time squared interaction, as well as a random intercept and a random slope for each patient. Time may be modeled as a continuous variable. The model may be simplified if there are problems with convergence, including a simpler variance-covariance matrix. The treatment by time squared interaction will be included if it improves the fit.

## **8 Pharmacokinetic / pharmacodynamic interactions**

Modeling of PK/PD data using a population approach may be performed as appropriate by the Novartis PK group and reported in a separate standalone report.

These data will be summarized by cohort, treatment and subject. Descriptive statistics will also be provided, such as mean, median, standard deviation, minimum and maximum, by cohort, treatment and time point.

## **9 Statistical methods for safety and tolerability data**

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

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

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

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

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

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

All laboratory data will be listed by cohort, treatment, subject and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by cohort, treatment and visit/time. Individual B-cell and neutrophil counts over time by cohort, treatment group will be presented graphically.

All information obtained on adverse events will be displayed by cohort, 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 within cohort. A subject with multiple adverse events within a body system is only counted once towards the total of this body system.

The frequency of patients who have had infections by Week 13 will be tabulated and compared between treatment groups within Cohorts 1 and 2 with Fisher's Exact test.

Immunogenicity results will be listed by cohort, treatment, subject and visit/sampling time point. No descriptive summary statistics will be provided.

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## **11 Reference list**

Meiners PM, Arends S, Brouwer E, et al (2012) Responsiveness of disease activity indices ESSPRI and ESSDAI in patients with primary Sjögren's syndrome treated with rituximab. *Ann Rheum Dis*; 71:1297-302.