

Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

CFZ533

Study CCFZ533X2204

**A multi-center, randomized, double-blind,
placebo-controlled, parallel group study to preliminarily
evaluate the safety, tolerability, pharmacokinetics and
efficacy of CFZ533 in patients with moderate to
severe myasthenia gravis**

RAP Module 3: Detailed Statistical Methodology

Personal Data

Document type: Amendment 1 RAP Module 3: Detailed Statistical Methodology
Document status: Final
Release date 18 November 2016

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8	Statistical methods for safety and tolerability data.....	15
8.1.1	Variables	15
8.1.2	Descriptive analyses	15
8.1.3	Graphical presentation of results.....	16
9	Statistical methods for Biomarker data	17
10	Reference list.....	17

List of tables

Table 5-1	Protocol deviation codes and analysis sets	9
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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 “**CCFZ533X2204**”.

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 NIBR RAP Addendum template for detailed information on the requirements of documenting changes to RAP documentation.

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

Such major changes could include (but are not limited to):

- change in statistical methodology
- substantial change in (derivation of) main endpoint
- substantial change in study design (e.g. protocol amendment introducing new multiple-dose cohorts in a so far single-dose trial)

Such changes may also require a protocol amendment to ensure consistency. In addition they need to be mentioned (high-level) in the CSR (section for changes to planned analysis).

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. Corporate Confidential Information

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.

Analyses and outputs related to additional exploratory ad-hoc requests used for reporting are regarded minor changes and should be documented in the RAP addendum (no RAP amendment necessary).

2 Study objectives and design

2.1 Study objectives

2.1.1 Primary objectives

- To evaluate the safety and tolerability of IV CFZ533 as an add-on therapy to standard of care in patients with moderate to severe Myasthenia gravis (MG) throughout the study
- To evaluate the efficacy of IV CFZ533 as an add-on therapy to standard of care in patients with moderate to severe MG

2.1.2 Secondary objectives

- To evaluate the efficacy of IV CFZ533 using relevant MG related outcome measures throughout the 24 weeks treatment period
- To evaluate the decay in efficacy of IV CFZ533 using relevant MG related outcome measures throughout the 24 weeks follow-up period
- To evaluate changes in patient's quality of life (QOL) throughout the 24 weeks treatment period
- To evaluate the PK of 2-hour IV infusion of CFZ533 at 10 mg/kg administered q4w for 6 doses (endpoint: free CFZ533 in plasma)
- To evaluate the PD of CFZ533 (CD40 saturation on B cells, extent/duration of target engagement (endpoints: free CD40 on B cells, total CD40 on B cells, and total soluble CD40 in plasma)
- To assess immunogenicity in CFZ533-treated patients and in placebo-treated patients (pre-existing anti-drug antibodies)

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2.2 Study design and treatment

This is a randomized double-blind, placebo controlled, non-confirmatory study to preliminarily evaluate the safety, tolerability, PK/PD, and efficacy of IV CFZ533 administered every four weeks (q4w) over a 24 week treatment period in patients with moderate to severe MG. The investigational drug or placebo will be administered in addition to standard of care therapy for MG.

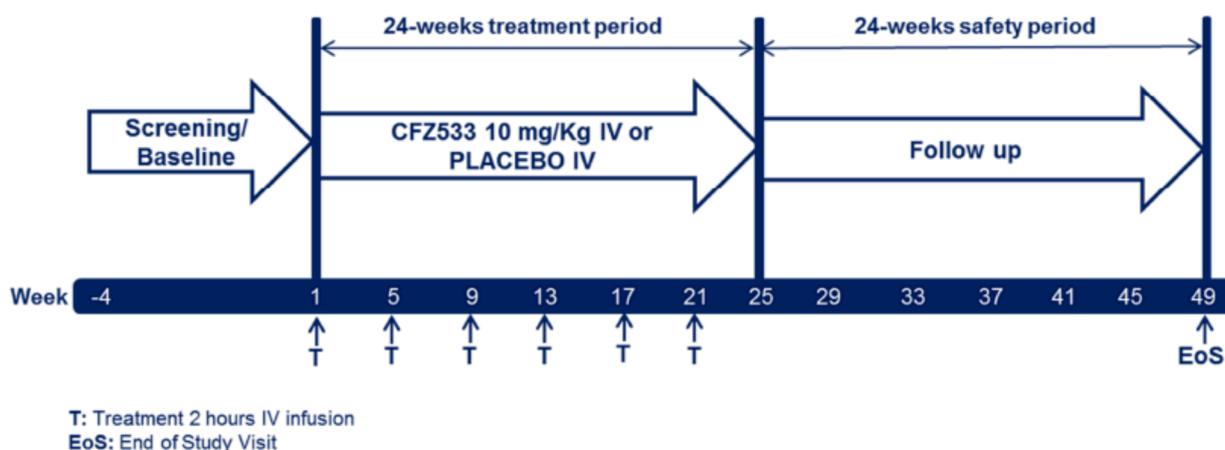
Patients should remain on their standard of care therapies and the dose should be maintained at a constant level during the study. For patients that are receiving corticosteroids at baseline, a predefined steroid tapering will be allowed after achievement of minimal manifestations (MM) state (Jaretzki et al 2000).

Patients on cholinesterase inhibitors (CI) should remain on stable doses throughout the study, but CIs should not be taken for at least 12 hours prior to QMG and MG composite testing at each visit, in order to reduce fluctuations in performance on functional tests due to the temporary symptomatic effects associated with CI use.

For each patient, there will be two screening visits. Most of the screening assessments are done during Screening Visit 1 (Day -28 to Day -8), while Screening Visit 2 (Day -7 to Day -3) is performed to collect a blood sample to allow laboratory results (chemistry, hematology, and pregnancy test, if applicable) to be available prior to randomization on Day 1. All laboratory results must be available prior to dosing (Day 1-Visit 3) and meet eligibility criteria. Once continued eligibility is confirmed, patients will be assigned a randomization number at Day 1 and receive CFZ533 or placebo via a 2-hour intravenous infusion. Patients will be dosed every four weeks (q4w) according to their randomization for a total of 6 doses on Day 1 ± 2 (Week 1), Day 29 ± 2 (Week 5), Day 57 ± 2 (Week 9), Day 85 ± 2 (Week 13), Day 113 ± 2 (Week 17) and Day 141 ± 2 (Week 21). The treatment period (24 weeks) will be followed by a safety follow-up period of other 24 weeks. The duration of the entire study including screening will be approximately 52 weeks.

An overview of the study design is given in Figure 2-1.

Figure 2-1 Study design



3 First interpretable results (FIR)

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

The study FIR template (mock slides) can be found in CREDI in the study RAP folder.

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 highlighted in RAP Module 7 and marked as “Key” in the M9.1 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.

The full analysis set (FAS) will include all patients who received any study drug.

The safety analysis set will include patients who received any study drug.

The PD analysis set will include all patients who received any study drug and with no protocol deviations with relevant impact on efficacy data.

The PK analysis set will include patients with available PK data and no protocol deviations with relevant impact on PK data.

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

Table 5-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion	
Subjects are excluded from all (<i>safety</i>) analysis in case of these PDs:		Exclude subject completely from all (<i>safety</i>) analysis sets	
<i>I##</i>	<i>ICF not obtained</i>		
<i>I##</i>	<i>ICF was signed after the other screening procedure; ICF wrong version was obtained.</i>		
<i>E##</i>	<i>xxxxxxx</i>		
Subjects are excluded from PK analysis in case of these PDs:		Exclude subject from PK analysis set	
<i>I06</i>	<i>Deviation from inclusion criterion 6.</i>		YES
<i>E##</i>	<i>xxxxxxx</i>		

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
<i>I06</i>	<i>Deviation from inclusion criterion 6.</i>	YES
<i>E##</i>	<i>xxxxxxx</i>	
Subjects are excluded from PK and PD analysis in case of these PDs:		Exclude subject from PK and PD analysis sets
<i>I06</i>	<i>Deviation from inclusion criterion 6.</i>	YES
<i>E##</i>	<i>xxxxxxx</i>	
Subjects are excluded from PD analysis at the impacted visit in case of these PDs:		Exclude subject from PD analysis set at the impacted visit
<i>M02</i>	<i>Use of Cholinesterase inhibitors less than 12 hours prior to QMG and MGC testing.</i>	YES

If updates to this table are needed, an amendment to RAP M3 needs to be implemented prior to DBL.

6 Statistical methods for Pharmacokinetic (PK) parameters

6.1.1 Variables

The following PK parameters will be determined, if data permit, using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher): C_{max}, C_{max,ss}, C_{min,ss}, T_{max}, AUC_{tau}, AUC_{tau,ss} and C_{av,ss} from the plasma concentration-time data.

In the zz.xpt file in GPSII (merge file), PK concentration (free CFZ533 in plasma) will be expressed in unit 'microg/mL' (in addition to 'nanog/mL'), and time will be expressed in unit 'day' (in addition to 'hours'). Two variables for the elapsed time will be provided: (i) elapsed time since first dose, and (ii) elapsed time since last dose.

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6.1.3 Statistical model, assumptions and hypotheses

Not applicable.

6.1.4 Model checking procedures

Not applicable.

6.1.5 Graphical presentation of results

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

Overlaying individual plasma concentration-time profiles will be generated.

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7 Statistical methods for Pharmacodynamic (PD) parameters

7.1 Primary objective

The primary objectives of this study are to preliminarily evaluate the safety, tolerability and efficacy of IV CFZ533 in moderate to severe Myasthenia Gravis patients after 24 weeks of treatment as an add-on therapy to standard of care as compared to placebo.

7.1.1 Variables

The primary efficacy variable is the change from baseline in QMG score after 24 weeks of treatment (at Week 25 visit). The baseline value will be the predose assessment on Day 1. It is assumed that the change from baseline in QMG score is normally distributed.

The analysis of safety and tolerability is descriptive and detailed below in Section 8.

7.1.2 Descriptive analyses

Descriptive summary statistics will be provided by treatment and visit/sampling time point. Summary statistics will include mean, SD, median, minimum and maximum.

7.1.4 Graphical presentation of results

Arithmetic mean (\pm SD) of QMG score and change from baseline in QMG score will be plotted across time.

The posterior probability distribution from the Bayesian analysis will be plotted at Week 25.

7.1.5 Handling of missing values/censoring/discontinuations

No imputation of missing data dropouts or any other reason will be done. The main analysis model will include all data of all patients in the PD analysis set, including dropouts.

7.2 Secondary objectives

7.2.1 Variables

Secondary efficacy/pharmacodynamic variables include:

- change from baseline in MGC score after 24 weeks of treatment (at Week 25 visit)
- proportion of patients requiring rescue therapy (i.e. IV immunoglobulins or plasma exchange).
- mean change from baseline in QMG Score and MGC Score at all visits
- proportion of patients with improvement by ≥ 3 points in QMG score
- proportion of patients with worsening by ≥ 3 points in QMG score
- proportion of patients intolerant to steroid taper (i.e the proportion of patients that will require to reinstitute their previous steroid dose)
- proportion of patients who discontinued due to inefficacy or worsening
- Mean change in the Myasthenia Gravis Activities of Daily Living Scales (MG-ADL, MG QOL-15).
- Free and total CD40 on B cells (peripheral blood)
- Total soluble CD40 in plasma.

The baseline value for all secondary variables will be the predose assessment on Day 1.

An improvement is a reduction in QMG score and worsening is an increase in QMG score.

7.2.2 Descriptive analyses

Descriptive summary statistics of efficacy data will be provided by treatment and visit/sampling time point. Summary statistics will include mean, SD, median, minimum and maximum.

7.2.3 Statistical model, assumptions and hypotheses

The changes from baseline in MGC scores at each visit of the treatment period (weeks 5, 9, 13, 17, 21 and 25) will be analyzed using a mixed effect model for repeated measurements. The model may investigate effects for treatment (CFZ533 or placebo), time (visit week), baseline MGC score, treatment by time and baseline by time interactions. An unstructured covariance matrix may be used to model the correlations between the measurements in the same subject. In case of convergence issues, the covariance matrix that best fit the data will be chosen. The estimated treatment differences at each visit will be provided with 90% CI and 2-sided p-values.

Other potentially influential factors such as sex, age at onset of the disease, markers of baseline severity of the disease or prednisone dose may be explored.

The changes from baseline in MG-ADL and MG QOL-15 at each visit until Week 25 will be analyzed using the main mixed model as described above for MGC.

The proportions of patients requiring rescue therapy between Week 1 and Week 25 (i.e. IV immunoglobulins or plasma exchange) will be summarized. Time to first rescue therapy will be described using Kaplan-Meier curves and compared between CFZ533 and placebo using the logrank test. In case of dropouts, the data will be censored at the last visit before or at Week 25.

The changes from baseline in MGC score at Week 25 will be analyzed using the Bayesian model described above.

The proportion of patients with improvement by ≥ 3 points in QMG score at Week 25, the proportion of patients with worsening by ≥ 3 points in QMG score at Week 25, the proportion of patients intolerant to steroid taper and the proportion of patients who discontinued due to inefficacy or worsening before Week 25 will be analyzed via logistic regression with treatment as a factor (and baseline value as a covariate if relevant) compared between CFZ533 and placebo. Additional covariates such as sex, gender, age at onset of MG, QMG score at baseline will be explored. Odds ratios together with 90% CI and p-values will be provided for comparisons of CFZ533 versus placebo utilizing the logistic regression model fitted.

7.2.4 Model checking procedures

In case of convergence issues, the covariance matrix that best fit the data will be chosen.

Diagnostic plots will be provided.

7.2.5 Graphical presentation of results

Arithmetic mean (\pm SD) of secondary variables (MGC, MG-ADL, MG QOL-15, CD40 on B cells and total soluble CD40 in plasma) and their change from baseline will be plotted across time.

The proportion of patients requiring rescue therapy, the proportion of patients with improvement by ≥ 3 points in QMG score, the proportion of patients with worsening by ≥ 3

points in QMG score, the proportion of patients intolerant to steroid taper and the proportion of patients who discontinued due to inefficacy or worsening will be shown via bar charts.

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8 Statistical methods for safety and tolerability data

8.1.1 Variables

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

8.1.2 Descriptive analyses

All safety analyses will be performed on the safety analysis set; patients will be analyzed as treated.

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.

Serum total immunoglobulin G (IgG) and M (IgM)

Serum total IgG and IgM and percentage change from baseline will be listed by subject and visit/time. No descriptive summary statistics will be provided.

Immunogenicity

All immunogenicity results will be listed by subject and visit/time. No descriptive summary statistics will be provided.

8.1.3 Graphical presentation of results

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

9 Statistical methods for Biomarker data

All biomarker data (except for hypothesis-free platforms) will be listed by treatment, subject, and visit/time. Summary statistics for each variable (absolute and change from baseline) 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.

In case of censored values (values below the LLOQ and/or values above the ULOQ), the summary statistics (arithmetic mean, SD, geometric mean and CV% of geometric mean) will be calculated as the maximum likelihood estimates using a parametric model for data that can be right censored and left censored assuming the data being normally or log-normally distributed.

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Concomitant immunosuppressive therapies trough levels

Plasma/blood concentrations for mycophenolic acid (MPA), azathioprine metabolite(s) or cyclosporine will be listed by treatment, subject, and visit/sampling time point. No descriptive summary statistics will be provided.

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10 Reference list

Jaretzki A, Barohn RJ, Ernstoff RM et al. (2000) Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. *Ann Thorac Surg.* 70(1):327-34.