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Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

CCFZ533

CCFZ533X2205

An open label study to evaluate the safety and efficacy of 12 week treatment with CFZ533 in patients with Graves' disease

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 *"CCFZ533X2205"*.

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

1.2 Study reference documentation

This SAP is based on protocol v01 (amended protocol) dated 16-Mar-2016.

1.3 Study objectives

1.3.1 Primary objective

To assess the effects of CFZ533 on thyroid function in Graves' disease (GD) after 12 week treatment.

1.3.2 Secondary Objective

To assess the safety and tolerability of CFZ533 (10 mg/kg IV for 12 weeks) up to 36 weeks.

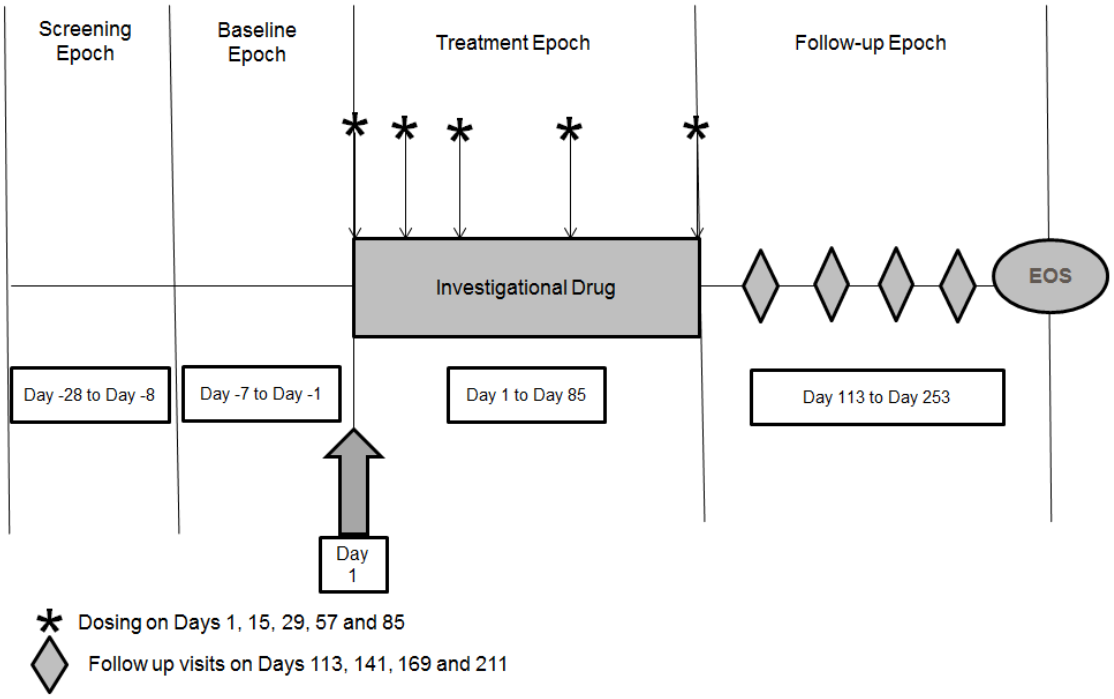
1.3.3 Exploratory objectives

1.4 Study design and treatment

This is a non-confirmatory, open-label, one treatment arm study in patients with newly diagnosed GD.

A total of approximately 15 patients will be enrolled and treated with CFZ533 to ensure approximately 12 completers. For each patient, the study will consist of a screening epoch of up to 28 days, a baseline evaluation, a 12-week treatment epoch, 24-week follow up epoch after the last dosing of CFZ533 on Study Day 85, and a study completion evaluation on Study Day 253. Patients who discontinue the drug before having completed 4 weeks of treatment and 4 week efficacy and safety evaluations will be replaced with a newly enrolled patient. The study design is presented in Figure 1-1.

Figure 1-1 Study design



2 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 TFL shells document and marked as "Key" in the Programming Deliverables Tracker (PDT) output list.

3 Interim analyses

4 Statistical methods: Analysis sets

For all analysis sets, patients will be analyzed according to the study treatment received.

All patients 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 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.

The PD analysis set will include all patients with any available PD data, who received any study drug and experienced no protocol deviations with relevant impact on PD data, who have completed at least 4 weeks of treatment with CFZ533.

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 PDs:		Exclude subject completely from all ***(safety)*** analysis sets
I01	Deviation from inclusion criteria 1 (ICF not obtained)	Yes
	No study drug taken	Yes
Subjects are excluded from PK analysis in case of these PDs:		Exclude subject from PK analysis set
I01	Deviation from inclusion criteria 1 (ICF not obtained)	Yes
	No study drug taken	Yes
Subjects are excluded from PD analysis in case of these PDs:		Exclude subject from PD analysis set
I01	Deviation from inclusion criteria 1 (ICF not obtained)	Yes
	No study drug taken	Yes

Category Deviation code	Text description of deviation	Data exclusion
	Subject took any prohibited medications interfering with efficacy	Yes
Subjects are excluded from PK and PD analysis in case of these PDs:		Exclude subject from PK and PD analysis sets
I01	Deviation from inclusion criteria 1 (ICF not obtained)	Yes
	No study drug taken	Yes

There are two categories of medications which are considered rescue medication. In order to identify these for programming purposes these are included in the protocol deviations dataset with codes of O01 and O02 (oral corticosteroids and anti-thyroid drugs) however they are not protocol deviations so will not be included in the protocol deviations listing, instead they will be included in a separate rescue medication listing.

In PD outputs the following rules will be applied to subjects who received rescue medication

- Data post rescue medication will be flagged in the listings with a * and a footnote added to explain.
- Figures showing individual profiles will appear as red lines from the point at which the rescue medication was taken and a footnote added to explain.
- In summary tables and summary figures datapoints after rescue medication will be excluded and a footnote added to explain.
- In the inferential analyses datapoints after rescue medication will be excluded and a footnote added to explain. For the longitudinal models the model is expected to provide unbiased results under the assumption that the rescue medication intake can be considered dependent only on previously observed values (MAR – missing at random).

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

Cmin 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.

The zz.xpt file in GPSII will combine PK output (free CFZ533 in plasma) as well as PD readouts including: free CD40 on blood B cells, total CD40 on blood B cells, total soluble CD40 in plasma, and total soluble CD154 in plasma. Also, for these PD readouts, two variables for the elapsed time will be provided (see above chapter).

Concentrations below the LLOQ will not be considered for PK parameter calculations.

5.2 Descriptive analyses

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5.2.1 Graphical presentation of results

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5.2.2 Pharmacokinetics/Pharmacodynamics relationships

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6 Statistical methods for Pharmacodynamic (PD) parameters

6.1 Primary objective

The primary aim of this study is to assess the effects of CFZ533 on thyroid function, focusing on TSH levels, total T3 and free T4 in GD after 12 weeks of treatment.

6.1.1 Variables

The effects of CFZ533 on thyroid function will be primarily assessed by the proportion of

patients whose TSH levels normalize (above 0.35 mU/L) after 12 weeks of treatment (TSH responders). They will also be assessed by the difference in mean total T3 and free T4 between baseline (Day 1, predose) and after 12 weeks of treatment, and the proportion of patients whose total T3 or free T4 levels normalize (below ULN) after 12 weeks of treatment.

6.1.2 Descriptive analyses

TSH levels will be summarized over time together with their changes from baseline. The frequency of TSH responders will be summarized for each timepoint. Same statistical analysis will be performed for the frequency of patients whose total T3 and free T4 levels normalize. Results will also be presented for free T3 and total T4.

6.1.3 Statistical model, assumptions and hypotheses

One of the main efficacy criteria for this study is to show that the proportion of patients with normalization of TSH (above 0.35 mU/L) after 12 weeks of treatment with CFZ533 is statistically greater than 5%, according to a 1-sided exact test for proportions with a 10% type I error. This will be achieved if we observe at least 3/12 responders since in that case the lower bound of an 80% confidence interval for the proportion of responders will be about 10%. The other efficacy criteria are that there is a significant reduction in average total T3 and free T4 after 12 weeks of treatment, according to a 1-sided paired t-test with 10% type I error for each of these two endpoints. Results will also be presented for free T3 and total T4 and at week 20.

6.1.3.1 Handling of missing values/censoring/discontinuations

Patients who discontinue after the 4 week efficacy assessment for any reason will be considered non-responders in the primary analysis (unless their last recorded TSH value was after 8 weeks of treatment and was above the lower limit of the normal range, 0.35 mU/L). Patients who discontinue before 4 weeks of treatment for any reason will be replaced and not counted for the calculation of responders. For total T3 and free T4, the last recorded value will be used for the change from baseline (Day 1, predose), provided it was obtained after at least 8 weeks of treatment.

6.1.3.2 Supportive analyses

In case more than 2 discontinuations occur in this study, additional methods may be used to assess sensitivity of the results to different imputation techniques to deal with the missing data.

Total and free T3 and T4 will be analyzed using a repeated measures model with baseline as a covariate and visit as the repeated effect. The difference from Day 1 at each timepoint will be presented along with the 80% CI and the 2 sided p-value.

6.1.3.3 Graphical presentation of results

Mean (SD) TSH levels and Mean (SD) change from baseline in TSH levels will be plotted over time. Overlaying TSH level profiles will also be presented. Similar figures will be presented for total and free T3 and T4. Overlaying profiles will have separate pages for all

subjects, subjects that have received rescue medication and subjects that received no rescue with the time of the start of the rescue medication indicated on the plot.

Bar charts of the number of TSH responders will be plotted over time. Similar bar charts will be plotted for the frequency of patients whose total and free T3 and T4 levels normalize.

6.2 Secondary and exploratory objectives

6.2.1 Variables

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6.2.2 Descriptive analyses

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6.2.2.1 Graphical presentation of results

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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 patient demographics, baseline characteristics, and treatment information.

7.1.2 Descriptive analyses

Patient demographics and other baseline characteristics

All data for background and demographic variables including background medication (type of medication and mean dose per day, with the average prednisone equivalent dose in mg presented for steroids) 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, patient, 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, patient 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, patient, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing is provided presenting all parameters in a patient 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 patient.

The number and percentage of patients with adverse events will be tabulated by body system and preferred term with a breakdown by treatment and repeated for adverse events that were suspected to be related to the study medication. A separate table will also be produced for adverse events of infection. A patient with multiple adverse events within a body system is only counted once towards the total of this body system and treatment.

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