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CFZ533 (iscalimab)

Study number CCFZ533X2202

A randomized, placebo-controlled, patient and investigator blinded study investigating the safety, tolerability, pharmacokinetics and preliminary efficacy of multiple doses of CFZ533 in patients with moderately active proliferative lupus nephritis

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 **"**CCFZ533X2202" and also for the requirements for the interim analyses.

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

1.2 Study reference documentation

This Statistical Analysis Plan is based on the protocol version 04 dated 26JUL2021.

1.3 Study objectives

1.3.1 Primary Objectives

- To evaluate the safety and tolerability of 24 weeks of treatment with CFZ533 as an add-on therapy to standard of care in moderately active lupus nephritis (LN) patients.
- To assess the effect of CFZ533 on renal proteinuria in moderately active lupus nephritis patients after 24 weeks of treatment as an add-on therapy to standard of care as compared to placebo.

1.3.2 Secondary Objectives

- To assess the effect of CFZ533 on relevant renal outcomes at different time points.
- To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of CFZ533 in LN patients, after multiple 10 mg/kg IV doses.
- To evaluate the immunogenicity of CFZ533 in LN patients, after multiple 10 mg/kg IV doses.

1.3.3 Exploratory Objectives

1.4 Study design and treatment

This is an exploratory, randomized (2:1 active:placebo), subject- and investigator-blind, placebo-controlled, multicenter study evaluating the safety, tolerability, pharmacokinetics and preliminary efficacy of multiple doses of 10 mg/kg CFZ533 administered intravenously (IV) in lupus nephritis patients.

The study will randomize approximately 60 subjects with moderately active lupus nephritis. The study comprises two periods. The 24-week treatment period will be followed by a 24-week safety follow-up period (starting on Day 169). The duration of the study (including a screening period of up to 4 weeks) for each subject will be approximately 53 weeks. The investigational drug or placebo will be administered on top of standard of care therapy for lupus nephritis. The randomization will be stratified by baseline daily dose equivalent of prednisone (≤10 mg, >10 mg). Patients who do not receive corticosteroids at baseline will be included in the ≤10 mg stratum.

Subjects will be screened within 29 days of the first study drug infusion. Eligibility will be confirmed at the baseline visit within one week before the first dose. All baseline safety evaluation results must be available prior to dosing, and meeting eligibility criteria. Eligible subjects will enter the treatment period, and will be randomized at a 2:1 ratio to receive treatment with either CFZ533 or placebo. Subjects will receive the intravenous infusion on Day 1 within seven days of the baseline visit, followed by PK, PD, and safety assessments until one hour after completed infusion.

All infusions will take place in a monitored facility with assessment of vital signs ahead of the infusion. Subjects will be discharged 1 hour post-dose following satisfactory review of safety data (AE events, vital signs) by the Investigator.

Each patient will come to the study site for the follow-up evaluations on Day 169, Day 197, Day 225, Day 253, Day 281, Day 309, and Day 337, respectively. Patients should remain on their standard of care therapies. Dose of standard of care (SoC) therapies (see eligibility criteria and permitted co-medications) must remain unchanged during the study. However, in case of SoC related toxicities, doses of concomitant medications may be adjusted at the investigator's discretion. For patients who are taking corticosteroids at baseline, a predefined steroid regimen (Table 1-1) will be implemented including a taper for patients who receive more than 10 mg per day at baseline. After Week 17 (Visit 106), patients should not receive a steroid dose higher than 10 mg per day (prednisone equivalent).

Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (also including serum amylase and lipase), hematology (including blood coagulation assays), blood chemistry, urinalysis, adverse event, serious adverse event and AEs of special interest.

Proteinuria will be assessed using urine samples collected in the patients' home (first morning void sample) and at clinic (clinic spot urine sample)

PK/PD and immunogenicity assessments at pre-dose, and during treatment and follow up periods include (i) free CFZ533 in plasma (Ctrough or Cmin, and Cmax in steady state conditions), total soluble CD40 in plasma, and (iii) anti-CFZ533 antibodies in plasma.

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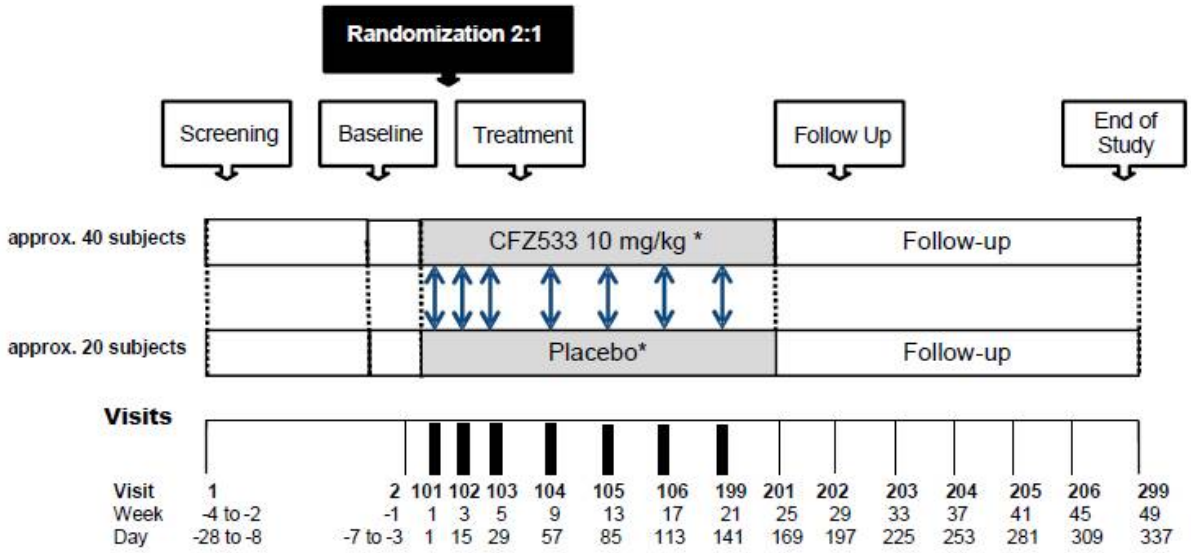
Table 1-1 Predefined steroid tapering scheme

Dose (x) at BL (prednisone equivalent) [mg/day]	Visit 103 (Day 29±2)	Visit 104 (Day 57±2)	Visit 105 (Day 85±2)	Visit 106 (Day 113±2)	Visit 199 (Day 141±2)	After Visit 201 (Day 169±3)
0<x≤10	Maintain the baseline dose			Half the baseline dose		As needed
10<x≤20	Maintain the baseline dose			10	10	As needed
20<x≤30	Maintain the baseline dose		20	10	10	As needed

Figure 1-1 Study design



* CFZ533 or placebo 10 mg/kg i.v. on Day 1, 15, 29, 57, 85, 113, and 141

2 First interpretable results (FIR)

3 Interim analyses

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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 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 experienced no protocol deviations with relevant impact on PD data.

Selected summaries with and without the data obtained after treatment discontinuation may also be presented.

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 PK analysis in case of these PDs:		Exclude subject from PK analysis set
INCL01	Understand the study procedures and provide written informed consent before any study related assessment is performed.	
INCL04	Histological diagnosis of proliferative lupus nephritis World Health Organization (WHO) ISN/RPS (Weening et al 2004) Class III or IV within 5 years of screening.	Exclude subject from PK analysis set
INCL06	First morning void or spot urine UPCR ≥0.5 mg/mg (56.52 mg/mmol) at Screening visit and Baseline visit	Exclude subject from PK analysis set
Subjects are excluded from PD analysis in case of these PDs:		Exclude subject from PD analysis set
INCL01	Understand the study procedures and provide written informed consent before any study related assessment is performed.	
INCL04	Histological diagnosis of proliferative lupus nephritis World Health Organization (WHO) ISN/RPS (Weening et al 2004) Class III or IV within 5 years of screening.	Exclude subject from PD analysis set
INCL06	First morning void or spot urine UPCR ≥0.5 mg/mg (56.52 mg/mmol) at Screening visit and Baseline visit	Exclude subject from PD analysis set
Subjects are excluded from PK and PD analysis in case of these PDs:		Exclude subject from PK and PD analysis sets
INCL01	Understand the study procedures and provide written informed consent before any study related assessment is performed.	
INCL04	Histological diagnosis of proliferative lupus nephritis World Health Organization (WHO) ISN/RPS (Weening et al 2004) Class III or IV within 5 years of screening.	Exclude subject from PK and PD analysis sets
INCL06	First morning void or spot urine UPCR ≥0.5 mg/mg (56.52 mg/mmol) at Screening visit and Baseline visit	Exclude subject from PK and PD analysis sets

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 pharmacokinetic parameters will be determined for free CFZ533 in plasma (i) Ctrough or Cmin, and Cmax will be directly derived from the bioanalytical data and listings, and (ii) AUClast from the last dose at Day 141 will be determined using the actual recorded

sampling times and non-compartmental methods with Phoenix WinNonlin (Version 8.0 or higher). The linear trapezoidal rule will be used for AUClast calculation.

The pharmacokinetics of CFZ533 is non-linear and characterized by target-mediated disposition where CD40 binding by CFZ533 is leading to CFZ533 elimination (this includes receptor-mediated endocytosis by the membrane bound CD40, and subsequent metabolism of the CFZ533-CD40 complexes). As such, it is expected that:

- The amount of drug-target complex does influence the pharmacokinetics of CFZ533,
- Tissue metabolism may have a significant impact on the disposition of CFZ533 (the volume of distribution will be dependent on clearance),
- The volume of distribution may not be accurately inferred from plasma concentration alone, and the values for the volume of distribution obtained from a non-compartmental analysis (NCA) may be incorrect,
- Volume of distribution and clearance parameters (as inferred from NCA analysis) would decrease when the dose increases.

The NCA approach is not appropriate due to violations of the assumptions that the disposition of the drug is linear, and that the elimination is from sites that are in rapid equilibrium with blood, therefore secondary PK parameters (e.g. clearance, volume of distribution or terminal elimination half-life) will not be determined in this study

For each PK and total soluble CD40 samples, the actual recorded sampling time will be captured, and the elapsed time since the first and since the last dose before sample collection will be calculated. PK samples which are collected +/- 30% of the scheduled post-dose timepoint will be excluded from the summary statistics.

5.2 Descriptive analyses

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5.2.1 Graphical presentation of results

Arithmetic mean (SD) profiles will be generated along with overlaying individual plasma concentration-time profiles and individual plasma concentration-time profiles.

5.3 Pharmacokinetic/pharmacodynamics interactions

PK/PD analysis (e.g. incl. free CFZ533 and total soluble CD40 in plasma) may be explored graphically. Modeling of PK/PD data using a population approach may be performed as appropriate and will be reported if necessary in a separate, standalone modeling and simulation report.

6 Statistical methods for Pharmacodynamic (PD) parameters

Baseline is defined as the last available value prior to dosing and will include Screening if no other value after Screening is available.

For UPCR and UACR where the analyses are split between first morning void and clinic spot samples then the last available value prior to dosing from the first morning void or clinic spot sample respectively will be used. For the analyses that use the first morning void when available and the clinic spot sample if it is not available then the last available first morning void prior to dosing will be used as the baseline, if there are no first morning void values available prior to dosing then the last available clinic spot sample prior to dosing will be used as the baseline for these analyses.

Summary of key estimands for efficacy

Estimands are defined for this trial to address the efficacy objectives of the trial and to provide supportive evidence for those objectives. These estimands are defined in detail in the subsequent sections and are summarized in Table 6-1. The analysis for other safety/efficacy/PK data are described in other sections of this SAP.

Table 6-1 Summary of key estimands

	Estimand	Variable estimand is based on	Section
P1	Primary 1 – renal proteinuria	Ratio from baseline in urinary protein creatinine ratio (UPCR) at Week 25	6.1
S2	Secondary 1 - renal	Proportion with complete renal remission (CRR)	6.2

6.1 Primary estimand 1

The primary estimand 1 addresses the second primary objective:

- To assess the effect of CFZ533 on renal proteinuria in moderately active lupus nephritis patients after 24 weeks of treatment as an add-on therapy to standard of care as compared to placebo.

This estimand addresses the scientific question of whether treatment with CFZ533 reduces UPCR in moderately active lupus nephritis patients after 24 weeks of treatment without death, rescue medication and treatment discontinuation as an add-on therapy to standard of care.

6.1.1 Definition of primary estimand 1: UPCR

- Population: moderately active proliferative lupus nephritis patients.
- Variable: Ratio from baseline in UPCR at Week 25
- Treatment: CFZ+SOC, Placebo+SOC
- Summary Measure: Ratio of Geometric Means of CFZ533 versus placebo.

Hypothetical strategy will be used to deal with death, rescue medication and treatment discontinuation inter-current events. Data from patients taking rescue medication during the trial (or failing to tolerate steroid taper, for patients receiving oral corticosteroid at baseline) will be excluded from the date of rescue medication intake or failure of the steroid taper. Data from patients who discontinue study treatment will also be excluded, from the date of study drug discontinuation. A medical assessment prior to database lock will determine which patients are deemed to have failed the steroid taper based on clinical relevance of the steroid dose taken and the potential impact on the primary endpoint.

No other inter-current events will be taken into account in the estimand.

Statistical analysis model

The ratio from baseline in UPCR will be log transformed prior to the analysis. A repeated measures model will be fitted with factors for treatment group (CFZ533 or placebo) and visit (e.g. Week 5, 9, 13 etc.). The model will also include a factor for the prednisone dose-equivalent at baseline (≤10 mg, >10 mg) based on the concomitant medication information in the database rather than the stratification factor from the randomization. Log-transformed baseline UPCR will be included in the model as a covariate along with the interactions between visit and all of the fixed effects and the log-transformed baseline by visit interaction. A normal errors model will be assumed with an unstructured covariance matrix to account for the correlation within subjects. The model will be estimated using maximum likelihood techniques. If there are values of 0 then 0.1 will be added to all the UPCR data prior to the log transformation.

At each of the visits, the difference between the CFZ533 and placebo group will be estimated (along with its corresponding 95% confidence interval) and then back-transformed to provide an estimate of the ratio between treatment groups.

Sensitivity analyses will be considered if a substantial proportion of patients (i.e. more than 15%) receive rescue medicine or discontinue from study treatment. Multiple imputation models may be used to assess the robustness of the missing at random assumption of the primary analysis.

In addition if more than 15% of patients fail to tolerate the steroid taper scheme, a supportive analysis of efficacy using time to lack of taper as endpoint will be conducted. Additional analyses including all patients regardless of their adherence to treatment will be performed.

The adequacy of the model will be assessed by inspecting residual plots.

Data will be listed by treatment and timepoint. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum and will be presented by treatment and timepoint. Outputs will be provided for the raw UPCR values and also the ratio from baseline. An additional summary will also be provided by baseline steroid dose and also for subjects with biopsies within 2 years prior to randomization and 5 years prior to randomization separately.

Geometric mean (95% CI) of ratio from baseline profiles will be presented along with geometric mean ratio to placebo profiles. These figures will use the data obtained from the above model. Additional profiles of geometric mean (SE) UPCR data will presented based on the raw data. For these plots the data will be log transformed and the mean and standard error calculated, the standard error will be added/subtracted from the mean on the log scale and then back transformed to obtain the error bars for the plot.

The above outputs will also cover the outputs needed for the secondary objective to assess UPCR at different timepoints.

The above analyses will also be repeated using only the data from the first morning void and clinic spot sample separately.

6.2 Secondary estimand 1

The secondary estimand 1 addresses the secondary objective:

- To assess the effect of CFZ533 on relevant renal outcomes at different time points.

This estimand addresses the scientific question of whether treatment with CFZ533 has a beneficial effect on renal outcomes at different timepoints without death, rescue medication and treatment discontinuation as an add-on therapy to standard of care.

6.2.1 Definition of secondary estimand 1: Complete renal remission (CRR)

- Population: moderately active proliferative lupus nephritis
- Variable: CRR at post dose timepoints
- Treatment: CFZ+SOC, Placebo+SOC
- Measure of intervention effect: Proportion of CFZ533 patients with CRR at post dose timepoints

CRR at a timepoint is defined as having UPCR $\leq$ 0.2 mg/mg as well as eGFR within 25% of baseline value and normal urine sediment. If a subject died, received rescue medication or discontinued from treatment then they will analyzed as not having CRR from the timepoint of the event. CRR status will be assessed using first morning void if available and if not then using the clinic spot sample.

Analysis

The proportion of patients fulfilling the definition of complete renal remission will be summarized by treatment and visit and displayed graphically in barcharts.

Composite strategy will be used to deal with death, rescue medication and treatment discontinuation inter-current events. If a subject died, received rescue medication or discontinued from treatment then they will be analyzed as not having CRR.

No other inter-current events will be taken into account in the estimand.

Additional analyses will be performed considering the first morning void and clinic spot samples separately.

6.2.2 Other secondary PD variables

For other secondary PD variables (UACR, total soluble CD40 in plasma, hematuria and cellular casts) data will be listed together with changes from baseline (ratio to baseline for UACR and total soluble CD40 in plasma) by treatment, subject, and visit/sampling time point. For hematuria and cellular cast data only positive results are reported therefore if a result was negative at baseline the baseline value will be imputed as 0.

Descriptive summary statistics will be provided by treatment and visit/sampling time point. Summary statistics will include mean, SD, CV, median, minimum and maximum. Geometric statistics will also be presented for UACR and total soluble CD40 in plasma. Mean (SD) profile plots (geometric mean and SE for UACR and total soluble CD40 in plasma) will be generated. For UACR outputs will be separated out by first morning void separately, clinic spot sample separately and using first morning void if available and if not then using the clinic spot sample.

6.3 Exploratory objectives

6.3.1 Variables

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6.3.2 Descriptive analyses

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7 Statistical methods for safety and tolerability data

Baseline is defined as the last available value prior to dosing and will include Screening if no other value after Screening is available.

All information obtained on adverse events will be displayed by treatment and subject.

Adverse events of special interest (AESI) are defined as any of the following adverse events:

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Statistical analyses comparing the event rates of AESI's and SAE's in the two treatment groups will be performed using a Cochran Mantel-Haenszel test stratified by prednisone dose-equivalent at baseline (≤10 mg, >10 mg).

If any abnormalities occur for a subject then all their vital signs data will be listed by treatment, subject, and visit/time and abnormalities (and relevant orthostatic changes) will be flagged.

Summary statistics will be provided by treatment and visit/time. Abnormalities will be defined as values outside of the below ranges:

Vital Sign Parameter	Reference Range
Systolic Blood Pressure	90-139 mmHg
Diastolic Blood Pressure	50-89 mmHg
Pulse Rate	45-90 bpm
Body Temperature	35.0-37.5 °C

If any abnormalities occur for a subject then all their ECG data will be listed by treatment, subject and visit/time and abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time. The criteria for abnormalities are detailed below:

ECG Parameter	Clinically Notable Criteria
PR	PR > 200 msec and increase by more than 20 msec from baseline
QRS	QRS complex > 120 msec
QTcF	Males: QTcF > 450 msec and increase of 30 msec or more from baseline Females: QTcF > 460 msec and increase of 30 msec or more from baseline

If any abnormalities (data outside of reference range) occur for a subject then all their laboratory data for that parameter will be listed by treatment, subject, and visit/time and 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.

Boxplots will be provided for vitals signs, ECG and lab data.

7.1 Other safety 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 if any abnormalities/positive result drug test occur.

Treatment

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

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on <on-treatment/treatment emergent> adverse events which are not serious adverse events with an incidence greater than X% and on <on-treatment/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 ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

Quantiferon Test

Quantiferon test data collected will be listed by treatment, patient and visit/time if positive results occur

Immunogenicity

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

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9 Reference list

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