NOVARTIS

Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

CFZ533

CCFZ533X2201

A 12-month randomized, multiple dose, open-label, study evaluating safety, tolerability, pharmacokinetics/pharmacodynamics (PK/PD) and efficacy of an anti-CD40 monoclonal antibody, CFZ533, in combination with mycophenolate mofetil (MMF) and corticosteroids (CS), with and without tacrolimus (Tac), in *de novo* renal transplant recipients

Statistical Analysis Plan (SAP) – Part 2

Document type:	Part 2 - SAP Documentation – NIBR
Document status:	Final Amendment 2
Release date:	16-Jan-2018
Number of pages:	26

Table of contents

List of tables

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 ***"CCFZ533X2201"*** Part 2 only.

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 v02 (incorporating Amendment 02) dated 11 April 2016.

1.3 Study objectives

1.3.1 Primary objective

- To assess the potential for CFZ533 to act as the primary immunosuppressant in a CNI-free regimen with MMF in *de novo* renal transplant patients as assessed by tBPAR at Month 3 post-transplantation.

1.3.2 Secondary objectives

- To assess the safety and tolerability of CFZ533 administered chronically in combination with MMF and CS up to 3 months against a control
- To assess the PK of multiple IV doses of CFZ533 during the 12-month treatment period
- To quantify the magnitude and duration of peripheral blood CD40 occupancy (free CD40 and total CD40 on B cells) during the treatment period following multiple IV doses of CFZ533
- To compare renal function in CFZ533 treatment arms to control at Month 3 post-transplantation as assessed by:
  - Estimated GFR
  - Proportion of patients with eGFR < 60 mL/min/1.73 m^2
  - Proportion of patients with negative eGFR slope
- To evaluate the immunogenicity of multiple IV doses of CFZ533 via the quantitative analysis of anti-CFZ533 antibodies
- To quantify the change from baseline and recovery of peripheral blood total soluble CD40 during the treatment period following multiple IV doses of CFZ533.

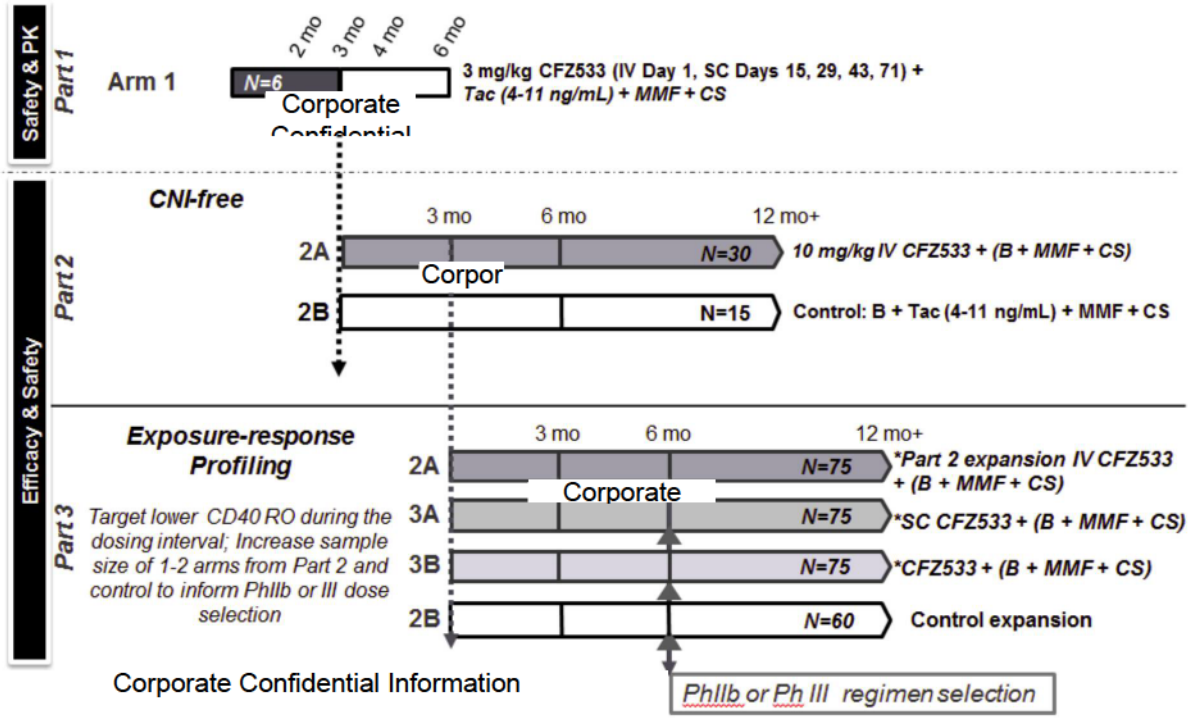
The assessment of safety and tolerability and comparison of renal function will also be assessed at Month 12.

1.4 Study design and treatment

1.4.1 General overview

Study CCFZ533X2201 is a randomized, three-part, 6- or 12-month, sequential, adaptive, controlled, open-label, multicenter, clinical proof-of-concept study to evaluate the efficacy, safety, tolerability, PK and PD of CFZ533 + MMF + CS, with standard exposure (Part 1) or no Tac (Part 2, 3), for initial and maintenance prophylaxis of organ rejection in adult *de novo* renal transplant recipients as compared to standard of care. As illustrated in Figure 1-1, each study part will evaluate a set of CFZ533 doses or treatment regimens in a parallel arm manner.

Figure 1-1 CCFZ533X2201 study design



Study Part 2 will continue the investigation of efficacy, safety, tolerability, PK and PD with the addition of induction therapy and avoidance of Tac. The initial 3 months of Part 2 will serve as the CNI-free, clinical proof-of-concept (PoC), portion of this trial. During the PoC portion of this study, the ability of CFZ533 to assume the role of the primary immunosuppressant in a regimen of CFZ533+MMF and CS will be evaluated.

1.4.2 Part 2 – Arms 2A-2B

Approximately 45 patients who meet the inclusion criteria will be randomized in a 2:1 fashion within 12 hours pre-transplant to receive one of the 2 treatment arms:

1. Arm 2A, n = 30: Basiliximab 20 mg (Days 0, 4) + CFZ533 at 10 mg/kg IV (17 doses) + MMF 1.0 g BID + CS
2. Arm 2B Control/SoC, n = 15: Basiliximab 20 mg (Days 0, 4) + Tac (4-11 ng/mL) + MMF 1.0 g BID + CS

Induction therapy must be started within 2 hours prior to transplantation, or according to local practice.

The first dose of CFZ533 will be administered IV pre-transplant or intra-operatively. Drug administration will begin after randomization and must be completed by the time of unclamping or up to 6 hours prior to the time of unclamping. Subsequent doses of CFZ533 will be administered IV (Arm 2A), over a period of 12 months.

Other study drugs must be started within 24 hours post-transplant. The second dose of basiliximab will be administered on Day 4, or according to local practice.

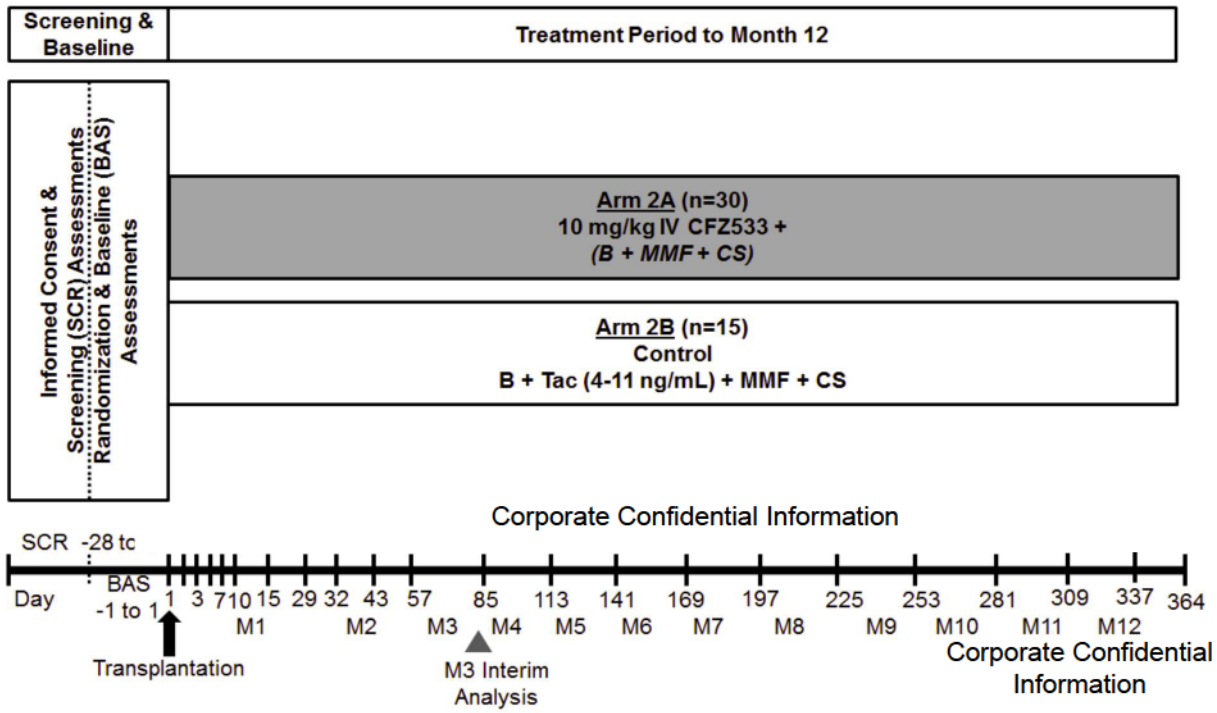
The day of randomization and transplant will be considered to be study Day 1.

Patients will then undergo Study Completion evaluations.

The primary endpoint of Part 2 will be assessed to determine whether the success criteria (safety and tBPAR) have been met when all patients have completed the Month 3 visit. If it is found that the data up to the Month 3 visit is inconclusive, a reevaluation (interim analysis) will occur after the Month 6 visit.

If the stopping rules are not met and the primary endpoint of Part 2 is fulfilled at Month 3, Part 3 (exposure-response profiling) will be initiated following consultation of the DMC. Cumulative efficacy and safety data will be collected on an ongoing basis during the conduct of the study.

Figure 1-2 Part 2 Design



1.4.3 Study "stopping" rules

The following stopping rules based on potential toxicities will serve as the basis for placing the study on hold. Although the stopping criteria do not incorporate an absolute requirement for causality, the potential relationship between an AE and CFZ533 will be evaluated carefully on a case-by-case basis between the Sponsor and the Investigator. Following a review of the AE(s), a decision to permanently discontinue enrollment or re-initiate CFZ533 dosing will be made by the DMC.

- Two (2) or more patients presenting with post-transplant lymphoproliferative disease or progressive multifocal leukoencephalopathy in the CFZ533 treatment arm.

In addition, specific stopping rules for the incidence of tBPAR will be applied. These rules are designed to ensure that an arm will be stopped if there is high probability (> 90%) that the true tBPAR rate is greater than 20%. Based on this stopping rule, the maximum number of patients with tBPAR for various different illustrative sample sizes would be as follows:

Table 1-1 Study stopping rules for tBPAR

Total number of patients (N)	Number of patients with tBPAR that would lead to stopping the treatment arm (n)	Observed tBPAR rate (n/N)
3	2	0.67
4	2	0.50
5	3	0.60
6	3	0.50
7	3	0.43
8	4	0.50
9	4	0.44
10	4	0.40
11	5	0.45
12	5	0.42
13	5	0.38
14	5	0.36
15	6	0.40
16	6	0.38
17	6	0.35
18	6	0.33
19	7	0.37
20	7	0.35
21	7	0.33
22	7	0.32
23	8	0.35
24	8	0.33
25	8	0.32
26	8	0.319
27	9	0.33
28	9	0.32
29	9	0.31
30	9	0.30

In addition to the automatic hold criteria and tBPAR criteria presented above, the DMC will review safety data regularly as outlined in their charter during quarterly and ad hoc meetings. The DMC can recommend stopping a specific study arm(s) or the entire trial if significant changes or effects that, in their collective opinion, are deemed unsafe or unethical to continue administering CFZ533.

2 First interpretable results (FIR)

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

4 Statistical methods: Analysis sets

For patients 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 will include all patients that received at least one dose of study drug and who were transplanted.

The modified Full Analysis Set (mFAS) will include all patients that received at least one dose of study drug and who were transplanted that also meet the following conditions:

- Donor age < 65 years
- Cold ischemic time (CIT) < 18 hours
- HLA mismatches at DR locus
- HLA total mismatches < 5

The Safety Analysis Set will include all patients that received at least one dose of study drug. All patients that receive their transplant along with any patient who receive study drug but have no transplant will be combined.

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 in the Full Analysis Set with any available PD data and no protocol deviations with relevant impact on PD data.

The protocol deviation codes are described in detail in the data management plan.

5 Statistical methods for Pharmacokinetic (PK) parameters

5.1 Variables

If data permit, typical exposure metrics and parameters could be determined using the actual recorded sampling times and non-compartmental method(s) with WinNonlin Pro or Phoenix, including (but not limited to): Cmax, Cmin, Cmin,ss, Tmax, from the plasma concentration-time data.

5.2 Descriptive analyses

CFZ533 plasma concentration data will be listed by treatment, transplant status (if required), patient, and visit/sampling time point. Tac and MPA trough levels will be measured and listed by treatment, visit and patient. If data permit, PK parameters will be calculated and listed by treatment and patient. Concentrations below the limit of quantification will not be considered for the calculation of PK parameters. 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.

5.2.1 Graphical presentation of results

The CFZ533 plasma concentration data (PK) will be presented graphically in a plot of the mean concentration (unit: µg/mL; log scale) over time (unit: day; elapsed time since first dose), overlaying individual profiles over time with an overlaid mean and individual time-concentration profiles by patient.

6 Statistical methods for Pharmacodynamic (PD) parameters

6.1 Primary objective

6.1.1 Variables

The primary variable is tBPAR after 3 months of treatment.

6.1.2 Descriptive analyses

The tBPAR data will be listed by treatment. The data will be summarized and will include the number (percentage) of patients that have a tBPAR.

6.1.3 Statistical model, assumptions and hypotheses

The number of patients with tBPAR is assumed to follow a binomial distribution, i.e.,

$r_i \sim \text{Binomial}(n_i, \theta_i)$

where r_i is the number of patients with tBPAR in treatment group i, n_i is the number of patients in treatment group i and θ_i is the probability of tBPAR.

The efficacy analysis for the first 3 months of Part 2 considers whether a CFZ533 treatment arm meets the pre-defined criteria for initiation of Part 3.

The pre-defined success criteria is considered to be a tBPAR rate difference between the CFZ533 arm and the control group of less than 20 percentage points with at least 60% level of proof.

$\Pr(\theta_{CFZ533} - \theta_{SoC} < 0.20 \mid \text{data}) > 60\%$

The required posterior probabilities will be estimated from simulations of the posterior distributions of $\theta_{CFZ533} - \theta_{SoC}$ and compared to the thresholds for the levels of proof.

The prior distributions will be assumed to be a non-informative Beta(1/3, 1/3) for CFZ533 and an informative prior of Beta(1, 13) for SoC. This informative prior corresponds to an approximate mean response rate of 7% with a 95% confidence interval of (0.2%, 24%) and was determined via a meta-analysis of control therapies.

The posterior mean tBPAR rates for each treatment group and for the difference in mean response rates between treatments will be tabulated together with the 95% credible intervals, the number of patients with tBPAR and the posterior probabilities of being above the thresholds, 10%, 15%, 20%, 25%.

6.1.3.1 Graphical presentation of results

A plot of the posterior probability distribution for the tBPAR rate and a bar chart corresponding to the posterior probability thresholds will be provided.

6.1.4 Supportive analyses

Kaplan-Meier estimates

In this analysis, patients who have not experienced tBPAR, will be censored with the censoring time as defined by the last contact day at or before the cut-off point (e.g., 1st IA Month 3 visit, 2nd IA Month 6 visit). The patients will be considered as completed at the date of their corresponding analysis cut-off point. In addition to the Kaplan-Meier plot, a log-rank test shall be performed to obtain estimates with CI's for each treatment arm and the difference between treatment arms.

During data review, it was noticed that some patients were switched from the randomized treatment to another regimen. Therefore in future IA's, more focus shall be placed on the Kaplan-Meier analysis.

Supportive Bayesian analysis

In addition the Bayesian analysis will be repeated with a model using a Poisson distribution to account for the patients that may switch treatment or discontinue early from the study. The following parametrization will be used:
The number of tBPAR events in group i is assumed to follow a Poisson distribution, i.e.
$y_i = \text{Poisson}(\mu_i)$,
where μ_i is the expected number of events in group i, with
$\mu_i = \lambda_{i,T} * t_{i.T,}$
with $t_{i,T}$ being the total follow up time in group i (times censored at treatment switch or discontinuation) up to analysis time point T and λ_i being the event rate in group i up to the analysis time point T. For sensitivity analysis of the primary analysis the analysis time point T is week 12 (i.e. week 13 visit, month 3 after transplantation). The probability of an tBPAR event occurring up to the analysis time point can then derived as $\theta_i = 1-\exp(-\lambda_i * T)$.

The pre-defined success criteria is considered to be a difference in the probability of tBPAR between the CFZ533 arm and the control group of less than 20 percentage points with at least 60% level of proof.
$\Pr(\theta_{CFZ533} - \theta_{SoC} < 0.20 \mid \text{data}) > 60\%$
The required posterior probabilities will be estimated from simulations of the posterior distributions of $\theta_{CFZ533} - \theta_{SoC}$ and compared to the thresholds for the levels of proof.

The prior distributions will be assumed to be a non-informative Beta(1/3,1/3) for θ_{CFZ533} and an informative prior of Beta(1, 13) for θ_{SoC}.

The same outputs and presentations of the results as for the primary analysis will be provided. The analysis will be repeated for the adjudicated data when applicable.

6.1.5 Adjudication analyses

Additional outputs will be provided for the adjudicated tBPAR data. The outputs to be provided include a listing of the data and summary statistics table, the primary and supportive Bayesian analysis tables and corresponding figures, and the Kaplan Meier analysis. Adjudicated outputs will only be provided if all events can be assessed by the adjudication committee.

6.2 Secondary and exploratory objectives

6.2.1 Variables

Composite failure is a secondary variable where patients are defined to be failures if they experience any one of the following events

tBPAR

graft loss

death

A date is defined for all events (e.g. borderline rejection, acute rejection) on the rejection level. In case of several events of the same type (e.g. two acute rejections) the earliest will be chosen for the analysis on the patient level.

The main part of the information for the efficacy evaluation comes from the Rejection eCRF page as well as the Biopsy eCRF page. For the derivation of the efficacy variables the

information from both pages need to be merged. The Rejection eCRF page is linked with the Biopsy eCRF page by the date of the (first) biopsy. Follow-up biopsies of the same rejection episode may be taken and are linked with the first biopsy by the date.

Borderline rejection

A biopsy is considered 'borderline' if, from the Biopsy eCRF page based on the pathologist's assessment, "Borderline changes = Yes" on the Biopsy eCRF page.

Acute rejection

Acute rejections are identified in the database from the Rejection eCRF page. One of the following conditions must be met:

- Primary final clinical diagnosis indicates an acute rejection (either "acute rejection" or "acute and chronic rejection")
- OR Antibody mediated rejection = "Yes" from the Kidney allograft biopsy eCRF page
- OR Acute T-cell mediated rejection = "Yes" from the Kidney allograft biopsy eCRF page

The date of event is the "Date rejection was first suspected" from Rejection eCRF page, or if missing the date of the first biopsy of the particular rejection episode.

Treated acute rejection

Treated acute rejections are a subset of acute rejections.

A treated acute rejection is defined if the following criteria are fulfilled:

- Acute rejection and
- "Was anti-rejection therapy administered = Yes" from the Rejection eCRF page.

The date of event is the "Date rejection was first suspected" from Rejection eCRF page, or if missing the date of the first biopsy of the particular rejection episode.

Treatments for acute rejection will be categorized into 3 groups: Steroids, Antibodies, and Other using the CRF information from the Rejection eCRF page (Were steroids administered? Was antibody treatment administered?).

Biopsy-proven acute rejection (BPAR)

A rejection is considered a biopsy-proven acute rejection if the following criterion is fulfilled:

"Acute T-cell mediated rejection = Yes" or "Antibody mediated rejection = Yes" or Borderline changes = "Yes" from the Biopsy eCRF page

The date of event is the "Date rejection was first suspected" from corresponding Rejection eCRF page, or if missing the date of the first biopsy of the particular rejection episode.

The BPAR episode can be classified into rejection types: t-cell mediated, antibody mediated, or a combination of those.

Acute antibody-mediated rejection (AMR)

A rejection is identified as an antibody-mediated rejection (also known as humoral rejections) if the following criterion is fulfilled:

- "Antibody mediated rejection = Yes" from the Biopsy eCRF page

The date of event is the "Date rejection was first suspected" from Rejection eCRF page, or if missing the date of the first biopsy of the particular rejection episode.

Treated biopsy-proven acute rejection (tBPAR)

Treated biopsy-proven rejections are a subset of biopsy-proven acute rejections.

A treated biopsy-proven acute rejection is defined if the following criteria are fulfilled:

- Biopsy-proven acute rejection and
- "Was anti-rejection therapy administered = Yes" from the Rejection eCRF page.

The date of event is the "Date rejection was first suspected" from Rejection eCRF page, or if missing the date of the first biopsy of the particular rejection episode.

Note that careful data cleaning is necessary to align the answer to "Was anti-rejection therapy administered?" with the concomitant medication eCRF page.

Steroid-treated biopsy proven acute rejection

Steroid-treated biopsy proven acute rejections are a subset of treated biopsy proven acute rejections. A steroid-treated biopsy proven acute rejection is defined if the following criteria are fulfilled:

- Treated biopsy proven acute rejection and
- "Were steroids administered = Yes" on the Rejection eCRF.

The date of event is the "Date rejection was first suspected" from Rejection eCRF page, or if missing the date of the first biopsy of the particular rejection episode.

Steroid-resistant biopsy proven acute rejection

Steroid-resistant biopsy proven acute rejections are a subset of steroid-treated biopsy proven acute rejections. A steroid-resistant biopsy proven acute rejection is defined if the following criteria are fulfilled:

- Steroid-treated biopsy proven acute rejection and
- "Was the rejection steroid resistant? = Yes" from the Rejection eCRF page

The date of event is the "Date rejection was first suspected" from Rejection eCRF page, or if missing the date of the first biopsy of the particular rejection episode.

Antibody-treated biopsy proven acute rejection

Antibody-treated biopsy proven acute rejections (BPAR with T-cell depleting therapy) are a subset of treated biopsy proven acute rejections. It is a clinically significant sub-component of treated BPAR as a marker of severity. An antibody-treated biopsy proven acute rejection is defined if the following criteria are fulfilled.

- Treated biopsy proven acute rejection and
- "Was antibody treatment administered = Yes" from the Rejection eCRF page

The date of event is the "Date rejection was first suspected" from Rejection eCRF page, or if missing the date of the first biopsy of the particular rejection episode.

Sub-clinical biopsy proven acute rejection

A sub-clinical biopsy proven acute rejection is defined as a BPAR *without* clinical suspicion of a rejection i.e. a biopsy was performed without the suspicion of an acute rejection (e.g. center-driven local-routine biopsy, protocol driven biopsy, etc.) but the result of that biopsy shows histological evidence of an acute rejection (Banff classification):

- BPAR and
- "Clinical suspicion of an acute rejection = No" on the Kidney Allograft Rejection eCRF or Reason for biopsy = "Routine biopsy per local practice" from the Biopsy page..

The date of event is the date of biopsy.

Graft Loss (GL)

The allograft will be presumed to be lost based on whichever of the following occurs first: the day the patient starts dialysis and is not able to subsequently be removed from dialysis, the day of transplantectomy, or the day irreversible loss of graft perfusion is demonstrated by appropriate imaging techniques. Primary graft non-function is a subset of graft loss.

A patient will be considered to have graft loss if in the Graft Loss eCRF page the following condition is met:

- "Has subject suffered a graft loss = Yes"

The date of graft loss is specified on the Graft Loss eCRF page. The date returned to regular dialysis or date of transplantectomy will be used if earlier.

Death

The endpoint death is derived from the Death eCRF page where also the date of death is captured.

6.2.2 Descriptive analyses

Rates of graft loss and death will also be summarized.

6.2.3 Statistical model, assumptions and hypotheses

Graft loss, death, graft loss or death and antibody-treated biopsy proven acute rejections will be analyzed in a similar way to the tBPAR and time to tBPAR, although without the non-inferiority test. Other efficacy variables displayed in Table 6-1 will be presented within frequency tables to show the proportion of events and the CFZ533 treatment arm event rate will be compared with the control arm event rate using Z-statistics based on two-sided confidence intervals for differences in event rates.

6.2.3.1 Graphical presentation of results

The free CD40 and total CD40 on whole blood B cells data will be presented graphically to show the arithmetic mean (SD) of free and total CD40 on whole blood B cells compared to mean pre-dose over time (%), overlaid patient profiles of free CD40 and total CD40 on whole blood B cells compared to mean pre-dose over time and overlaid profiles of free CD40 on whole blood B cells based on total CD40 (%). Arithmetic mean (SD) of free CD40 on whole blood B cells based on total CD40 (%), arithmetic mean (SD) free CD40 decrease on B cells compared to mean pre-dose (%) and arithmetic mean (SD) free CD40 decrease on B cells compared to mean pre-dose (based on total CD40 available on B cells) (%) will also be presented. Additional overlaying individual profile plots of free CD40 decrease on B cells compared to mean pre-dose (%) and free CD40 decrease on B cells compared to mean pre-dose (based on total CD40 available on B cells) (%) will also be presented.

Total soluble CD40 and total soluble CD154 data will be presented graphically in the form of individual patient panel plots by parameter, arithmetic mean (SD) over time plots and a panel plot presenting the soluble CD40, soluble CD154 for each patient separately.

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.

The following B-cell subsets are also used as safety markers: mature B cells, naive B cell, transitional B cells, memory B cells, plasma cells, plasma blasts. Overlaid patient profiles for each of these markers over time shall be presented graphically.

7.1.2 Descriptive analyses

Patient demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and patient. Patient demographics will include age, sex, race, ethnicity, height, weight and BMI. Other baseline characteristics that shall be listed include relevant medical history, current medical conditions, results of laboratory screens, transplant history, donor characteristics (e.g., age, sex, race, type, CIT) and any other relevant information.

Summary statistics will be presented for the patients in the Full analysis set. Continuous variables will be presented with mean, median, standard deviation, minimum and maximum, and the number of non-missing observations.

Categorical data will be displayed via absolute and relative frequencies for each category (including a category labeled as "missing" when appropriate).

Table 7-1 Demographic variables and disease characteristics

Variable
Recipient demographics:
Age (continuous and categorized (< 50, ≥ 50) and (< 65, ≥ 65))
Gender
Race
Ethnicity
Vital signs at baseline:
Height
Body weight
BMI
Pulse (bpm)
Systolic blood pressure, Diastolic blood pressure (mmHg)
Donor demographics:
Age (continuous and categorized (< 50, ≥ 50) and (< 65, ≥ 65))

Variable
Gender
Race
Ethnicity
Donor characteristics:
Donor category (living related, living unrelated, deceased heart beating)
Hypotension prior to procurement (no, yes, unknown)
Donor and recipient serology:
EBV, CMV (negative, positive, not done)
HCV Ab, HBsAG, HBsAb, HCV RNA (negative, positive, not done)
Recipient background information:
End stage disease leading to transplantation
Current dialysis (yes/no)
Time since continuous dialysis first started
Number of previous kidney transplantations
Number of previous blood transfusions
Total number of HLA mismatches across Loci A, B, and DR (categorical: 0, 1, 2)
Recipient/donor gender combination
Recipient/donor race combination
Transplantation procedure:
Cold ischemia time (deceased donors only: continuous and categorized: < 12 hours, ≥ 12 to 24 hours, ≥ 24 to 30 hours, > 30 hours)

Study medication

Data for CFZ533 administration and concomitant therapies will be listed by treatment group and patient. The duration (days) of CFZ533 study medication administration will be summarized and listed. The duration will be calculated by subtracting the date of the last administration of study medication from the date of first administration and then adding the dosing interval for CFZ533. In calculating the duration of treatment, days of temporary interruption of study medication for any reason will be included, i.e, any days of interruptions will not be excluded from the duration of treatment. Further, the frequency of dose changes (including temporary dose interruption) will be presented by reason for the change.

Average daily doses of each treatment will be presented in a summary table and will be listed by treatment and patient. “Zero” will be used for periods of temporary interruption of study medication for any reason.

The number and percentage of patients who prematurely discontinued study medication will be summarized by reason for discontinuation.

If the number of events allow, Kaplan-Meier (KM) estimates of time to discontinuation of study medication curve will be constructed and presented graphically. In this analysis, patients

who have not discontinued study medication will be censored with the censoring time as defined by the last contact day.

Concomitant immunosuppressants

The dose of administered Basiliximab, MMF, Tac and CS will be listed by treatment and patient.

The dose of antibodies used for the treatment of acute rejection episodes will be summarized by treatment and listed by treatment and patient.

Other co-medications

Concomitant medications, other than immunosuppressants and CS mentioned above, will be listed by patient and summarized by therapeutic class and preferred term by presenting the number and percentage of patients using each medication for each treatment group.

Calculated eGFR

The main safety endpoint is calculated eGFR.

Patients will be considered as "on treatment", whilst they are taking their assigned randomized treatment. If a patient switches to an alternative treatment or stops taking their assigned randomized treatment, this data will be excluded from the summaries, figures and analysis for eGFR data.

Calculated eGFR as determined by the central lab will be summarized by visit. The calculated eGFR will be presented graphically to show the overlaid patient profiles and mean profile over time.

The following imputation method will be applied at each relevant timepoint for patients with missing eGFR values:

1. Patients that lose their graft before the timepoint in question will be assigned a value of zero for their missing eGFR value.
2. Patients that die or are lost to follow-up with a functioning graft before the timepoint in question will have an imputed value using the last-observation-carried-forward (LOCF) method.

Graft loss patients do not have a functioning graft, hence the lowest possible eGFR value (zero) will be assigned to such patients with missing eGFR values. In contrast, patients that die with a functioning graft, die for different reasons such as suicide, car accidents, cancer, therefore if they have a missing eGFR value, an imputed value using the LOCF method will be used. Similarly, patients who are lost to follow-up and have renal function, but are missing a Month 6 or Month 12 value for various reasons (e.g. moving from the area or not being able to make the site visit during the Month 6 or Month 12 visit) will have an imputed value using LOCF method for any missing eGFR value.

The mean eGFR results will be estimated from a longitudinal repeated measures mixed effects model using all the individual data collected until the timepoint of interest (1st IA Month 3 visit, 2nd IA Month 6 visit) whilst the patient is on treatment. From the model, estimates of the average at the timepoint of interest, treatment difference and 90% confidence

intervals will be obtained. The model will include fixed effects for treatment, time, donor age, donor type (living or deceased) and donor characteristic, treatment by time interaction and donor type by treatment by time interaction. An unstructured variance-covariance structure shall be used, however in the case that the model fails to converge, alternative structures would be tested. The estimates of the adjusted means and two-sided 90% CIs obtained from the model will be plotted over time.

The donor characteristic is a category that could have the result of "standard" or "expanded".

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.

Special clinical laboratory evaluations

Coagulation parameters prothrombin time and partial thromboplastin time will be listed by treatment, patient and visit/time. The coagulation parameters will also be presented graphically to show the overlaid patient profiles and mean profile over time for each parameter separately. Additionally overlaid patient profiles and mean profile over time will be presented graphically for platelets.

Cytokine assessments via multiplex cytokine including TNFa, IFNg, IL1b, IL2, IL4, IL8, IL10, IL12p, IL70 and IL13 will be listed by treatment, patient, and visit/time. The cytokine assessments will also be presented graphically to show the overlaid patient profiles and mean profile over time for each parameter separately.

Donor specific antibodies will be listed by patient and visit.

Immunogenicity data consisting of anti-CFZ533 antibodies information will be listed by patient and visit.

Virology monitoring results for hepatitis B, hepatitis C, HIV, Epstein-Barr Virus (EBV), cytomegalovirus (CMV) and BK virus will be listed by patient, and visit/time and if normal ranges are available, abnormalities will be flagged. The frequency of EBV, CMV and BK virus will also be summarized by treatment.

Adverse events

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

AEs and infections collected are to be coded with the MedDRA dictionary that gives preferred term and primary system organ class information. AEs and infection preferred terms are to be analyzed as a whole under the heading of AEs. Depending on the number of AEs in Part 2, the incidence of AEs will be summarized by body system, severity and relationship to study drug by the following where possible:

- AEs by primary SOC and PT
- AEs rated to have relationship to study drug by SOC and PT
- AEs by primary SOC, PT, and maximum severity
- SAEs by SOC and PT
- SAEs rated to have relationship to study drug by SOC and PT
- Deaths by SOC and PT
- AEs leading to discontinuation of a study drug by SOC and PT
- AEs leading to dose adjustment or interruptions of a study drug by SOC and PT
- Infections by type of infection (viral, bacterial, fungal, and others) and microorganism of infection
- Serious infections by type of infection and micro-organism of infection
- New onset diabetes mellitus
- AEs by standardized MedDRA query (SMQ) levels (broad and narrow search)
- AEs by standardized MedDRA query (SMQ) and preferred term (broad and narrow search)

In all tables about incidence rates of AEs / Infections, if a patient has multiple occurrences of an AE, this patient will be counted only once in the corresponding AE category. If a patient has multiple adverse events within a system organ class, s/he will be counted only once for that class. If a patient has multiple severity ratings for an AE while on treatment, s/he is only counted under the maximum rating. In the tables, only adverse events occurring at or after first drug intake are included.

Information pertaining to AEs noted during the study will be listed by patient, including the verbatim term given by the investigator, the PT and SOC given by the MedDRA dictionary, start and end date, causality, severity, and relationship to study drug as assessed by the investigator.

BK-polyoma viremia and nephropathy

The following variables will be summarized by treatment and listed by treatment group and patient:

Occurrence of BK-polyoma viremia any time post-transplantation

Occurrence of BK-polyoma virus nephropathy any time post-transplantation

The difference of the investigational regimens to the control regimen will be summarized by risk ratios and appropriate CIs.

Tuberculosis surveillance

Tuberculosis (TB) test data collected will be listed by patient and visit.

Pregnancy test

Pregnancy test results for all females will be listed by patient and visit.

Desirability of outcome ranking (DOOR)

Composite endpoint:

a) Survived; without graft loss and without tBPAR
b) Survived; without graft loss and with tBPAR
c) Survived; with graft loss and without tBPAR
d) Survived; with graft loss and with tBPAR
e) death

Long term renal function:

a) Normal creatinine; without BK and without tBPAR

b) Normal creatinine; with BK and without tBPAR

c) Normal creatinine; without BK and with tBPAR

d) Normal creatinine; with BK and with tBPAR

e) Elevated creatinine; without BK and without tBPAR

f) Elevated creatinine; with BK and without tBPAR

g) Elevated creatinine; without BK and with tBPAR

h) Elevated creatinine; with BK and with tBPAR

Where Normal creatinine is the most recent creatinine no higher than 25% above Nadir and Elevated creatinine is the most recent creatinine greater than 25% above Nadir

7.1.3 Graphical presentation

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

A figure to represent the desirability of outcome ranking will be created.

9 Reference list

Levey A, Coresh J, and Balk E (2003) National Kidney Foundation Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. Ann Intern Med;139:137-147.