Clinical Development

CFZ533/iscalimab

CFZ533A2201 / NCT03663335

A partially-blinded, active-controlled, multicenter, randomized study evaluating efficacy, safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) of an anti-CD40 monoclonal antibody, CFZ533, in *de novo* and maintenance kidney transplant recipients (CIRRUS I)

Statistical Analysis Plan (SAP)

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14-Jul-2021	Prior to IA DBL	Preparation of IA DBL	Complete update to SAP to add analyses addressing go/no-go criteria for internal decision making and address analyses challenges/limitations from dry run for interim analysis	All sections
08-Feb-2022	Prior to final DBL	Reduction of the analyses performed after decision was made to stop the study	Update to reflect the analyses that will appear in the final CSR after the decision was made to terminate the study at the Interim Analysis	All sections

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ADaM	Analysis Data Model
AE	Adverse event
AICD	Automatic implanted cardiac defibrillator
AMR	Antibody mediated rejection
AP	Angina pectoris
aPTT	Activated partial thromboplastin time
AR	Acute rejection
ATC	Anatomical Therapeutic Classification
AUC	Area under the curve
BP	Blood pressure
BPAR	Biopsy-proven acute rejection
BMI	Body mass index
CABG	Coronary artery bypass graft surgery
Cmax	Maximum concentration
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CS	Corticosteroids
Ctrough	Trough concentration
DAR	Dose administration record
DGF	Delayed graft function
DMC	Data monitoring committee
DSA	Donor specific antibodies
EBV	Epstein Barr virus
ECD	Extended criteria donor
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
EOS	End of study
EU	European Union
FAS	Full analysis set
GL	Graft loss
HBsAg	Hepatitis B surface antigen
HCP	Health care provider
HCV	Hepatitis C virus
HIS	Histology analysis set
HIV	Human immunodeficiency virus
HLT	High level term
IA	Interim analysis
ICF	Informed consent
IFTA	interstitial fibrosis/tubular atrophy
i.v./IV	Intravenous
KTx	Kidney transplant

LACAN	Latin America + Canada
MACE	Major adverse cardiac event
MAR	Missing at random
MDRD	Modification of diet in renal disease
MedDRA	Medical dictionary for Drug Regulatory Affairs
MMF	Mycophenolate mofetil
MNAR	Missing not at random
MI	Multiple imputation
NODM	New onset diabetes mellitus
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic
PK	Pharmacokinetic
PRA	Panel reactive antibodies
PT	Preferred term or prothrombin time
PTLD	Post-transplant lymphoproliferative disorder
Q2W	Every 2 weeks
RAN	Randomized set
rATG	Rabbit anti-thymoglobulin
SAF	Safety set
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SCD	Standard criteria donor
[redacted]	[redacted]
SCR	Screened set
SD	Standard deviation
SE	Standard error
SDTM	Study data tabulation model
SMQ	Standard MedDRA query
SOC	System organ class
STEMI	ST elevation
TAC	Tacrolimus
[redacted]	[redacted]
[redacted]	[redacted]
TFLs	Tables, figures, listings
Tmax	Maximum time
Trt	treatment
Tx	Transplant
UPCR	Urine protein creatinine ratio
US	United States
WHO	World Health Organization

1 Introduction

This document presents the detailed statistical analysis plan (SAP) for Study CFZ533A2201, "A partially-blinded, active-controlled, multicenter, randomized study evaluating efficacy, safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of an anti-CD40 monoclonal antibody, CFZ533, in *de novo* and maintenance kidney transplant recipients (CIRRUS I)".

Analysis of Cohort 1 (in adult *de novo* kidney transplant recipients) and Cohort 2 (in a maintenance kidney transplant population) will be handled separately (e.g., primary secondary, and exploratory analyses in Cohort 1 will be performed only on Cohort 1 patients and primary, secondary, and exploratory analyses in Cohort 2 will be performed only on Cohort 2 patients).

This SAP will include the details for the analysis of Cohort 1 and Cohort 2.

For each Cohort, the following is performed:

- **Interim analysis (IA):** performed on data which is collected up to and including a data cut-off date of 12-Mar-2021
- **Primary analysis:** performed when all patients complete Month 12 visit (i.e. reach Day 463) or discontinue prematurely
- **Additional analyses:** performed when all patients complete Year 2, 3, 4, and 5

The analyses will result in one clinical study report (CSR) for both Cohort 1 and Cohort 2.

On the 26th of August, 2021 the decision was made to stop Study CFZ533A2201 based on the interim analysis performed which has led to a decision that the risk-benefit was no longer favorable to continue clinical development in the disease area. Given the decision to terminate the study early, an abbreviated clinical study report will be created for this study. Analyses covered in the original SAP and Amendments 1-3 have been reduced and/or simplified accordingly.

Regular DMC analyses were performed by a Contract Research Organization, [redacted] and detailed information regarding DMC analysis were provided in a separate DMC SAP.

The SAP is based on the following documents:

- Clinical Trial Protocol version 04
- Electronic case report form (eCRF) v13.0
- Electronic case retrieval form (eCRS)

1.1 Study design

Study CCFZ533A2201 is a Phase 2b, randomized, partially-blinded (for the initial 12 months of treatment), active-controlled, multicenter, 60-month dose range finding study of iscalimab (CFZ533) to evaluate the efficacy, safety, tolerability, PK and PD in adult *de novo* kidney transplant recipients (Cohort 1) and a maintenance kidney transplant population (6-24 months post-transplant) (Cohort 2).

This study will consist of a screening period, 12-month primary treatment period, 48-month open label treatment extension period, and a safety follow up period of 60 days after the end of study visit at Month 60.

Patients who enroll into the study under protocol amendment v01 (or later versions) are expected to consent to the entire study duration comprising 60 months. However, patients who enrolled into the study under the initial protocol v00 and do not want to extend their participation to 60 months, may complete the study at Month 12. Once all applicable approvals are received, these patients will sign an amended ICF and will complete assessments up to Month 12 as per protocol v01. After this point these patients will be discontinued from study treatment and managed per local practice.

With amendment 04, the enrollment is considered complete.

Cohort 1 – *de novo* kidney transplant patients:

Cohort 1 consists of an adult *de novo* kidney transplant recipient population.

A total of 200 patients who meet the inclusion criteria and none of the exclusion criteria will be randomized prior to transplantation, at a ratio of 1.5:1.5:1 to CFZ533 600 mg every two weeks (Q2W) (Arm 1), CFZ533 300 mg Q2W (Arm 2) or TAC control (Arm 3) (Figure 1-1).

For all patients, induction therapy, either basiliximab or rabbit anti-thymocyte globulin (rATG), must be started on the day of transplantation. No other induction therapy is allowed. The choice of induction therapy is at the investigators' discretion.

Randomization will be stratified for donor category (living vs. deceased) and induction therapy (basiliximab vs. rATG).

The percentage of randomized patients on each induction therapy will be limited to a range of 40-60% driven by the rate of recruitment into each individual stratum.

Cohort 2 – maintenance patients:

Cohort 2 consists of a maintenance kidney transplant population (6-24 months post-transplant).

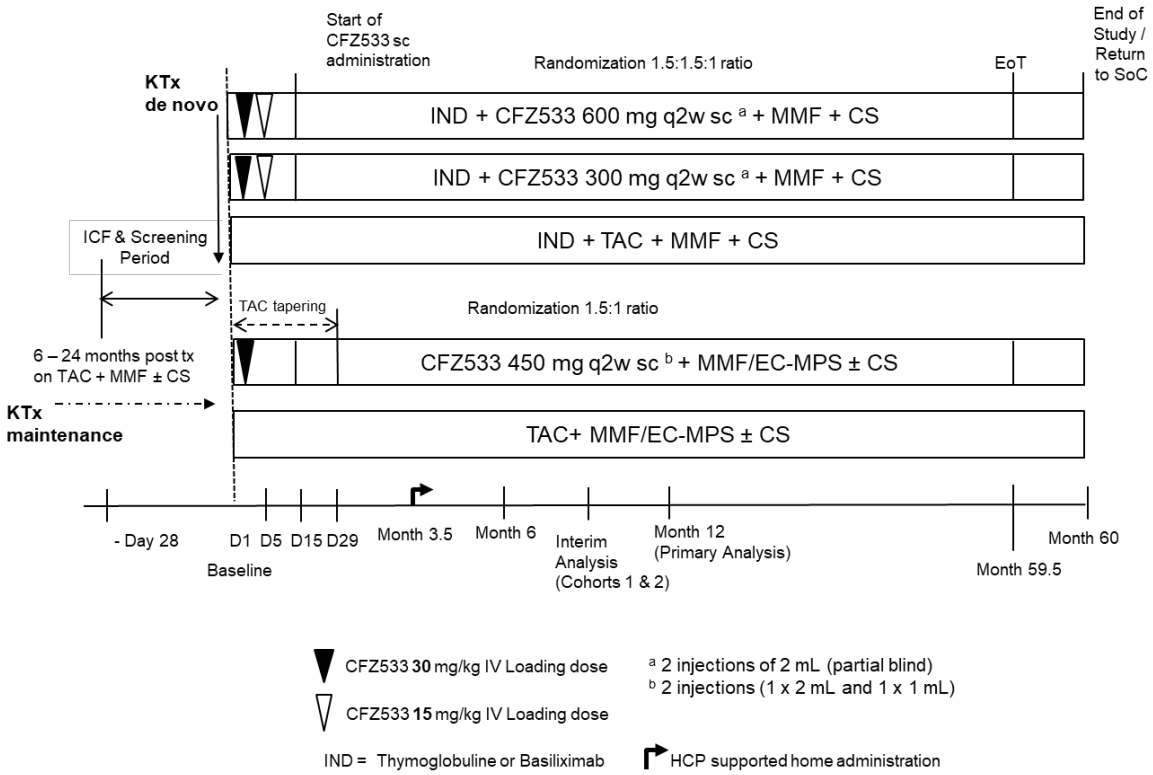
A total of 125 maintenance patients, who meet the inclusion criteria and none of the exclusion criteria, on a regimen containing TAC+MMF/EC-MPS±CS and who are 6 to 24 months post renal transplantation will be randomized, at a ratio of 1.5:1 to CFZ533 450 mg SC Q2W (Arm 1) or TAC control (Arm 2) (Figure 1-1).

In case a patient is switched from Myfortic® to MMF for medical reasons (not protocol driven), this switch must have occurred at least two weeks prior to baseline visit.

Randomization will be stratified for corticosteriod use (yes/no) and time since transplant (6 - ≤ 12M vs. 12-24M).

The percentage of randomized patients who are 6 to ≤ 12 months post-renal transplantation and the percentage of randomized patients who are 12 to 24 months post-renal transplantation will be limited to a range of 40-60% driven by the rate of recruitment into each individual stratum.

Figure 1-1 Study Design



1.2 Study objectives and endpoints

The study objectives endpoints for the abbreviated CSR can be found in Table 1-1.

Table 1-1 Objectives and related endpoints

Cohort 1 – *de novo* patients

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
To demonstrate that CFZ533 600 mg and/or 300 mg bi-weekly (Q2W), subcutaneous (SC), are non-inferior to a TAC-based regimen with respect to the proportion of patients who experience the composite efficacy failure event ([BPAR], Graft Loss or Death) over 12 months post-transplantation	Proportion of patients with composite efficacy failure event (BPAR, Graft Loss or Death) over 12 months post-transplantation
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
To demonstrate that CFZ533 600 mg and/or 300 mg Q2W SC are superior to a TAC-based regimen with respect to the mean estimated glomerular filtration rate (eGFR) over 12 months post-transplantation	Mean eGFR at 12 months post-transplantation

Cohort 1 – *de novo* patients

Objective(s)	Endpoint(s)

To assess the safety and tolerability of CFZ533 regimens compared to a TAC-based regimen	Proportion of patients up to end of study with:
	• Adverse events (AEs)
	• Serious adverse events (SAEs)
	• AEs related to study drug
	• AEs of special interest:
	  • Infections, including opportunistic infections
	  • Malignancies, including post-transplant lymphoproliferative disorder (PTLD)
	  • Thromboembolic events
	  • Major adverse cardiovascular events (MACEs)
	  • New onset diabetes mellitus (NODM)
	Means and mean change over time of:
	  • Vital sign parameters
	  • Lab parameters
	Proportion of patients up to end of study with:
	  • Premature discontinuation from study
	  • Premature discontinuation of study drug
	  • Dose interruption
	  • Dose adjustment

To assess the pharmacokinetics of CFZ533 during the treatment period and explore the dose-exposure relationship	Free CFZ533 plasma concentrations over time
To assess the immunogenicity of CFZ533 during the treatment period	Semi-quantitative analysis of anti-CFZ533 antibodies in plasma (CFZ533-treated patients only)

Exploratory Objective(s)	Endpoint(s) for exploratory objective(s)
[redacted]	

Cohort 1 – *de novo* patients

Objective(s)	Endpoint(s)
[redacted]	

Cohort 2 – maintenance patients

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
To demonstrate that CFZ533 450 mg bi-weekly (Q2W), subcutaneous (SC), is non-inferior to a TAC-based regimen with respect to the proportion of patients who experience the composite event efficacy failure event (BPAR, Graft Loss or Death) over 12 months post-conversion	Proportion of patients with composite efficacy failure event (BPAR, Graft Loss or Death) over 12 months post-conversion
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
To demonstrate that CFZ533 450 mg Q2W SC are superior to a TAC-based regimen with respect to the mean eGFR over 12 months post-conversion	Mean change in eGFR from baseline to 12 months post-conversion

To assess the safety and tolerability of CFZ533 regimen compared to a TAC-based regimen	Proportion of patients up to end of study with:
	• Adverse events (AEs)
	• Serious adverse events (SAEs)
	• AEs related to study drug
	• AEs of special interest:
	  • Infections, including opportunistic infections
	  • Malignancies, including post-transplant lymphoproliferative disorder (PTLD)
	  • Thromboembolic events

Cohort 2 – maintenance patients

Objective(s)	Endpoint(s)
	• Major adverse cardiovascular events (MACEs) • New-onset diabetes mellitus (NODM) • Means and mean change over time of: • Vital sign parameters • Lab parameters • Proportion of patients up to end of study with: • Premature discontinuation from study • Premature discontinuation of study drug • Dose interruption • Dose adjustment
To assess the pharmacokinetics of CFZ533 during the treatment period and explore the dose-exposure relationship (together with PK data from Cohort 1)	Free CFZ533 plasma concentrations over time
To evaluate the immunogenicity of CFZ533 during the treatment period.	Semi-quantitative analysis of anti-CFZ533 antibodies in plasma (CFZ533-treated patients only)

Exploratory Objective(s)	Endpoint(s) for exploratory objective(s)
[redacted]	

Cohort 2 – maintenance patients

Objective(s)	Endpoint(s)
[redacted]	

2 Statistical methods

2.1 Data analysis general information

The interim and primary CSR analyses will be performed by Novartis personnel. The most recent version of SAS or R available in the validated statistical programming environment of Novartis will be used for the analysis.

The following general data conventions will apply:

- An interim analysis is planned from the data cut-off date of 12-Mar-2021. Interim analysis objectives will be performed based on patients in each Cohort who have completed Month 12 or discontinued prematurely at the data cut-off date.
- The primary endpoint analysis will take place when all patients in each Cohort have completed Month 12 or discontinued prematurely.
- Categorical data will be presented as frequencies and percentages for each category including a category labeled as "missing" when appropriate.
- Continuous variables will be presented with number of non-missing observations, mean, standard deviation, lower quartile (25^{th} percentile), median, upper quartile (75^{th} percentile), minimum, and maximum.
- 95% confidence limits will be presented.
- 2-sided p-values will be presented but no adjustment for multiplicity will be made.
- Listings will only be provided for variables explicitly indicated in this SAP.
- Rules for imputing incomplete dates are described in Section 5.2.

2.1.1 General definitions

2.1.1.1 Study treatment

The following drugs will be used in this study and will be administered in accordance with this protocol and where applicable, current local labeling. Not all dosage forms listed are available in each country, dependent on local approval status and regulations.

Investigational treatment

Novartis Global Clinical Supply (GCS) will supply the following investigational products:

- CFZ533 in a liquid in vial presentation is provided in vials of 1 mL at 150 mg/mL. This can be administered in both cohorts as a solution for intravenous infusion or as a solution for subcutaneous administration.
- CFZ533 Placebo 1 mL liquid in vial presentation, used in Cohort 1 for subcutaneous administration.
- CFZ533 300 mg/2 mL pre-filled syringes (PFS) - To be administered in both cohorts as solution for subcutaneous administration.
- CFZ533 Placebo 0 mg/2 mL PFS - To be administered in Cohort 1 as solution for subcutaneous administration.
- CFZ533 150 mg/1 mL PFS - To be administered in Cohort 2 as solution for subcutaneous administration.

Patients will switch from 150 mg/1 mL injection from vial (LIVI) to PFS once they have completed all their Month 12 visit assessments required for the primary endpoint analysis and PFS is available. Instruction for administration of CFZ533 PFS will be provided in a separate Instructions for Use document.

The PFS will be supplied in a blinded manner for Cohort 1, Arms 1 and 2 until completion of primary endpoint analysis at Month 12. Patients will continue to receive their randomized dose after Month 12.

Instructions for preparation and administration of CFZ533 and matching placebo are described in a separate pharmacy manual.

Control and Other study treatment

Concomitant medication will be used according to the local label:

- TAC (e.g., Prograf® or generics) as 0.5 mg, 1.0 mg or 5.0 mg capsules or tablets.
- TAC once daily formulations (e.g., Advagraf, Envarsus) as 0.5 mg, 0.75 mg, 1 mg, 3 mg, 4 mg or 5 mg prolonged-release capsules (only applicable for Cohort 2).
- Mycophenolate mofetil (MMF, e.g., CellCept® or generics) 500 mg film-coated tablets, or 250 mg capsules, or 500 mg vial for IV administration.
- Enteric-coated mycophenolate sodium (e.g., Myfortic® or generics) 180 mg or 360 mg tablets (only applicable for Cohort 2 or in case of persistent MMF intolerance in Cohort 1)
- Basiliximab as 20 mg lyophilized vial for IV administration following reconstitution with sterile water.
- Rabbit anti-thymocyte globulin (rATG, Thymoglobulin) will be provided locally as 25 mg lyophilized vial or as locally approved dosage form.

CS for oral and IV administration, MMF/EC-MPS, TAC, basiliximab and rATG will be supplied locally.

Note that only MMF (CellCept® or generic equivalent) is allowed in Cohort 1, EC-MPS (Myfortic® or generic equivalent) use is only permitted in Cohort 2 or in case of persistent MMF intolerance in Cohort 1.

Additional treatment

No additional treatment beyond study regimen (CFZ533-investigational drug, TAC, MMF/EC-MPS, corticosteroids-concomitant immunosuppressive drugs and basiliximab or rATG-induction therapy) is allowed in this trial; however, treatment of acute rejection (e.g., bolus steroids or anti-T-cell antibodies) should be according to local practice.

2.1.1.2 Treatment arms

Cohort 1 – *de novo* kidney transplant patients:

Patients in Cohort 1 will be randomized at baseline to one of the following three treatment arms in a 1.5:1.5:1 ratio and will be dosed accordingly:

- **Arm 1 (CFZ533 600 mg Q2W SC), n=75:** CFZ533 loading doses will be 30 mg/kg IV on day of transplant (Day 1), with a second dose of 15 mg/kg IV on Day 5 and SC administration of 600 mg (2 injections of 2 mL CFZ533 at 150 mg/mL) Q2W will begin on Day 15, in combination with MMF and CS (as per local practice) up to 59.5 months post-transplant.
- **Arm 2 (CFZ533 300 mg Q2W SC), n=75:** CFZ533 loading doses will be 30 mg/kg IV on day of transplant (Day 1), with a second dose of 15 mg/kg IV on Day 5 and SC administration of 300 mg (1 injection of 2 mL CFZ533 at 150 mg/mL, and 1 injection of 2 mL of the generic placebo) every 2 weeks (Q2W) will begin on Day 15, in combination with MMF and CS up to 59.5 months post-transplant. After completion of the primary endpoint analysis at Month 12, placebo injections will be removed once unblinded study treatment kits are available.
- **Arm 3 (Control/Standard of Care), n=50:** TAC + MMF + CS up to 60 months post-transplant.

All patients will receive induction therapy:

- Basiliximab: Two doses of 20 mg (first dose within 2 hours prior to transplantation and second dose at 4 days after transplantation) OR
- rATG: starting dose at 1 to 1.5 mg/kg/day as per US and EU approved labels (starting Day 1, and the last dose can be administered as per local label).

Cohort 2 – maintenance patients:

Patients in Cohort 2 will be randomized at baseline to one of the following two treatment arms in a 1.5:1 ratio and will be dosed accordingly:

- **Arm 1 (CFZ533 450 mg Q2W SC), n=75:** patients enrolled 6 to 24 months post-transplantation. On Day 1, patients will be administered the first dose of CFZ533 at 30 mg/kg IV, concomitantly with MMF/EC-MPS and approximately 50% of the current TAC dose. At Day 15, CFZ533 will be administered SC at 450 mg (1 injection of 2 mL and 1 injection of 1 mL CFZ533 at 150 mg/mL) concomitantly with MMF/EC-MPS and

TAC, the latter reduced by a further 50% approximately. By Day 29, patients will be fully tapered off their TAC. Subsequent doses of 450 mg SC (Q2W) will be administered in combination with MMF/EC-MPS with or without corticosteroids, up to Month 59.5 visit.

- **Arm 2 (TAC+MMF/EC-MPS ±CS), n=50:** Patients who received a primary kidney allograft 6 to 24 Months prior enrollment and are treated with TAC+MMF/EC-MPS ±CS will continue on the same regimen. Once daily TAC formulations (Advagraf, Envarsus, etc.) are permitted.

2.1.1.3 Study days

Study Day 1 (or Day 1 or reference start date) is defined as the day of first dose of study treatment.

All other study days are labeled as the number of days relative to Day 1. Therefore, for a particular date, study day will be calculated as follows:

- for dates on or after the date of first administration of study treatment:

  Study day = Assessment date – date of first dose of study treatment + 1
- for dates prior to the date of first administration of study treatment:

  Study day = Assessment date – date of first dose of study treatment

Moreover, duration of an event is calculated as:

Duration of an event = Event end date – event start date + 1

A study month will be defined as 28 days.

2.1.1.4 Baseline

The baseline value is generally defined as the last assessment before date and time of first administration of study drug; if only the date is available, the last assessment before or at the date of first administration of study drug will be used.

2.1.1.5 Post-baseline measurement

Post-baseline measurements are defined as assessments performed after start of study treatment.

When change from baseline is of interest the following formula will be used for each scheduled visit and time-point where baseline and post-baseline values are both available:

Change from baseline = post-baseline value – baseline value.

2.1.1.6 Visits

The visits defined in the protocol are used to guide investigators whereas the “re-aligned” visit windows in Table 5-1 (called visit windows in the following) will be used for the analyses.

2.1.1.7 On-treatment/treatment-emergent

The following definitions apply:

- start of study treatment:
  - CFZ533 arms: day of first dose of CFZ533;

  - control arms: min (day of first dose of TAC, day of first dose of MMF)
- end of study treatment
  - CFZ533 arms: day of last dose of CFZ533 + 14 days
  - control arms: day of last dose of TAC

The treatment period is the period from baseline to end of study treatment such that

[baseline, end of study treatment].

The follow up period is the period from the end of study treatment to end of study (EOS) such that

(end of study treatment, EOS].

Unless stated otherwise, measurements collected during the treatment period will be considered as on-treatment/treatment-emergent.

A treatment-emergent adverse event (TEAE) is defined as any AE that started after the start of study treatment through the end of study treatment, i.e. [start of study treatment, end of study treatment]. If the AE start date is the same as the start of study treatment, but time is not available for comparison, the AE will be considered to be treatment-emergent.

2.1.1.8 Last contact date

Last contact date is defined as the date the patient completes the study or discontinues prematurely. If a patient discontinues the study due to "lost to follow up," the latest date out of assessment dates and event/medication start and end dates will be used as last contact date.

For patients ongoing at time of the interim or primary analyses, the cutoff date will be used as last contact date.

2.1.1.9 Stratification factors

Cohort 1 – *de novo* kidney transplant patients:

Randomization will be stratified for donor category (living vs. deceased) and induction therapy (basiliximab vs. rATG).

The strata, donor category (living vs. deceased) and induction therapy (basiliximab vs. rATG), will be used directly from the eCRF.

Cohort 2 – maintenance patients:

Randomization will be stratified for corticosteriod use (yes/no) and time since transplant (6 - ≤ 12M vs. 12-24M).

The strata, corticosteriod use (yes/no) and time since transplant (6 - ≤ 12M vs. 12-24M), will be used directly from the eCRF.

2.2 Analysis sets

The analysis sets are defined as follows:

- **Screened set (SCR):** all patients who signed the ICF and includes only uniquely screened patients (i.e. only the chronologically last screened data is counted in the case of re-screened patients)
- **Full analysis set (FAS):** all patients who are transplanted and randomized, excluding mis-randomized patients, where mis-randomized patients are defined as cases where IRT contacts were made by the Investigator/qualified site staff either prematurely or inappropriately for confirmation of the patient's final randomization eligibility and treatment was not administered to the patient. Following the intention to-treat (ITT) principle, patients will be analyzed according to the treatment arm they were randomized to.
- **Safety set (SAF):** all patients in the FAS who take at least one dose of study medication whether being randomized or not. Patients will be analyzed according to the treatment they received.
- **PK analysis set (PK):** 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 PD, e.g. if a dose was taken more than 7 days after the planned date

Unless otherwise specified, all efficacy analysis will be performed on the FAS and safety analyses will be performed on the SAF.

The total patients in the SCR, FAS, and SAF analysis sets will be summarized in terms of the numbers and percentages by Cohort and treatment.

Protocol deviations by criteria leading to exclusion in the SCR, FAS, and SAF analysis sets will be provided by Cohort and treatment.

A listing of patients excluded from analysis sets will be provided.

2.2.1 Subgroup of interest

The following subgroups of interest will be used for selected safety and efficacy analyses:

- *de novo* cohort
  - Living vs. deceased donors
  - Induction therapy (basiliximab, rATG)
  - rATG dose (<3 mg, >= 3 mg)
- maintenance cohort
  - Time since Tx (6 - ≤ 12 months, > 12-24 months)
  - Corticosteroid use (yes/no)

Subgroups may need to be combined if there is not a sufficient number of patients (e.g. at least 10%) in a respective subgroup.

For tables presenting results from statistical models, the treatment effects in the subgroup will be derived using an additional covariate as a fixed effect and the appropriate interaction terms in the model, if necessary.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The subject disposition at Month 12 will be provided for the FAS by Cohort and treatment and will include:

- the disposition reason (received at least one dose of study treatment, completed treatment at Month 12, discontinued treatment at Month 12, discontinued study)
- the primary reason for discontinuing treatment (obtained from the Disposition form in the eCRF)
- the primary reason for discontinuing study (obtained from the Disposition form in the eCRF)

Protocol deviations by deviation category will be provided for the FAS by Cohort and treatment.

The Kaplan-Meier point estimates and 95% confidence interval for the rate of treatment discontinuation up to Month 12 will be presented in a table and plot by Cohort and treatment as detailed in using the FAS. The difference in rates of treatment discontinuation at Month 12 between treatments and 95% confidence interval using Greenwood's formula will be provided by Cohort.

For Cohort 1, stratified Kaplan-Meier estimates will be also provided for survival analysis of the time to treatment discontinuation for the following subgroups: induction therapy (rATG vs. basiliximab), donor type (living vs. deceased).

Details on survival analysis can be found in Section 5.8.1.

Listings of randomization, subject disposition, and protocol deviations will be provided by Cohort.

2.3.2 Background and demographics characteristics

Based on the FAS, summary statistics will be provided by Cohort and treatment for the following background and baseline characteristics:

- **Recipient demographics:**
  - Age (years)
  - Age group (< 60, ≥60 years)
  - Gender (Male, Female)
  - Race (obtained from the Demographics form in the eCRF)
  - Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
  - Region (US, EU, LACAN, AMEA)
  - Weight (kg)
  - Height (cm)
  - BMI (kg/m2)
- **Donor demographics:**

  - Age (years)
  - Age group (< 60, ≥60 years)
  - Gender (Male, Female)
  - Race (obtained from the Demographics form in the eCRF)
  - Donor category (deceased non heart beating, deceased heart beating, living related, living unrelated)
- **Recipient baseline characteristics:**
  - eGFR (MDRD-4) (<30, 30-<45, >=45-60, ≥60 mL/min/1.73m^2)
  - Diabetic status prior to randomization (Yes, No) (see Section 2.3.2.1)
  - Spot urine protein/creatinine ratio (UPCR) categories (<30, 30-<300, 300-<1000, 1000-<3000, >=3000)
  - Presence of donor specific antibodies (DSA) at randomization (Yes, No)
  - Delayed graft function (DGF) status at baseline (Yes, No) (see Section 2.3.2.3) (*de novo* cohort)
  - Induction therapy (rATG, basiliximab) (*de novo* cohort)
  - Corticosteroid use (Yes, No) (maintenance cohort)
  - Time since treatment (days) (maintenance cohort)
- **Recipient transplant background information:**
  - End stage disease leading to transplantation
  - Current dialysis (Yes, No) (*de novo* cohort)
  - Time since continuous dialysis started (days)
  - Most recent PRA (%)
  - Peak PRA (%)
  - HLA matching (1, 2, 3, 4, 5, 6; <3, >=3)
- **Recipient and donor viral serology:**
  - cytomegalovirus IgG Antibody (positive, negative)
  - cytomegalovirus IgM Antibody (positive, negative)
  - Epstein-Barr Virus IgG Antibody (positive, negative)
  - Epstein-Barr Virus IgM Antibody (positive, negative)
  - BKV IgG (positive, negative)
  - BKV IgM (positive negative)
  - Hepatitis C Virus antibody (HCVAb) (positive negative)
  - Hepatitis B Virus Surface antigen (HBsAg) (positive, negative)
  - Hepatitis B core antibody (HBcAb) (positive, negative)
  - HIV (positive, negative)
  - Donor/recipient IgG constellation (D+R+, D+R-, D-R+, D-R-, partially/fully missing): CMV IgG, CMV IgM, EBV IgG, EBV IgM, BKV IgG, BKV IgM

For variables which are collected multiple times before the randomized study medication starts, the last available values on or prior to the randomization will be used for summary if not specified otherwise.

2.3.2.1 Diabetic status

A patient is identified as not having diabetes prior to randomization if all of the following conditions are met:

- Reason for transplantation was not diabetes mellitus
- Diabetes mellitus was not included in the medical history
- Glucose (random) < 11 mmol/L at the time of transplantation
- Diabetes mellitus was not recorded as reason for any medication given prior to transplantation
- HbA1c < 5.7 at randomization/enrollment

If the response to any of the above items is missing, but the remaining criteria are "yes", then the patient will be classified as no history of diabetes.

The date of onset will be the earliest date when any of the above conditions is met. Depending on the onset date, a patient will be identified as having DM prior to randomization if the date is prior to or at randomization.

2.3.2.2 Delayed graft function

DGF status at baseline (within 14 days after the date of reperfusion) will be summarized. Patients are considered to have DGF when:

- From the Dialysis eCRF page, a dialysis is performed within 14 days after the date of reperfusion and DGF is the reported reason *or*
- From the AE eCRF page, DGF is reported as an AE (MedDRA lower level term includes words: "graft dysfunction", "delayed graft function", or "graft function delayed") and start date is within 14 days after the date of reperfusion *or*
- From the DAR eCRF page, DGF is the reported reason for change in the DAR page of the eCRF and start date is within 14 days after the date of reperfusion *or*
- From the REJ eCRF page, the "primary clinical diagnosis is "15 = delayed graft function" and the "Date rejection was first suspected" is within 14 days after the date of reperfusion.

The start date of DGF is obtained from the transplantation procedure eCRF page, date of reperfusion. The end date of DGF is obtained from the Dialysis eCRF page, from the end date of the last dialysis session where the reason for dialysis was DGF. If DGF was reported as an AE without requiring dialysis, then the AE end date will be used. If the end date is still missing, then the end date of study medication from DAR panel with DGF reason will be used. Otherwise, the end date will remain missing.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment/compliance

The analysis of study treatments will based on the SAF.

Administration

The duration (days) of exposure to study medication administration will be calculated by subtracting the date of the last administration of study medication from the date of first administration; for CFZ533, the dosing interval will be added (e.g. 14 days for treatment administered once every 2 weeks). Periods of temporary interruption of study medication for any reason will be included.

Duration (days) of exposure to randomized study medication will be by

- summary statistics for the continuous duration of exposure (days); and,
- frequency and percent for the duration of exposure categories which are the following for the De Novo cohort

  CFZ533: ≤ 14 days, 15- ≤ 28 days 29- ≤ 42 days, 43- ≤ 56 days, 57- ≤ 70 days, 71- ≤ 84 days, 85- ≤ 112 days, 113 - ≤ 140 days, 141- ≤168 days, 169- ≤ 196 days, 197- ≤ 224 days, 225- ≤ 252 days, 253- ≤ 280 days, 281- ≤ 308 days, 309- ≤336 days, 337-≤ 463 days, 464 - ≤ 672 days, 673 - ≤ 1008 days 1009 - ≤1176 days)

  Tacrolimus: <=28 days, 29-<=56 days, 57-<=84 days, 85-<=168 days, 169-<=224 days, 225-<=280 days, 281-<=336 days, 337-<=504 days, 505-<=672 days, 673-<=1008 days

Frequency and percent for the duration of exposure categories which are the following for the maintenance cohort:

CFZ533: <=28 days, 29- ≤ 42 days, 43- ≤ 56 days, 57- ≤ 70 days, 71- ≤ 84 days, 85- ≤ 112 days, 113 - ≤ 140 days, 141- ≤168 days, 169- ≤ 196 days, 197- ≤ 224 days, 225- ≤ 252 days, 253- ≤ 280 days, 281- ≤ 308 days, 309- ≤336 days, 337-≤ 463 days, 464 - ≤ 672 days, 673 - ≤ 1008 days

Tacrolimus: <=28 days, 29-<=56 days, 57-<=84 days, 85-<=168 days, 169-<=224 days, 225-<=280 days, 281-<=336 days, 337-<=504 days, 505-<=672 days, 673-<=1008 days

Dose interruptions and changes

The number and percentage of patients with:

- reason and number of dose interruptions (any, 1, 2, 3, ≥3)
- reason and number of dose changes (any, 1, 2, 3, ≥3)
- reason for permanent discontinuations

Will be summarized by Cohort and treatment.

2.4.2 Relevant medical history/current medical conditions

Frequencies and percentages of relevant medical history/current medical conditions will be presented by primary system organ class, preferred term, and treatment arm for each Cohort based on the FAS.

2.4.3 Prior, concomitant and post therapies

Prior/concomitant therapies will be summarized based on the SAF.

All medications recorded on the Concomitant medications / significant non-drug therapies eCRF page will be classified as *prior* or *concomitant* medications and grouped by ATC codes and by *anatomical main group* (the 1st level of the ATC codes).

Prior medications will be drugs taken prior to the first dose of randomized study medication regardless of whether they continue thereafter; any medication given at least once between the day of first dose of randomized study medication and the last day of randomized study medication is considered a concomitant medication, including those started before randomization and continued into the treatment period.

Number and percentages of patients receiving at least one drug of a particular ATC code and at least one drug in a particular anatomical main group for prior and concomitant medications will be presented by Cohort, treatment, ATC class 1, and preferred term.

Concomitant immunosuppressive therapies other than randomized study medication taken after discontinuation of study drug and concomitant immunosuppressant therapies other than randomized study medication taken for treatment of allograft rejection by Cohort, treatment, ATC class 1 and preferred term.

2.5 Analysis of the primary objective

The Bayesian decision rule will be applied for the primary endpoint at the final analysis without adjustment for multiplicity.

2.5.1 Primary endpoint

The primary objective is to demonstrate that CFZ533 regimens are non-inferior to control with respect to the proportion of patients who experience the composite efficacy failure event up to Month 12 post-transplantation (Cohort 1) or post-conversion (Cohort 2).

The primary endpoint for each CFZ533 regimen is evaluated separately as a non-inferiority comparison to the SoC.

The composite efficacy failure event defined as any of the following:

- BPAR (BANFF ≥ 1A) based on the central and adjudicated assessments
- graft loss
- death

up to Month 12 post-transplantation (Cohort 1) or post-conversion (Cohort 2). The derivation for the composite efficacy failure is found in Section 5.7.8.

The estimand definition is as follows:

- **Population**: defined through appropriate inclusion/exclusion criteria to reflect the targeted population; adult male and female *de novo* renal transplant recipients of a primary graft from a deceased or living donor (Cohort 1), or adult male and female maintenance renal transplant recipients of a primary graft received 6 to 24 months prior to enrollment (Cohort 2)
- **Treatment**: the randomized treatment; CFZ533 600 mg + MMF + CS, CFZ533 300 mg + MMF + CS, TAC + MMF + CS (Cohort 1), or CFZ533 450 mg + MMF/EC-MPS +/- CS, TAC + MMF/EC-MPS +/- CS (Cohort 2)
- **Endpoint**: the binary composite outcome at 12 months post-transplantation (Cohort 1) or post-conversion (Cohort 2) of BPAR, graft loss, or death
- **Handling of remaining intercurrent events**: regardless of treatment and study discontinuation (treatment policy) prior to Month 12 post-transplantation (Cohort 1) or post-conversion (Cohort 2) (i.e., Day 463)
- **Summary measure**: difference in the proportion of composite efficacy failure between the CFZ533 arm(s) and control

The estimand will be evaluated as a non-inferiority analysis in the FAS population.

2.5.2 Statistical hypothesis, model, and method of analysis

The number of composite (BPAR, graft loss, death) events is assumed to follow a Poisson distribution, i.e., $y_i = \text{Poisson}(\mu_i)$, where $\mu_i = \lambda_{i,T} t_{i,T}$ is the expected number of events in group i, $t_{i,T}$ is the total follow up time in group i up to time T (= 12 months), and λ_i is the event rate in group i up to time T (= 12 months). The probability of a composite event occurring can then be derived as $\theta_i = 1 - \exp(-\lambda_i T)$.

The pre-defined success criteria is considered to be a composite rate difference between at least one of the CFZ533 arms and the control group of less than a non-inferiority (NI) margin of 20% in the *de novo* cohort (Cohort 1) and 12% in the maintenance cohort (Cohort 2), and certainty greater than 90% as defined below:

$$\Pr(\theta_{\text{CFZ533}} - \theta_{\text{SoC}} < \text{NI} \mid \text{data}) > 0.90$$

where i = CFZ533 for each of the CFZ533 300 mg + MMF + CS, CFZ533 600 mg + MMF + CS arms (Cohort 1) or CFZ533 450 mg + MMF +/- CS arm (Cohort 2) and i = SoC for the TAC + MMF + CS arm (Cohort 1) or TAC + MMF +/- CS arm (Cohort 2).

Prior distributions are assumed to be a non-informative Beta(1,1) for both the CFZ533 and control arms. Posterior mean composite rates for each treatment group and the difference in mean response rates between treatments will be presented together with 95% credible intervals.

Required posterior probabilities will be estimated from simulations of the posterior distribution of $\theta_{\text{CFZ533}} - \theta_{\text{SoC}}$ and compared to the thresholds for the levels of certainty. Prior distributions are assumed to be a non-informative Beta(1,1) for both the CFZ533 and control arms.

Posterior differences in mean composite efficacy response rates between treatments (i.e $\theta_{\text{CFZ533}} - \theta_{\text{SoC}}$) and 95% credible intervals and the posterior probabilities (i.e. $\Pr(\theta_{\text{CFZ533}} - \theta_{\text{SoC}} < \text{NI} \mid \text{data})$) for

- NI = 10%, 15%, 20%, 25%, 30% (Cohort 1); or,

- NI = 5%, 10%, 12%, 15% (Cohort 2)

will be presented by Cohort.

2.5.3 Handling of missing values/censoring/discontinuations

The primary composite efficacy endpoint up to Month 12 post-transplantation (Cohort 1) or post-conversion (Cohort 2) will be analyzed regardless of treatment or study discontinuation (treatment policy).

Historically, the composite failure endpoint has been analyzed based on for-cause biopsies only. In this study, per-protocol biopsies will be used to address intercurrent and missing data handling strategies.

If a subject is missing a biopsy result:

- **as defined in** Section 2.5.1**:** the missing biopsy result will be imputed using a random generation from a binomial distribution with the composite rate at Month 12 from the same arm, using for-cause and per-protocol biopsy data in each Cohort, as the missing biopsy result
- **due to study discontinuation, treatment discontinuation, or lost to follow-up:** the missing biopsy result will be imputed using a random generation from a binomial (or Poisson, if possible) distribution with the composite rate at Month 12 from the TAC arm, using for-cause and per-protocol biopsy data in each Cohort, as the missing biopsy result

2.5.4 Supplementary analyses

A figure of the proportion of subjects experiencing composite efficacy failure (BPAR, graft loss, or death) by time (0-3 months, >3-6 months, >6-9 months, >9-12 months) will be presented by Cohort and treatment.

A figure of the estimates, differences, and 95% confidence intervals of the differences in proportion of subjects experiencing composite efficacy failure will be presented by Cohort.

The Kaplan-Meier point estimates and 95% confidence interval for rate of

- the primary composite efficacy failure (BPAR, graft loss, or death)
-

through Month 12 will be presented in a table and/or plot by Cohort and treatment using the FAS. The difference in rates of the primary composite efficacy failure (BPAR, graft loss, or death) at Month 12 between treatments and 95% confidence interval using Greenwood's formula will be provided by Cohort.

For Cohort 1, stratified Kaplan-Meier estimates will be also provided for survival analysis of the time to composite efficacy failure for the following subgroups: induction therapy (rATG vs. basiliximab), donor type (living vs. deceased).

Details on survival analysis can be found in Section 5.8.1.

2.5.5 Supportive analyses

For Cohort 1 in, stratified Kaplan-Meier estimates will be also provided for analysis of the time to composite efficacy failure for the following subgroups: induction therapy (rATG vs. basiliximab), donor type (living vs. deceased). Details on survival analysis can be found in Section 5.8.1.

2.6 Analysis of the key secondary objective

Not applicable.

2.7 Analysis of secondary efficacy variables

Not applicable.

2.8 Safety analyses

2.8.1 Estimated GFR using the MDRD-4 formula

The objective is to demonstrate that CFZ533 regimens are superior to a control with respect to mean eGFR over 12 months post-transplantation (Cohort 1) or mean change in GFR from pre-conversion baseline to Month 12 (Cohort 2).

The secondary eGFR endpoint for each CFZ533 regimen is evaluated separately as a superiority comparison to the SoC.

In the *de novo* population (Cohort 1), baseline kidney function is not a reliable baseline and, therefore, the mean eGFR at Month 12 post-transplantation is the endpoint of interest. In a maintenance population (Cohort 2), we can obtain a reliable baseline kidney function and the mean change from baseline at Month 12 post-conversion of eGFR is the endpoint of interest.

Estimated GFR using central laboratory serum creatinine values will be calculated using the MDRD-4 formula and summarized for each arm of the study. The MDRD-4 formula is defined as follows (Levey et al 2006):

$$\text{GFR } [\text{mL/min/1.73m}^2] = 175*(C^{-1.154})*(A^{-0.203})*G*R$$

where C is the serum concentration of creatinine (mg/dL), A is age (years), G=0.742 when gender is female (otherwise G=1), and R=1.212 when race is black (otherwise R=1).

The estimand is:

- **Population**: defined through appropriate inclusion/exclusion criteria to reflect the targeted population; adult male and female de novo renal transplant recipients of a primary graft from a deceased or living donor (Cohort 1), or adult male and female maintenance renal transplant recipients of a primary graft received 6 to 24 months prior to enrollment (Cohort 2)
- **Treatment**: the randomized treatment; CFZ533 600 mg + MMF + CS, CFZ533 300 mg + MMF + CS, TAC + MMF + CS (Cohort 1), or CFZ533 450 mg + MMF/EC-MPS +/- CS, TAC + MMF/EC-MPS +/- CS (Cohort 2)
- **Endpoint**: eGFR over 12 months post-transplantation (Cohort 1) or change from baseline to Month 12 post-conversion in eGFR (Cohort 2)

- **Intercurrent events**: A composite strategy will be used to account for the intercurrent events of graft loss and death regardless of treatment and study discontinuation (treatment policy) up to Month 12 post-transplantation (Cohort 1) or post-conversion (Cohort 2)
- **Summary measure**: the difference in mean eGFR over 12 months post-transplantation (Cohort 1) or the difference in mean change from baseline to Month 12 post-conversion in eGFR (Cohort 2) on CFZ533 arm(s) compared to control

Statistical model, hypothesis, and method of analysis

The hypothesis of interest will is:

- **The null hypothesis:** the mean Month 12 post-transplantation eGFR (Cohort 1) or the mean change from baseline to Month 12 post-conversion in eGFR (Cohort 2) for a CFZ533 treatment arm is not superior to that of the control arm; vs,
- **The alternative hypothesis:** the mean Month 12 post-transplantation eGFR (Cohort 1) or the mean change from baseline to Month 12 post-conversion in eGFR (Cohort 2) for a CFZ533 treatment arm is superior to that of the control arm.

The mean Month 12 post-transplantation eGFR (Cohort 1) or the mean change from baseline to Month 12 post-conversion in eGFR (Cohort 2) for each treatment arm (with 95% confidence intervals), treatment differences in mean responses (with 95% confidence intervals), and 2-sided p-value will be obtained using an ANOVA (Cohort 1) and ANCOVA (Cohort 2) adjusting for treatment group and with factors for stratification factors of donor category and induction therapy (Cohort 1) or corticosteroid use and time since transplant (Cohort 2) and variable for baseline eGFR (Cohort 2 only) and presented by Cohort.

Handling of missing values/censoring/discontinuations

The secondary estimand will account for the difference intercurrent events as follows:

- **Graft loss or death:** a value of 0 will be imputed for the Month 12 eGFR measurement if on/after the time of graft loss or death (composite strategy)
- **Treatment/study discontinuation or loss to follow-up:** observed data will be analyzed (treatment policy)

Supplementary analyses

A shift table of change from baseline in eGFR by chronic kidney disease (CKD) categories will be provided by Cohort and treatment.

A line plot of mean eGFR on treatment over time with 95% confidence intervals will be provided by Cohort and treatment.

Supportive analyses

For Cohort 1, analysis for eGFR will be repeated for the following subgroups: induction therapy (rATG vs. basiliximab), donor type (living vs. deceased).

2.8.2 Adverse Events

AEs and infections collected are to be coded with the MedDRA dictionary that gives preferred term and primary system organ class (SOC) information. AEs and infection preferred terms are to be analyzed as a whole under the heading of AEs for each treatment arm. The analysis will be based on the SAF population.

Adverse events will be summarized cumulatively from randomization to the analysis visit window (e.g., Month 12, Month 60).

All information obtained on AEs 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 (SOC) information. AEs and infection preferred terms are to be analyzed as a whole under the heading of AEs for each treatment arm. The proportion of patients with AEs will be summarized as follows:

- An overview of AEs by category (AEs, SAEs, Fatal SAEs, AEs leading to discontinuation, AEs leading to dose adjustment/interruption, AEs requiring additional therapy) and related to study treatment
- AEs by primary SOC and preferred term
-
- AEs by primary SOC and preferred term (with rate >=10%)
- AEs related to study treatment by SOC and preferred term
- AEs by primary SOC, preferred term, and maximum severity
- AEs by primary SOC, preferred term, and maximum severity (with rate >=5%)
- SAEs by SOC and preferred term
- SAEs rated to have relationship to study drug by SOC and preferred term
- Deaths by SOC and preferred term
-
- AEs leading to discontinuation of a study drug by SOC and preferred term
- AEs rated to have relationship to study drug leading to discontinuation by SOC and preferred term
- AEs leading to dose adjustment or interruptions of a study drug by SOC and preferred term
- AEs leading to discontinuation, dose adjustment, or interruptions of a study drug by SOC and preferred term
-
- Serious infections by type of infection and micro-organism of infection
-
- MACE by SOC and preferred term
- Thromboembolic events by SOC and preferred term
- AEs of special interest (AESI) by safety topic

MACEs will be identified from the checkbox on the AE CRF.

MACEs include: acute myocardial infarction with ST elevation (STEMI), acute myocardial infarction without ST elevation (Non STEMI), congestive heart failure, PCI (balloon angioplasty, stent angioplasty, other), AICD, CABG, cerebral vascular accident (thrombotic stroke, embolic stroke, hemorrhagic stroke, other), peripheral vascular diseases, AP (AP leading to hospitalization, AP leading to intervention, AP without intervention).

Thromboembolic events are defined as those PTs in the embolic and thrombotic events SMQ plus the HLT of coagulation and bleeding analyses.

In all tables about proportion 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 AEs 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.

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

A listing of SAEs and deaths will be provided.

2.8.3 Disclosure reporting

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on <on-treatment/treatment emergent> AEs which are not SAEs with an incidence greater than 5% and on <on-treatment/treatment emergent> SAEs and SAE suspected to be related to study treatment will be provided by Cohort, treatment, system organ class and preferred term on the SAF.

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.

2.8.4 BK-polyoma viremia and nephropathy

For the analyses proposed in this section, the SAF will be used.

The following variables will be summarized by cohort and treatment:

- Occurrence of BK-polyoma viremia any time post-transplant
- Occurrence of BK-polyoma virus nephropathy any time post-transplant

For a CFZ533 group with $n1$ subjects at risk, independent from the control group with $n0$ subjects at risk, of whom $x1$ and $x0$ experience a certain event with probability $\pi1$ and $\pi0$ respectively, the relative risk is estimated as:

$$p1/p0 \text{ with } p1 = x1/n1 \text{ and } p0 = x0/n0.$$

Let $x1$ be the number of patients with BK event in a CFZ group, $x0$ be the number of patients with BK event in the control group, $n1 - x1$ be the number of patients without BK event in a CFZ group, $n0 - x0$ be the number of patients without BK event in the control group, and $SE(\ln RR) = \sqrt{1/x_1 + 1/x_0 + 1/(x_1 + x_0) + 1/(n_1 + n_2 - x_1 - x_0)}$.

The asymptotic 95% CI based on the back-transformed large sample confidence limits on the log-transformed relative risk estimate (Altman DG, 1991) is computed as:

$$\exp\{\ln RR \pm 1.96\, SE(\ln RR)\}.$$

The SAS procedure PROC FREQ with option RELRISK in the TABLES statement will be used to provide the asymptotic $100(1-\alpha)\%$ confidence interval on the relative risk.

If either $x1$ or $x0$ equals 0, the RR will not be computed. In this case, the relative risk will be approximated by the odds ratio with an exact confidence interval as specified below.

For a CFZ533 group with n_1 subjects at risk, independent from the control group with n_0 subjects at risk, of whom x_1 and x_0 experience a certain event with probability π_1 and π_0 respectively, the odds ratio is estimated as

$$\frac{p_1(1-p_1)}{p_0(1-p_0)}$$

with $p_1 = x_1/n_1$ and $p_0 = x_0/n_0$.

The SAS procedure PROC FREQ with statement EXACT OR will be used to provide the conditional exact $100(1-\alpha)\%$ confidence interval on the odds ratio.

2.8.5 Other safety endpoints

Laboratory data

The following summaries will be provided for all laboratory data (urinalysis, hematology, and clinical chemistry) will be provided:

- Summary statistics by Cohort, treatment, and visit.
- Summary statistics for change by Cohort, treatment, and visit.
- Treatment-emergent clinically notable abnormalities by Cohort and treatment

Values outside of the clinically notable limits will be flagged as abnormalities for all laboratory data (including urinalysis, hematology, and clinical chemistry) (see Section 5.4)..

Liver enzymes

Values outside of the clinically notable limits will be flagged as abnormalities for all liver enzymes (see Section 5.4). Newly-occurring liver enzyme abnormalities will be summarized by Cohort and treatment.

[redacted]

Vital signs

Values outside of the clinically notable limits will be flagged as abnormalities for vital signs (see Section 5.5). The proportions of patients with clinically notable vital sign abnormalities will be summarized by Cohort, treatment, and visit.

ECG evaluations

Summary statistics for ECG parameters will be provided by Cohort, treatment, and visit.

New onset of diabetes mellitus (NODM)

New onset diabetes is defined as

1. All of the following should be true (no diabetes mellitus pre-transplant/conversion):
    - Reason for transplantation was not diabetes mellitus
    - Diabetes mellitus was not included in the medical history
    - Glucose (random) < 11 mmol/L at the time of transplantation
    - Diabetes mellitus was not recorded as reason for any medication given prior to transplantation
    - HbA1c < 5.7 at randomization/enrollment

2. And at least one of the following should be true (diabetes mellitus onset after transplant/conversion):
   - Two consecutive fasting plasma glucose (FPG) ≥ 126 mg/dL (7.0 mmol/L) at any time after Day 29 or a random plasma glucose (RPG) ≥ 200 mg/dL (11.1 mmol/L)
   - HbA1c ≥ 6.5% (only from Month 3 forward)
   - Diabetes mellitus reported as an AE that is prevalent after Day 29
   - Any concomitant medication with ATC level 2 code 'A10' (drugs used in diabetes mellitus), if prevalent after Day 29 AND is taken for at least 30 days

The proportion of patients developing new onset diabetes mellitus (NODM) after transplantation/conversion will be summarized by treatment group.

The probabilities of developing NODM will be compared between treatment groups using logistic regression models with treatment group and HbA1c levels at randomization/enrollment as explanatory variables. Death, graft loss, or loss to follow up without NODM before the analysis time point will not be counted as developing NODM. This analysis will be performed using patients in the SAF population who do not have DM at randomization/enrollment.

Note that patients with steroid-induced diabetes are excluded.

Immunogenicity

Blood samples for immunogenicity testing will be collected from all CFZ533-treated patients only, at selected time points, as defined in the Assessment Schedule. The presence of anti-CFZ533 antibodies will be assessed using screening and confirmatory assays. An integrated PK/PD and immunogenicity approach, focusing on the clinical and functional consequences of anti-drug antibodies (ADAs) will be applied. The consequences of an immune response to CFZ533 may be correlated with a loss of exposure (free CFZ533 measures), [redacted] and/or the appearance of immune-related adverse events.

A summary ADA results will be presented by treatment group. A patient-level listing of ADA finding will also be presented by treatment group

All immunogenicity results will be listed by Cohort, treatment, patient, and visit/time point.

2.9 Pharmacokinetic endpoints

Plasma concentrations will be expressed in µg/mL. All concentrations below the limit of quantification or missing data will be labeled as such in the concentration data listings. Concentrations below the Limit of Quantification will be treated as zero in summary statistics for concentration data only.

Descriptive summary statistics for total [redacted] CFZ533 plasma concentrations and other PK parameters as described in protocol Section 6.6.1 will be provided by Cohort, treatment and visit/sampling time point. Summary statistics will include frequency (n, %) of concentrations below the LLOQ, mean (arithmetic and geometric), SD, coefficient of variation (CV) (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will

be treated as zero in summary statistics. A geometric mean will not be reported if the dataset includes zero values.

Individual and [redacted] CFZ533plasma concentrations will be summarized and plotted over time by Cohort and treatment.

CFZ533 [redacted] plasma concentration data will be listed by treatment, subject, and visit/sampling time point.

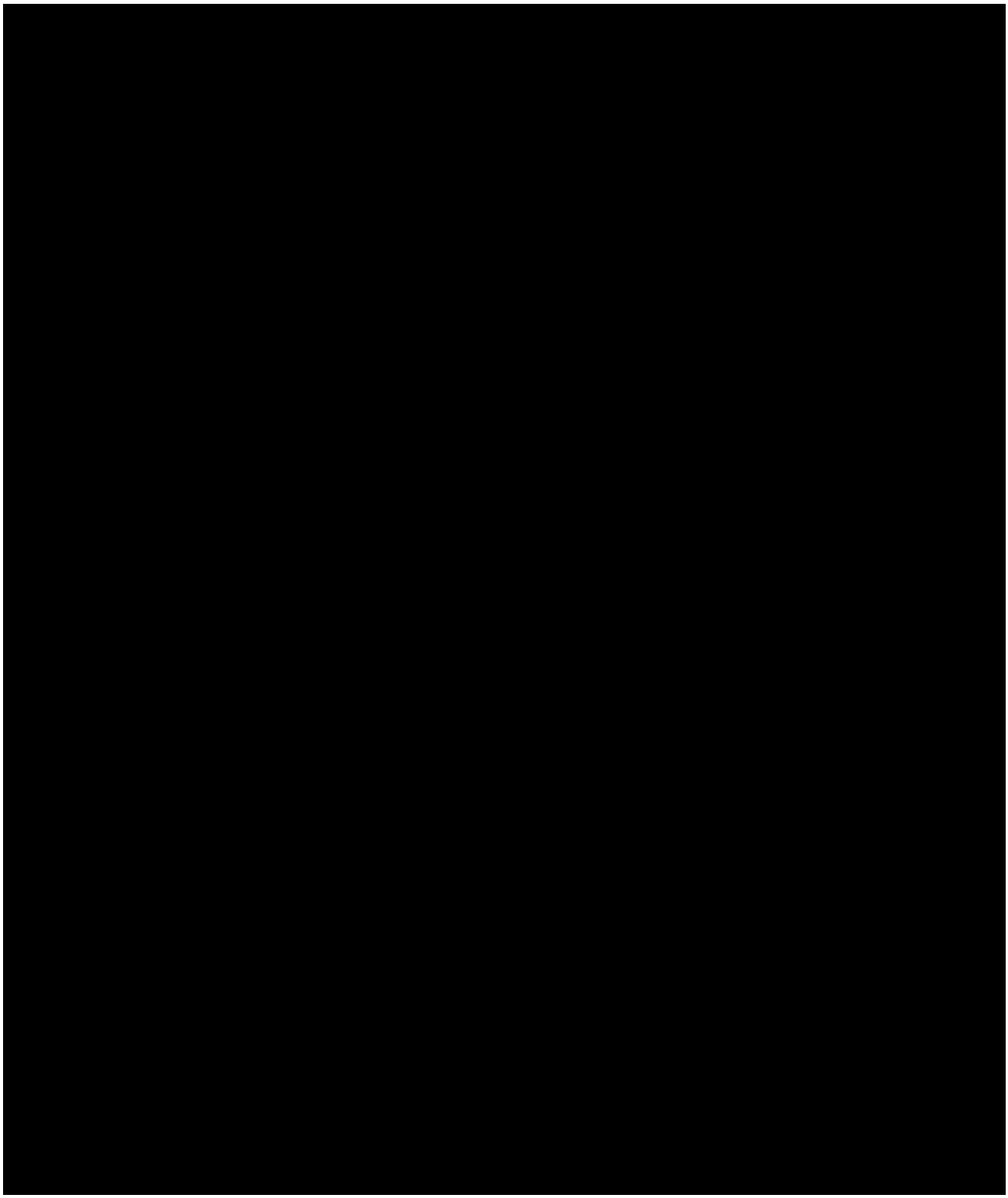
Average TAC and MMF trough levels will be provided by Cohort, treatment, and visit.

A box-and-whisker plot of CFZ533 [redacted] plasma concentrations over time (log transformed and linear) will be provided by Cohort and treatment.

Any other PK analyses will be described in a separate report (e.g., a CSR addendum).

2.10 Other Exploratory analyses

[redacted]



2.10.3 Exploratory analyses related to COVID-19

The proportion of subjects experiencing composite efficacy failure (BPAR, graft loss, or death) will be presented by COVID-19 phase, Cohort, and treatment. The components (BPAR, graft loss, death, and lost to follow up) contributing to the composite efficacy failure will be also presented. For the components, a subjects will be considered to experience the component event only if was the event considered in the composite derivation (i.e. only if the component was the first event observed).

A listing of

- COVID-19 related protocol deviations
- suspected or confirmed SARS-CoV-2 infections

will be provided by Cohort.

2.11 Interim analysis

An interim analysis will be conducted from the data cut-off on 12-Mar-2021 with the purpose to enable (1) overall benefit-risk assessment and (2) planning of subsequent clinical trials.

All data available on the interim analysis data cut-off will be used for the TFLs.

At the time of this IA, all available PK data from both Cohorts 1 and 2 will be summarized at the treatment group level in order to assess if CFZ533 plasma exposures are within the predicted target range, including the between subject variability in *de novo* and maintenance patients.

For the interim analysis, exploratory analyses related to COVID-19 will not be performed.

Cohort 1 (*de novo*)

It is expected that approximately 176 patients in all arms of Cohort 1 will complete their Month 12 visit or have discontinued the study on/by the interim analysis data cut-off.

Table 2-1 shows power for primary composite efficacy analysis in the de novo cohort (Cohort 1) at interim analysis under various scenarios. These calculations assume n= 66 in each CFZ533 arm and n=44 in the SoC arm and one-sided alpha=0.1. All calculations were performed in Rstudio and details are provided in the sample size documentation.

Table 2-1 Power (%) to demonstrate non-inferiority (NI=20%) at the time of the interim analysis (Cohort 1 – *de novo*)

Composite failure rate of CFZ533A	Composite failure rate of control				
	12%	15%	19%	21%	25%
15%	90	94	97	98	99
19%	72	81	90	93	97
21%	62	73	84	88	95
25%	40	52	68	75	85

Cohort 2 (maintenance)

It is expected that approximately 58 patients in all arms of Cohort 2 will have completed their Month 12 visit or have discontinued the study on/by the interim analysis data cut-off.

Table 2-2 shows power for primary composite efficacy analysis in the maintenance cohort (Cohort 2) at interim analysis under various scenarios. These calculations assume n=35 in the CFZ533 arm and n=23 in the SoC arm and one-sided alpha=0.1. All calculations were performed in Rstudio and details are provided in the sample size documentation.

Table 2-2 Power (%) to demonstrate non-inferiority (NI=12%) at the time of the interim analysis (Cohort 2 – maintenance)

Composite failure rate of CFZ533A	Composite failure rate of control			
	3%	6%	9%	12%
6%	62	73	81	87
8%	47	59	69	77
10%	34	46	57	66
12%	24	36	46	56

3 Sample size calculation

3.1 Stopping rule

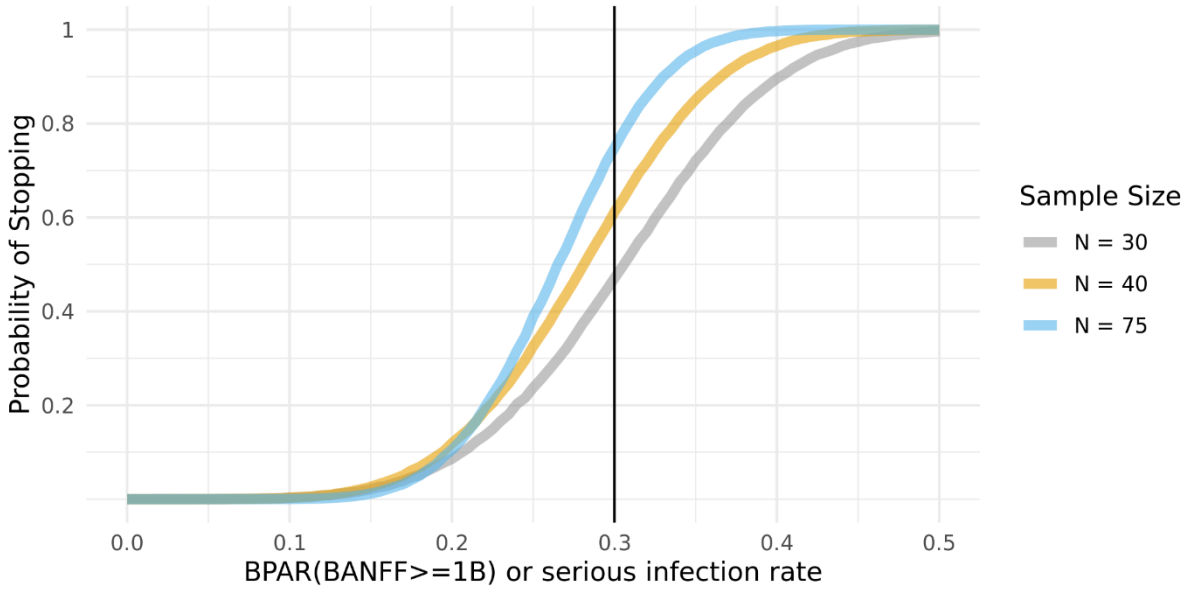
Cohort 1 – *de novo*

The stopping rules as defined in protocol Section 5.6.2.2 are designed to ensure enrollment in a CFZ533 treatment arm will be stopped if there is a high probability (>90%) that the true BPAR (BANFF>=1B or ABMR) rate or true serious infection rate is greater than 30%. The stopping rules apply until enrollment is completed. The enrollment is considered complete with Amendment 04 and, therefore, the stopping rule evaluation will no longer be applicable.

SAEs reported due to any hospitalization related to pre-emptive treatment for asymptomatic viral loads (e.g., CMV, BKV, EBV) will not be considered as a failure for serious infection and are excluded from the stopping rule analysis.

Figure 3-1indicates the probability of stopping for an arm for various true BPAR (BANFF>=1B) and serious infection rates. The stopping rules ensure the chance of stopping enrollment in a CFZ533 arm are sufficiently high for true high BPAR (BANFF>=1B or ABMR) and serious infection rates while remaining appropriately low when the true rates are low.

Figure 3-1 **Probability of stopping enrollment in the *de novo* cohort (Cohort 1) for various true BPAR or serious infection rates**

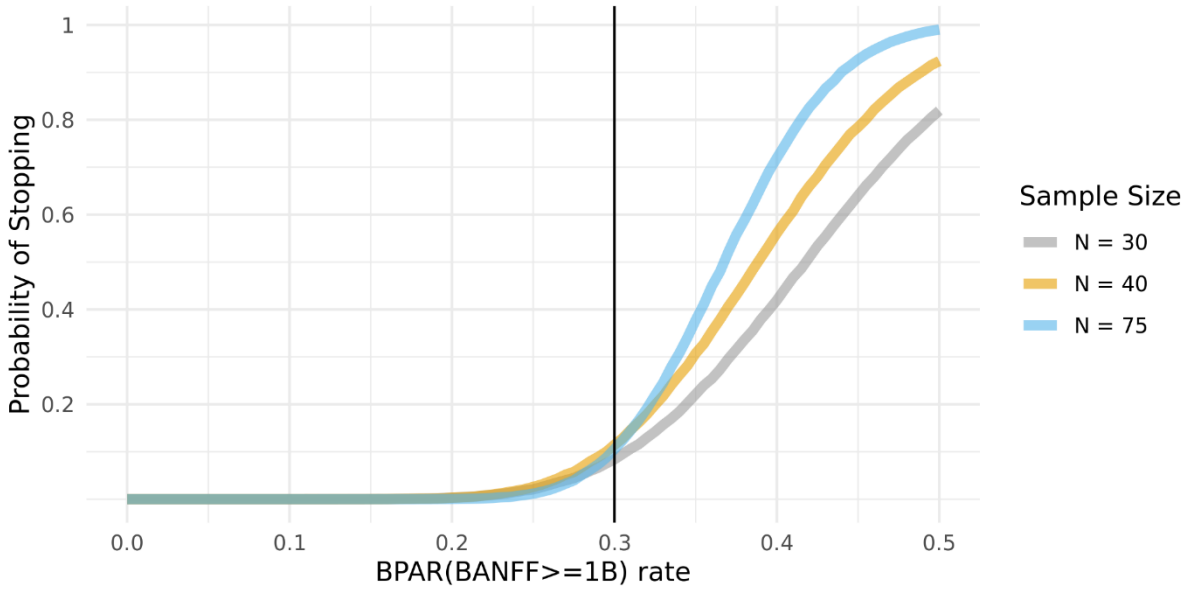


Cohort 2 - maintenance

The stopping rules as defined in protocol Sectioon 5.6.2.2 are designed to ensure enrollment in the CFZ533 arm will be stopped if there is a high probability (>90%) that the true BPAR (BANFF>=1B) rate is greater than 30%.

Figure 3-2 indicates the probability of stopping for an arm for various true BPAR (BANFF>=1B). The stopping rule ensures the chance of stopping enrollment in the CFZ533 arm are sufficiently high for true high BPAR (BANFF>=1B or ABMR) while remaining appropriately low when the true rate is low.

Figure 3-2 **Probability of stopping enrollment in the maintenance cohort (Cohort 2) for various true BPAR rates**



3.2 Power considerations

Cohort 1 – *de novo*

The primary objective is to demonstrate that a CFZ533 regimen is non-inferior to the control regimen with regard to composite efficacy failure at Month 12. The assumptions for the sample size calculation are as follows:

- Month 12 composite efficacy failure rate for the control arm is 15%
- Month 12 composite efficacy failure rate for CFZ533 arm is 21%
- Level of certainty is 90%
- Non-inferiority margin (NI) is 20%
- Patients spend an average of 80% of the anticipated 12 months in the study and then discontinue

Based on these assumptions, a sample size of 75 patients in a CFZ533 arm and 50 patients in the control arm will have 77% power to show that the CFZ533 arm is not more than 20% worse than control arm with respect to the Month 12 composite efficacy failure rate. Table 3-1 displays the power when the CFZ533 composite rate is 15, 19, 21 or 25% compared to 15% in the control arm. Power calculations performed in R (R version 3.6.1).

Table 3-1 **Power to demonstrate non-inferiority (NI=20%) with 75 patients in a CFZ533 arm and 50 patients in the control arm at the Month 12 analysis (Cohort 1 – *de novo*)**

Composite failure rate of CFZ533	Power
15%	96%
19%	85%

21%	**77**%
25%	55%

Cohort 2 – maintenance

The primary objective is to demonstrate that the CFZ533 regimen is non-inferior to the control regimen with regard to composite efficacy failure at Month 12. The assumptions for the sample size calculation are as follows:

- Month 12 composite efficacy failure rate for the control arm is 4% (based on CNI control in the ELEVATE (de Fijter et al 2017) and CONVERT (Schena et al 2009) studies)
- Month 12 composite efficacy failure rate for CFZ533 arm is 8%
- Level of certainty is 90%
- Non-inferiority margin (NI) is 12%
- Patients spend an average of 80% of the anticipated 12 months in the study and then discontinue

Based on these assumptions, a sample size of 75 patients in CFZ533 and 50 patients in the control arm will have 72% power to show that the CFZ533 arm is not more than 12% worse than control arm with respect to the Month 12 composite efficacy failure rate. Table 3-2 displays the power when the CFZ533 composite efficacy failure rate is 5, 6, 7, 8, 9 or 10%, compared to 4% in the control arm. Power calculations performed in R (R version 3.6.1).

Table 3-2 Power to demonstrate non-inferiority (NI=20%) with 75 patients in a CFZ533 arm and 50 patients in the control arm at the Month 12 analysis (Cohort 1 – de novo)

Composite failure rate of CFZ533	Power
5%	93%
6%	86%
7%	80%
8%	**72%**
9%	62%
10%	52%

3.3 Rationale for the assumptions of the sample size calculations

Cohort 1 (*de novo*): Rationale for a NI-margin (20%)

The primary endpoint within 12 months after transplantation will be considered in NI-margin justification. The NI-margin should not be larger than the amount of efficacy the control arm has over the putative placebo. Therefore, the NI-margin needs to be established depending on the control effect. The control effect needs to be determined by assessing the difference between the putative placebo and the control arm using data from previously conducted clinical trials. The treatment arms are:

- Experimental: B+MMF+CS+CFZ533
- Control: B+MMF+CS+TAC
- Putative Placebo: B+MMF+CS

Where B = basiliximab (Simulect®), CS = corticosteroids, MMF = mycophenolate mofetil, TAC = tacrolimus.

Ideally, data should come from multiple randomized trials that compare control and putative placebo arms within the same trial. Since there are no trials available which allow for direct comparison, comparisons come from separate sources.

One published trial studied a regimen similar to putative placebo (Vincenti et al 2001). The rate of composite endpoint at Month 12 was 58.16% (=57/98) with exact 95% CI of (47.77%, 68.05%), where 57 events included 52 biopsy-proven rejections, 3 deaths, and 2 graft loss events which were not due to rejection.

Two studies (Silva et al 2007, Krämer et al 2010) contained similar treatment arms of B+MMF+CS+TAC and control arm, as shown in Table 3-3). The composite failure events of BPAR, graft loss, death or lost to follow-up at Month 12 was utilized. The pooled composite failure rate using a weighted noniterative method (DerSimonian and Laird 1986) was 20.10% with a 95% CI of (13.59%, 26.62%).

- The conservative estimator is the upper bound 26.62%. Comparing this to the conservatively lower bound estimator from the Vincenti study of 47.77%, a difference of 47.77-26.62 = 21.15% as the control effect was obtained. The NI margin of 20% is justified since it is less than the control effect of 21.15%.
- Alternatively, the differences between putative placebo (58.16%) and each control arm showed in Table 3-3 could be considered. The weighted noniterative mean estimate is 38.06% and the 97.5% CI is (30.78%, 45.34%). The control effect could be estimated as the lower limit 30.78%, a more conservative estimate than a 95% CI lower limit. NI-margin is then set as 2/3 of the 97.5% CI lower limit which is 20% for a conservative estimate. Hence, an NI-margin of 20% is justified based on the meta-analysis.

Table 3-3 Month 12 composite failure rates (BPAR, graft loss, death, or lost to follow-up) from Astagraf™ studies

Study	Year	Events (n)	Population (N)	Rate (n/N)
Astagraf™ Study 1 (SCD)	2007	32	212	15.1%
Astagraf™ Study 1 XL (SCD)	2007	30	214	14.0%
Astagraf™ Study 2 (ECD)	2013	78	336	23.2%
Astagraf™ Study 2 XL (ECD)	2013	93	331	28.1%
Weighted Pooling Analysis (DerSimonian and Laird 1986)	**Mean**	**SE (Mean)**		**95% CI**
	20.10%	0.03324		(13.59%, 26.62%)

SCD: Standard Criteria Donor; ECD: Extended Criteria Donor; XL: Tacrolimus extended-release formula.

Cohort 2 (maintenance): Rationale for a NI-margin (12%)

The effectiveness of TAC control in the maintenance population is excellent. The event rate in the control arm is expected to be quite low (4% - based on CNI control in the ELEVATE (de Fijter et al 2017) and CONVERT (Schena et al 2009) studies). The upper bound of a 95% CI based on 50 control patients would be 9.4%. The sample size needed to use this NI margin is infeasibly high for a Phase 2 trial (200 CFZ533 patients vs. 133 TAC patients for ~80% power).

A NI margin of 12% was deemed sufficiently small for a Phase 2 trial of the size proposed as it allows for no more than a 3% difference in composite event rates for 80% power (α=0.10, 1-sided).

4 Change to protocol specified analyses

4.1 Protocol Section 9.5.2.1

MMRM method was proposed to analyzed eGFR in the protocol. Due to limitations in sample size at selected visits, implementation of a MMRM is no longer appropriate and an alternative analysis method, ANCOVA, is proposed. See Section 2.8.1.

A jump-to-reference imputation was proposed to impute missing all eGFR measurements in each Cohort when the missing data is due to treatment/study discontinuation or loss to follow-up. Due to limitations in sample size at selected visits, implementation of a jump-to-reference imputation is no longer appropriate and an alternative missing data strategy to analyze observed eGFR for patients who discontinued study or treatment or are lost to follow up (treatment policy). See Section 2.8.1.

4.2 Protocol Section 9.6.3

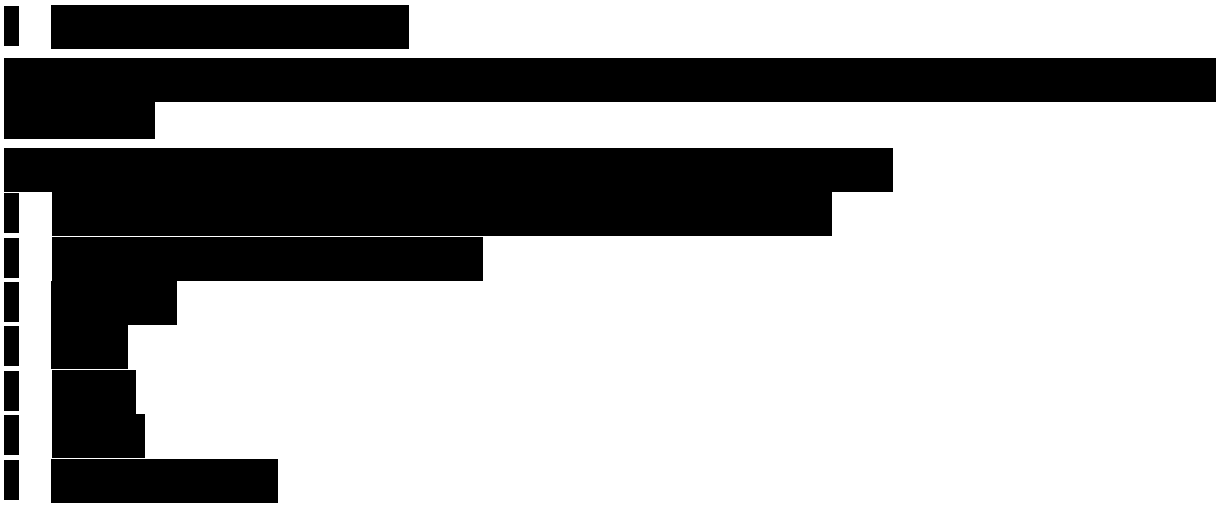
A repeated measures ANOVA was proposed to analyze SF-36v2 MCS and PCS scores. Due to limitations in sample size at selected visits, implementation of a repeated measures ANOVA is no longer appropriate and an alternative analysis method, ANOVA, is proposed. See Section 2.11.1.

A repeated measures ANOVA was proposed to analyze the number of symptoms each patient experienced on the MTSOSD-59R. Due to limitations in sample size at selected visits, implementation of a repeated measures ANOVA is no longer appropriate and an alternative analysis method, ANOVA, proposed. See Section 2.12.1.

4.3 Protocol Section 9.6.1

The following efficacy related endpoints were to be evaluated per the objectives specified in the protocol:

- composite of BPAR, Death, Graft Loss or Loss to Follow-up
- composite of Graft loss and death
- Graft loss
- Death
- BPAR



5 Appendix

5.1 Analysis visit windows

Analysis visit windows will be used to summarize the data by visit and are defined in terms of weeks. These will be based on the study schedule of evaluation and comprised a set of days "around" the nominal visits. Analysis visit windows are non-overlapping. All together they cover the entire study period. They are aligned to the dosing regimen, which is every 2 weeks, meaning a month is targeted to cover 4 weeks or 28 days.

As patients do not necessarily have their examinations at the exact scheduled time, it might be misleading if all data with the same nominal visit number are lumped together for a by-visit analysis. Thus, all data (including reported unscheduled assessments) are "re-aligned" according to the window schema given below. Note that the visit windows defined in the protocol are used to guide investigators whereas the 're-aligned' analysis visit windows in (simply called visit windows in the following) will be used for the analyses.

Table 5-1 Analysis visit windows

Re-aligned Visit	Visit Window	Start day of Visit window	Midpoint	End day of visit window
1	Screening	Day of ICF		Day of transplant-1
2	Baseline	Day of transplant		Up to start of study drug
3	Day 1		Start of study drug = Day 1	
4	Day 5	2	5	8
5	Day 15	9	15	22
6	Day 29	23	29	37
7	Month 1.5	38	43	49
8	Month 2	50	57	63
9	Month 2.5	64	71	77

Re-aligned Visit	Visit Window	Start day of Visit window	Midpoint	End day of visit window
10	Month 3	78	85	98
11	Month 4	99	113	140
12	Month 6	141	169	196
13	Month 8	197	225	252
14	Month 10	253	281	308
15	Month 12*	309	337	379
16	Month 15	380	421	463
17	Month 18	464	505	547
18	Month 21	548	589	631
19	Month 24	632	673	715
20	Month 27	716	757	799
21	Month 30	800	841	883
22	Month 33	884	925	967
23	Month 36	968	1009	1051
24	Month 39	1052	1093	1135
25	Month 42	1136	1177	1219

Days are relative to first treatment date, *Month 12 visit window has been extended to 309 to ≤ 463 days for patients unable attend visit due to COVID-19. Under this window schema, multiple records of a patient are re-aligned into the same visit as follows:

- For post-randomization continuous values, for a given patient, if multiple numeric measurements for a given variable are reported in the same visit window (e.g. Month 6), then the average of these measurements will be presented except for CFZ533, TAC, and MMF trough level measurements, eGFR, and liver tests.
- For trough levels, the last value observed within a visit window is taken
  - For eGFR, the closest value to the planned visit (screening visit: date of transplant; randomization visit: Day 1; other visits: midpoint of the visit window is taken (if tie, take the average)
  - For liver tests (bilirubin, SGOT, SGPT), the following algorithm is applied:
    a. If an AR occurs within a visit window with multiple liver tests reported, the time of the event is the date rejection first suspected, and the liver test to be summarized are the closest to that event (if tie, take the average)
    b. If no rejection occurs, the last assessment within the visit window is taken.
- For categorical values, the worst value of all records observed in the visit window is used.
- For change from baseline analysis of renal function parameters (maintenance cohort), the

baseline is defined as the last available value on or before the visit, e.g.

- For change from randomization, the baseline is the last available value on or before Day 1 post-randomization.

5.2 Imputation rules

5.2.1 Study drug

Although not the rule, partially or completely missing dates occur. Known dates with this issue are the start date on the Medical History eCRF page, start and end dates on the Concomitant Medications eCRF page, or Surgical and Medical Procedures page eCRF page, and occasionally the start and end dates on the AEs eCRF.

Any date incompletely reported is split into its day, month, and year components. In SAS, a numerical date value can only be defined if all these date components are known; incomplete dates are to be handled as text strings (character-type variables); as such, they could not be easily processed. An imputation rule for incomplete dates will be performed.

5.2.2 AE date imputation

This algorithm is expressed in the Variable Source Derivation column as **#IMPUTAEV(*event*)** where *event* is the partial start date of the AE. Table 5-2 explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed. Note, if the imputed AE (or CM) start is after AE (or CM) end date, then set AE (or CM) start equal to AE (or CM) end date. Missing AE end dates will not be imputed.

Table 5-2 Imputation logic for partial AE dates

	Day	Month	Year
Partial AE (or Concomitant Medication) Start Date	Not used	MON	YYYY
Treatment Start Date (TRTSDT)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	NC	NC	NC	NC
YYYY < TRTY	(D)	(C)	(C)	(C)
YYYY = TRTY	(B)	(C)	(A)	(A)
YYYY > TRTY	(E)	(A)	(A)	(A)

The following table is the legend to the logic matrix.

Relationship	
Before Treatment Start	Partial date indicates AE (or CM) start date prior to Treatment Start Date
After Treatment Start	Partial date indicates AE (or CM) start date after Treatment Start Date

Uncertain	Partial date insufficient to determine relationship of AE (or CM) start date to Treatment Start Date
Imputation Calculation	
NC / Blank Uncertain	No convention
(A) After Treatment Start or Uncertain	MAX(01MONYYYY, TRTSDT+1)
(B) Uncertain	TRTSDT+1
(C) Before Treatment Start	15MONYYYY
(D) Before Treatment Start	01JULYYYY
(E) After Treatment Start	01JANYYYY

5.2.3 Concomitant medication date imputation

The notation used is in the logic matrix of Table 5-3. Missing end dates will not be imputed.

Table 5-3 Imputation logic for partial concomitant medication dates

	Day	Month	Year
Partial Conmed. end Date	Not used	MON	YYYY
Last Contact Date (LASTDT)	Not used	LSTM	LSTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < LSTM	MON = LSTM	MON > LSTM
YYYY MISSING	NC	NC	NC	NC
YYYY < LSTY	(C)	(A)	(A)	(A)
YYYY = LSTY	(B)	(A)	(B)	(A)
YYYY > LSTY	(C)	(A)	(A)	(A)

The following table is the legend to the logic matrix.

Relationship	
Before Last contact date	Partial date indicates CM end date prior to Last Contact Date
After Last contact date	Partial date indicates CM end date after Last Contact Date
Uncertain	Partial date insufficient to determine relationship of CM end date to Last Contact Date
Imputation Calculation	
NC / Blank Uncertain	No convention
(A) Before/After Last contact date	Last day MONYYYY
(B) Uncertain	LASTDT
(C) Before/After Last contact date	31DECYYYY

At the M12 analysis, if the above logic is applied and the imputed end date is after the cut-off date, then the imputed end date will be replaced with the cut-off date.

5.2.4 Virology date imputation

Partially missing virology dates will follow the AE imputation rules found in Section 5.2.2.

5.3 AEs coding/grading

AEs and infections collected are to be coded with the MedDRA dictionary that gives preferred term and primary system organ class (SOC) information. AEs and infection preferred terms are to be analyzed as a whole under the heading of AEs for each treatment arm.

AEs must be accompanied by the following information:

- the severity grade. If severity grade is selected, add the following:
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment (no/yes)
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- whether it constitutes a SAE and which seriousness criteria have been met.
- action taken regarding [investigational] treatment

5.4 Laboratory parameters derivations

Table 5-4 presents the criteria to be used to define expanded limits and notable abnormalities of key laboratory tests.

Table 5-4 Clinically notable lab abnormalities

Laboratory variable	Standard Units	SI units
Liver function and related variables		
AST (SGOT)	≥3 × ULN	≥3 × ULN
ALT (SGPT)	≥3 × ULN	≥3 × ULN
Bilirubin	≥3 × ULN	≥3 × ULN
Renal function, metabolic, and electrolyte variables		
Urea	≥5 × ULN	≥5 × ULN
Creatinine	After Wk4: ≥3 mg/dL OR >30% above value from preceding visit	After Wk4: ≥ 265 µmol/L OR >30% above value from preceding visit
Uric acid	M ≥12 mg/dL	M ≥714 µmol/L
	F ≥9 mg/dL	F ≥535 µmol/L
Glucose	<45 mg/dL	<2.5 mmol/L
	>250 mg/dL	>13.9 mmol/L
Cholesterol	≥350 mg/dL	≥9.1 mmol/L
Triglycerides	≥750 mg/dL	≥8.5 mmol/L
CK (MB)	None	None

Laboratory variable	Standard Units	SI units
Potassium	≤3.0 mEq/L	≤3 mmol/L
	≥6.0 mEq/L	≥6 mmol/L
Calcium	≤6 mg/dL	≤1.5 mmol/L
	≥13 mg/dL	≥3.2 mmol/L
Magnesium	< 1.0 mg/dL	< 0.4 mmol/L
	> 3.6 mg/dL	> 1.5 mmol/L
Amylase	≥ 2 x ULN	≥ 2 x ULN
Lipase	≥ 2 x ULN	≥ 2 x ULN
Hematology variables		
Hemoglobin	<7 g/dL	<4.39 mmol/L
Platelets (thrombocytes)	<50 k/mm3	<50 × 109/L
	≥700 k/mm3	≥700 × 109/L
Leukocytes (WBCs)	≤2.0 k/mm3	≤ 2.0 × 109/L
	≥16 k/mm3	≥16 × 109/L
Hematology variables: differentiated		
Granulocytes (poly, neutrophils)	≤1,000/mm3	≤1 x 109/L
Eosinophils	≥12%	≥12%
Lymphocytes	≤1,000/mm3	≤1 x 109/L

Conversion factors from standard (US) units into SI units are given in Table 5-5.

Table 5-5 Conversion Factors from Standard (US) into SI units

Laboratory Variable	Standard Unit	Conversion Factor*	SI Unit
Platelets	%	1	%
Hematocrit	%	1	%
Hemoglobin	g/dL	0.6206	mmol/L
RBC	10^6/mm^3	1	10^{12}/L
WBC	10^3/mm^3	1	10^9/L
Sodium	mEq/L	1	mmol/L
Potassium	mEq/L	1	mmol/L
Chloride	mEq/L	1	mmol/L
Calcium	mg/dL	0.2495	mmol/L
Magnesium	mg/dL	0.4114	mmol/L
	mEq/L	0.5	mmol/L
Inorganic phosphate	mg/dL	0.3229	mmol/L
Urea**	Urea[mg/dL]	0.1665	mmol/L
Creatinine	mg/dL	88.4	µmol/L
Glucose	mg/dL	0.05551	mmol/L
HbA1c	%	1	%
Uric acid	mg/dL	0.05948	mmol/L
AST (SGOT)	U/L	1	U/L
ALT(SGPT)	U/L	1	U/L
Alkaline phosphatase	U/L	1	U/L

Laboratory Variable	Standard Unit	Conversion Factor*	SI Unit
GGT	U/L	1	U/L
Total bilirubin	mg/dL	17.1	umol/L
Total cholesterol	mg/dL	0.02586	mmol/L
High Density	mg/dL	0.02586	mmol/L
Low Density	mg/dL	0.02586	mmol/L
Triglycerides	mg/dL	0.01129	mmol/L
Creatinine phosphokinase	U/L	1	U/L
Lipase	U/L	1	U/L
Amylase	U/L	1	U/L
Albumin	g/dL	10	g/L
Protein	g/dL	10	g/L
Urinary protein:creatinine	mg/g	0.113	mg/mmol

5.5 Clinically notable vital signs

Table 5-6 presents the criteria that will be used to define notable abnormalities of vital signs data.

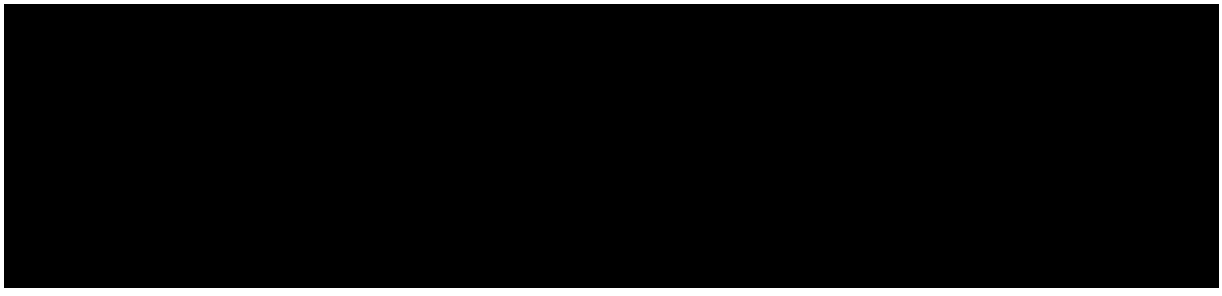
Table 5-6 clinically notable vital signs

Vital sign variable	Notable Criteria
Systolic BP (mm/Hg)	Either an increase of ≥30 that results in ≥180 or >200(mm/Hg) OR a decrease of ≥30 that results in ≤90 or <75 (mm/Hg)
Diastolic BP (mm/Hg)	Either an increase of ≥20 that results in ≥105 or >115 (mm/Hg) OR a decrease of ≥20 that results in ≤50 or <40 (mm/Hg)

5.6 Derivation of Efficacy Variables

Central pathology readings are electronically transferred from [redacted] (central pathologists) through [redacted] (central lab) and variables are documented in the Biopsy Data Transfer Specifications.

All efficacy endpoints regarding biopsy described will be summarized based on the **central** pathologists' evaluation of all biopsy readings. Derivations for treated rejections include information from the eCRF and **central** pathologists' evaluation of all biopsy readings.



[redacted]

5.6.2 Efficacy endpoint derivations based on local readings

The following derivations are used to identify efficacy endpoints based on local readings:

[redacted]

5.6.5 Death

Death will be recorded at either Study Completion, Follow-up, or as the outcome of an AE/Infection, if it occurs.

The date of Death will be the date of death recorded on the Disposition eCRF.

5.6.6 Graft loss

Graft loss is defined as any of the following:

- Graft loss (the allograft will be presumed to be lost on the day the patient starts dialysis and is not able to subsequently be removed from dialysis);
- Retransplant;

Graft losses will be identified from Graft Loss CRF page.

5.6.7 Lost to follow-up

A Lost to Follow-up patient is one who did not experience BPAR, graft loss, or death and whose last day of contact is prior to the day of the lower limit of the Month 12 visit window.

The date of lost to follow-up is the last contact date.

5.6.8 Composite efficacy failure

The composite efficacy failure event is defined as:

- experienced (= "Y") if:
  - a per-protocol central and adjudicated assessment is available; AND
  - a subject experiences any one of the following **any** of the following:
    - death; OR,
    - graft loss; OR,
    - BPAR, defined as

    - BANFF ≥ 1A from a for-cause central and adjudicated assessment (if performed); OR,
    - BANFF ≥ 1A from the per-protocol central and adjudicated assessment.
- not experienced (= "N") if:
  - a per-protocol central and adjudicated assessment is available; AND
  - a subject has experienced all of the following **all** of the following:
    - no death; AND,
    - no graft loss; AND
    - no BPAR, defined as,
      - no BANFF ≥ 1A from a for-cause central and adjudicated assessment (if performed); AND,
      - no BANFF ≥ 1A from the per-protocol central and adjudicated assessment.
- missing (= "NA") if:
  - a per-protocol central and adjudicated assessment is not available; OR
  - a subject is not flagged as either experienced (= "Y") or not experienced (= "N") as defined above.

up to Month 12 post-transplantation (Cohort 1) or post-conversion (Cohort 2) (i.e., Day 463).

For the survival analysis of the composite efficacy failure outcome, the following derivations will apply:

- the **survival event indicator** will be defined as 1 if the composite efficacy failure is experienced (= "Y") and 0 otherwise
- the **censoring indicator** will be defined as 1 if the survival event is 0 and 0 otherwise
- the **event date** is derived as follows:
  - if survival event indicator is 1, the date will be the earliest date among death, graft loss, or BPAR
  - If the survival event indicator is 0 and the subject discontinued study, the date will be the study discontinuation date
  - If the survival event indicator is 0 and the patient reached EOS (Month 60 visit), the date will be the date of the EOS (Month 60 visit)
  - If the survival event indicator is 0 and the patient did not reach EOS (Month 60 visit), the date will be the date of last follow up. For the interim analysis, if the survival event indicator is 0 and the patient did not reach EOS (Month 60 visit) but is still on study at the time of the data cut off, te date will be the data cut-off date (i.e. 12-Mar-2021).
- the **event time** (in days) will be the *event date - date of first dose of study treatment*

5.7 Statistical models

5.7.1 Posterior Probability

R code will be provided to calculate posterior probability estimates. Posterior probability estimates will be used to evaluate the primary objective "To demonstrate that CFZ533 600 mg and/or 300 mg bi-weekly (Q2W), subcutaneous (SC), are non-inferior to a TAC-based regimen with respect to the proportion of patients who experience the composite efficacy failure event ([BPAR], Graft Loss or Death) over 12 months post-transplantation" in Cohort 1 or "To demonstrate that CFZ533 450 mg Q2W SC is non-inferior to a TAC-based regimen with respect to the proportion of patients who experience the composite event efficacy failure event (BPAR, Graft Loss or Death) over 12 months post- conversion" in Cohort 2. An R code template is in Table 5-7. SAS code may be derived. A glossary of terms for Kaplan-Meier estimates is in Table 5-8.

Table 5-7 R code template for Posterior Probability analysis

```
lambdaCFZ <- rgamma(n=10000,shape=1+rejectionsCFZ,rate=12+exposureTimeCFZ)
posteriorSampleCFZ <- 1-exp(-lambdaCFZ*12) ; # posterior probability for CFZ arm
lambdaSoC <- rgamma(n=10000,shape=1+rejectionsSoC,rate=12+exposureTimeSoC)
posteriorSampleSoC <- 1-exp(-lambdaSoC*12) ; # posterior probability for SoC arm
post_prob <- mean(posteriorSampleCFZ - posteriorSampleSoC < NI) ; # NI
post_check <- post_prob > probNI ; # check go/no-go
```

Table 5-8 Glossary of terms for Posterior Probability analysis

Term	Definition
rejectionsCFZ	Number of rejections for CFZ arm
exposureTimeCFZ	Sum of all exposure times for CFZ arm
rejectionsSoC	Number of rejections for PBO arm
exposureTimeSoC	Sum of all exposure times for SoC arm
NI	Non-inferiority margin
probNI	Certainty level (default = 0.9)

5.7.2 Survival Analysis

Kaplain-Meier estimates and associated confidence intervals will be estimated at the following Visit windows and associated time points (days):

Table 5-9 Visit windows and associated time points (in days) to be used for survival analysis

Visits Window	Time point (days)
Day 1	1
Day 5	5
Day 15	15
Day 29	29
Month 2	63
Month 3	98
Month 4	140
Month 6	196
Month 8	252
Month 10	308
Month 12	463
Month 18*	631
Month 21*	799
Month 24*	1135
Month 27*	1387
Month 30*	1638

* Provided only for Kaplan-Meier tables and figures beyond Month 12

The PROC LIFETEST procedure is SAS 9.3 will be used to estimate survival using the Kaplan-Meier estimates. SAS code template to obtain Kaplan-Meier estimates are in Table 5-10. A glossary of terms for Kaplan-Meier estimates is in Table 5-11.

Table 5-7 SAS code template to obtain Kaplan-Meier estimates

```
* Kaplan-Meier estimates;
PROC LIFETEST data=data2 method=km conftype=linear
    plots=survival(cl  atrisk=(&timelist)  nocensor failure) timelist=&timelist reduceout;
    time time1*cnsr (1);
    by trt;
    survival out = survci;
RUN;

* Stratified Kaplan-Meier estimates;
PROC LIFETEST data=data2 method=km conftype=linear
    plots=survival(cl  atrisk=(&timelist)  nocensor failure) timelist=&timelist reduceout;
    time time1*cnsr (1);
    strata strat1 / group=trt;
    survival out = survci;
RUN;
```

Table 5-11 Glossary of terms for Table 5-11

Term	Definition
data2	Name of input dataset
trt	Treatment group
time1	Survival time, the time to the event or censoring
cnsr	Censoring indicator: 1=censored, 0=not censored
strat1	Factor on which to stratify
timelist	Survival times to display

The 95% confidence interval for the difference in composite failure rates will be estimated using Greenwood's formula constructed as follows:

$$(r_{CFZ533} - r_{SoC}) \pm Z_{0.025} * \sqrt{\{SE^2_{CFZ533} + SE^2_{SoC}\}}$$

where

- r_{CFZ533} is the Kaplan-Meier estimate of the failure rate for each of the CFZ533 arms
- r_{SoC} is the Kaplan-Meier estimate of the failure rate for the TAC arm

- SE_{CFZ533} is the estimated standard error using Greenwood's formula of the failure rate for each of the CFZ533 arms
- SE_{SoC} is the estimated standard error using Greenwood's of the failure rate for the TAC arm

5.8 Rule of exclusion criteria of analysis sets

Table 5-8 Subject Classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
SCR	NA	Not having ICF; Not having screening epoch disposition page
FAS	NA	Not in RAN; Not transplanted; Mistakenly randomized and no study drug taken
SAF	NA	Not in FAS; No study drug taken

6 References

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