NOVARTIS

Global Clinical Development - General Medicine

CFZ533 - Iscalimab

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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)

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List of abbreviations

ABMR	Antibody Mediated Rejection
AC	Adjudication Committee
ADAs	Anti-Drug Antibodies
AE	Adverse Event
ALT	Alanine Aminotransferase
ANOVA	Analysis of variance
[redacted]	[redacted]
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the plasma Concentration-time curve
BMI	Body mass index
BMJ	British Medical Journal
BKV	BK polyomavirus
b.i.d.	twice a day
BPAR	Biopsy Proven Acute Rejection
BP	Bodily Pain
[redacted]	[redacted]
CFR	US Code of Federal Regulations
CNI	Calcineurin Inhibitor
CRF	Case Report/Record Form (paper or electronic)
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration [mass/volume]
CMV	Cytomegalovirus
COVID-19	Coronavirus Disease 2019
CPO	Country Pharma Organization
CS	Corticosteroids
CsA-EM	Cyclosporine A Microemulsion
CTMS	Clinical Trial Management System
Ctrough	The observed plasma concentration that is just prior to the beginning of, or at the end of a dosing interval
CV	Coefficient of Variation
DBD	Brain Dead Donor
DCD	Donation after Cardiac Death
DGF	Delayed Graft Function
DMC	Data Monitoring Committee
DSA	Donor-Specific Antibodies
EBV	Epstein Barr Virus
ECG	Electrocardiogram
EC-MPS	Enteric-coated mycophenolate sodium
EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
FAS	Full Analysis Set
FSH	Follicle-stimulating Hormone

[redacted]

FU	Follow-up
g+ptc	Microcirculation inflammation
g/g	Gram/gram
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GFR	Glomerular Filtration Rate
GH	General Health
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLA	Human Leucocyte Antigens
[redacted]	[redacted]
i+t	Interstitial inflammation and tubulitis
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFTA	Interstitial Fibrosis and Tubular Atrophy
IgG	Immunoglobulin G
IgM	immunoglobulin M
IMP	Investigational Medicinal Product
INN	International Nonproprietary Name
IV	Intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV-Ig	Intravenous Immunoglobulin
KLH	Keyhole Limpet Hemocyanin
LFT	Liver function test
LIVI	Liquid in Vial
LPLV	Last Patient Last Visit
mAB	Monoclonal Antibody
MACE	Major Adverse Cardiovascular Events
MCS	Mental Component Summary
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MFI	Mean Fluorescence Intensity
MH	Mental Health
MMF	Mycophenolate Mofetil
MMRM	Mixed effect Model for Repeated Measurements
MNAR	Missing not at random

[redacted]

MPA	Mycophenolic Acid
[redacted]	[redacted]
NHP	Non-Human Primate
NI	Non-inferiority
NODM	New Onset Diabetes Mellitus
PCS	Physical Component Summary
PD	Pharmacodynamic
PF	Physical Functioning
PFS	Pre-filled syringe
PK	Pharmacokinetic
PML	Progressive Multifocal Leukoencephalopathy
p.o.	oral(ly)
PoC	Proof of Concept
PRA	Panel Reactive Antibodies
PTLD	Post-Transplant Lymphoproliferative Disease
RAN	Randomized set
rATG	Rabbit anti-thymocyte globulin
RE	Role-Emotional
RNA	Ribonucleic Acid
RP	Role-Physical
Q2W	Bi-weekly (every 2 weeks)
Q4W	Every 4 weeks
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
[redacted]	[redacted]
SC	Subcutaneous
SCR	Screened set
SET	Self-Evaluated Transition
SF	Short Form
SF	Social Functioning
SoC	Standard of Care
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reactions
SVR12	Sustained Viral Response after 12 weeks of HCV treatment
TAC	Tacrolimus
[redacted]	[redacted]
TB	Tuberculosis
tBPAR	treated BPAR
TCMR	T cell‑mediated rejection
TG	Transplant glomerulopathy
UPCR	Urine Protein Creatinine Ratio

[redacted]

VT	Vitality
WBC	White Blood cells
WHO	World Health Organization
WoC	Withdrawal of (study) Consent

[redacted]

Glossary of terms

Back table biopsy	Open biopsy at transplantation
Cohort	A specific group of patients/subjects fulfilling certain criteria
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the patient in a time unit (e.g., 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
eSource DDE	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications reduce the use of paper capture source data during clinical visits. eSource combines source documents and electronic case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g., prior to starting any of the procedures described in the protocol)
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Medication pack number	A unique identifier on the label of each investigational drug package
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients/subjects with established disease and in those with newly-diagnosed disease.
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent
Period	The subdivisions of the trial design (e.g., Screening, Treatment, Follow up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.

[redacted]

Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug(s), placebo/comparator active drug run-ins
Study Treatment Discontinuation	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

[redacted]

Amendment 04 (Mar-2021)

Amendment rationale

[redacted] The FDA further recommended completing the CIRRUS 1 trial as originally planned and to utilize the gained information in the design of future Phase 3 trials. Consistent with this feedback, the following changes have been implemented in this protocol amendment:

1. The primary objective for Cohort 1 has been changed to demonstrate that the CFZ533 600 mg and/or 300 mg bi-weekly (Q2W) subcutaneous (SC) doses are non-inferior to a tacrolimus (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.
2. [redacted]
3. The primary objective for Cohort 2 has been changed 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 efficacy failure event (BPAR, Graft Loss or Death) over 12 months post-conversion.
4. [redacted]
5. Include details about an unplanned interim analysis in Cohorts 1 and 2.

Consistent with this recommendation, this trial will be regarded as a Phase 2b dose-finding study with the sample size currently achieved in the study considered sufficient to support dose selection and inform Phase 3 study strategy. To that effect, further enrollment in this study has been stopped as of 09-Feb-2021. The primary objective in protocol v00 dated 30-Apr-2018 was to assess the composite efficacy failure event, based on a sample size of 200 patients in Cohort 1 (75 patient in each of the CFZ533 treatment arms and 50 patients in the control arm) and 125 patients in Cohort 2 (75 patients in the CFZ533 treatment arm and 50 patients in the control arm). At the time of this amendment release (Mar-2021), 304 patients have been randomized to Cohort 1 and 116 to Cohort 2.

The decision to stop enrollment permanently is not driven by any safety concern, as confirmed by the last DMC meeting, held on 14-Dec-2020.

Furthermore, the amendment introduces administration of CFZ533 via pre-filled syringes (PFS) to patients randomized to CFZ533, following completion of Month 12 visit assessments. This change will help reduce the patient burden, as PFS will allow self-administration (or administration by a caregiver) and consequently result in a reduction of the number of mandatory on-site visits (or home nursing where provided) after the Month 12 visit. The PFS is intended for use by healthcare professionals, caregivers assisting with the injection, or patients

[redacted]

self-administering at home. The caregivers and/or patients will be allowed to use the PFS only after proper training by the study team.

Changes to the protocol:

- List of abbreviations: List of abbreviations was updated to align with changes throughout the protocol.
- Protocol summary: Summary was updated to align with changes throughout the protocol.
- Section 1.1: [redacted]. Number of completed clinical trials was updated to match with current Investigator's Brochure Edition 10
- Section 1.2: Purpose of study was aligned with the study being a Phase 2b study with the traditional 1-year composite efficacy failure endpoint.
- Section 2.1:
  - The primary objective was changed to the composite endpoint (BPAR, graft loss, death). The composite endpoint was removed as a secondary efficacy endpoint.
  - [redacted]
- Section 3.1: Figure 3-1 and the total number of participants to be randomized in both Cohorts were updated. The option to start using PFS after completion of Month 12 visit assessments, upon availability, was introduced.
- Section 3.2: Use of PFS is allowed once patients complete all their Month 12 visit assessments required for the primary endpoint analysis to avoid any impact on the main study analysis. PFS will be supplied in a blinded kit until completion of Month 12 primary analysis to keep blinding to the dose.
- Section 3.5: Details on the interim analysis at 12-Mar-2021 data cut-off and stopping enrollment on 9-Feb-2021 have been added. Furthermore, it was clarified that additional analysis will be performed as described in the SAP.
- Section 3.6: Updated number of completed trials and added polyomavirus and cytomegalovirus as example of viral infections.
- Section 3.7: Rationale for Public Health Emergency mitigation procedures in case of Public Health emergency to ensure patient safety and trial integrity have been added.
- Section 4 and Section 5.2: Number of patients randomized has been updated.
- Section 5.1.1: Details for the PFS formulation and switch after Month 12 visit assessments to PFS have been added.
- Section 5.4: Updated to clarify that Sponsor will remain blinded until data base lock for the interim analysis.
- Section 5.5.2.1: Details regarding the time of implementation, training, site oversight, dispensation, transport and administration of the PFS have been added.

[redacted]

- Section 5.5.4.1 and Section 5.5.4.2: Addition of information that PFS can be administered by patients/their caregivers at home or by the investigator/delegated site staff at site.
- Tables 5-1, Table 5-2, Table 5-3 and Table 5-4 were added to clarify the intended use of different CFZ533 formulations (LIVI, PFS, as explained above).
- Section 5.6.2.2 and Section 9.8.1: As recruitment is now complete, the stopping rule analysis will no longer be applicable.
- Section 6:
  - Information on PFS and self-administrations has been included.
  - Removed assessments for transcriptomics
  - Dose record completed by patients was added once they are switched to PFS.
  - Removed central assessment for DSA at Month 12
  - ECG assessments are required only every 6 months instead of every 3 months following Month 12 in both Cohorts.
  - Footnote 10, Cohort 1 and footnote 11, Cohort 2 Assessment Schedule, clarified that vital signs to be taken at all on-site visits
  - In Cohort 2 Assessment Schedule, dosing at Months 19 and 41 can be done by in-home nurse (or self-administration with PFS).

[redacted]

- Section 6.5.4.4 and Section 9.5.2.3: Criteria and their timing for New Onset of Diabetes Mellitus was amended to align with other transplant protocols within the program.
- Section 6.5.4.4: PCR was added as a possible qualitative serology test for BK polyomavirus
- Section 7.5: Self-administration at home may also result in medication errors was added.
- Section 9.2: Patient demographics will not be listed following SAP leaning. Details about which background and demographic variables to summarize have been added.
- Section 9.4: The primary efficacy endpoint was changed to the composite efficacy outcome (BPAR, graft loss, death). Statistical analysis methodology (including estimand, missing data strategy, and supplemental analyses) was updated for the change in endpoint.
- Section 9.4.5: Subgroup evaluations for the primary estimand were added.
- Section 9.5: Section title was changed to include only secondary objectives.
- Section 9.5.1: Content was removed and replaced with not applicable. No secondary efficacy objectives are included in the protocol objectives.
- Section 9.5.2.1: Estimand and missing data strategy were updated for the evaluation of eGFR. Subgroup evaluations for the secondary eGFR estimand were added.

[redacted]

- Section 9.5.2.2: Adverse events were moved to a separate subsection for secondary safety analyses. In addition, AEs rated to have relationship to study drug leading to discontinuation by SOC and preferred termwere added.
- Section 9.5.2.3: Listings were removed to adhere to Protocol and SAP leaning. Study day time point was updated for the definition of new onset diabetes mellitus.
- Section 9.5.3: Clarification was provided about data found in outputs provided for plasma concentrations.
- Section 9.5.7: Clarification was provided about location of PK/PD analyses (e.g., separate modeling report) and expected results found in the report.
- Section 9.7: An unplanned interim analysis has been added and is scheduled to be conducted using data cut-off of 12-Mar-2021. Power considerations for the primary efficacy objective (e.g., composite efficacy endpoint) given the expected sample sizes at interim analysis have been added for Cohort 1 and Cohort 2.
- Section 9.8.1: Figures for the stopping rule given were updated given the sample size calculation using the primary composite endpoint.
- Section 9.8.3: Rationale for power calculations were updated to reflect the change in primary endpoint.
- Section 9.8.4: The power calculations for the secondary objectives were removed. Since the hierarchical testing strategy has been removed, the power calculation is no longer relevant.
- Section 10.2: Informed consent or re-consent process was updated to allow remote consenting in case of a Public Health emergency.
- Section 10.6: Patient engagement initiatives were added.
- Appendix 3: The stopping rule tables were updated to reflect the sample sizes calculated for the primary composite endpoint in each Cohort.
- Appendix 4: Blinding table was updated to include blinding status after interim analysis.
- Appendix 6: Additional guidance was added for the PFS.

- Multiple sections were updated to replace COVID-19 with Public Health emergency to be more inclusive.
- Other minor wording changes were done throughout the protocol.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 03 (Dec-2020)

Amendment rationale

The key purpose of the amendment is to incorporate potential adaptations of study visits and IMP shipments during the COVID-19 pandemic, add a new exclusion criteria with regards to body weight to ensure appropriate dosing of CFZ533, and to clarify that SAEs due to pre-emptive treatment due to asymptomatic viral loads will be excluded from the stopping rule analysis.

At the time of this amendment release (15Dec2020), approximately 365 patients have been randomized.

In addition, the amendment introduces the following key changes:

- New Exclusion criterion #31 is added to ensure appropriate dosing of CFZ533. Body weight limits were introduced to exclude patients who are underweight (<30 kg) or >180 kg.
- To remove Exclusion criterion #25 (patients at risk of QT-related cardiac arrythmia). Based on mechanism of action (i.e. targeted monoclonal antibody) and available data of CFZ533 across several studies, CFZ533 does not have an influence on cardiac repolarization and hence this exclusion criterion is not deemed necessary.
- To optimize evaluation of efficacy, follow-up duration will be increased for patients prematurely discontinuing treatment (up to Month 60) with phone calls every 6 months to obtain data related to patient survival, graft loss and changes in immunosuppressive treatment. [redacted] This extended follow up will also improve safety monitoring and SAEs related to study treatment will be collected and reported during these calls.
- To provide revised guidance to the investigator to commence other immunosuppressive treatment only 4 weeks after the last CFZ533 dose (instead of previously recommended 2 weeks) to lower the risk of over-immunosuppression. Based on the known pharmacokinetics properties of CFZ533 in the target patient population, doses included in the study are expected to provide sufficiently robust immunosuppression in the broad population at least 4 weeks post dose.
- To increase the safety follow-up duration from 60 days to 12 weeks for study completers after end of study visits at Month 60 (corresponding to 14 weeks after last CFZ533 dose). The same duration of safety follow-up (14 weeks after last CFZ533 dose) was also included for early treatment discontinuations. The change allows alignment with other transplant trial protocols within the program. Importantly, considering the possible extent of inter-individual variability of duration of target engagement in tissues and associated pharmacology, the extended duration of the safety follow-up period allows monitoring of SAEs in the treated population associated with loss of engagement of CD40 pathway.
- The body-weight calculated IV loading doses of CFZ533 are administered on Days 1 and 5 in Cohort 1 and Day 1 in Cohort 2. To accommodate for possible body-weight fluctuations, the protocol allows a deviation of the administered amount of CFZ533 in the

[redacted]

range of +/- 10% from the calculated body weight-based IV dose of CFZ533 on respective days.

- Incorporation of new wording related to potential adaptations of the study during the COVID-19 pandemic (IMP shipments, phone calls, local labs, delay of assessments). A study-specific medical and safety risk assessment was performed, and it was concluded that based on the current data, the benefit/risk of CFZ533 due to the COVID-19 pandemic remains unchanged. Infections are already described as a potential risk in Section 3.6 and no further updates are considered necessary for this amendment.
- Specific to Cohort 2: Patients on an existing immunosuppressive regimen of Enteric-coated mycophenolate sodium (EC-MPS) are permitted for inclusion. EC-MPS and MMF have shown to be similar in both efficacy and safety (Salvadori et al 2004, Budde et al 2004, Budde et al 2006, Salvadori et al 2006, Johnston et al 2006).
- It is clarified that SAEs reported due to any hospitalization related to pre-emptive treatment for asymptomatic viral loads (e.g., CMV, BKV, EBV) will be excluded from the stopping rule analysis in Cohort 1.
- Additional guidance has been included for biopsy collections in patients who prematurely discontinue treatment prior to Month 12. The Month 12 Biopsy is needed to calculate the primary efficacy endpoint.
- The protocol amendment includes several clarifications based on investigator comments/questions. Details are listed below in the changes to the protocol.

Changes to the protocol

- List of abbreviations: List of abbreviations is updated to align with changes throughout the protocol.
- Protocol summary: Summary is updated to align with changes throughout the protocol.
- Section 3.1:
  - Include information that placebo will be removed from the study after completion of the primary analysis at Month 12. Same changes were applied throughout the document (Section 5.1.1, Section 5.2, Section 5.5.2.1, Section 5.5.4.1 and Appendix 6).
  - Possibility to allow use of either EC-MPS or MMF is included for Cohort 2. Same changes were applied throughout the document (Section 1.2, Section 3.3.2, Section 3.4, Section 4.1, Section 5.1.1, Section 5.1.2, Section 5.2, Section 5.5.4.2, Section 5.5.5, Section 5.5.7, Section 5.5.9, Section 5.6.2.1, Table 6-2, Section 6.3, Section 6.5.4.4, Section 6.5.6, Section 9.3.2, Section 9.4.2, Section 9.5.1.2 and Section 9.5.3.1).
  - Figure 3-1 was udated to align with other sections.
- Section 3.3.2.2: EC-MPS administration will be based on local standard of care.
- Section 3.4: Rational for allowance of EC-MPS in Cohort 2 has been added.
- Section 3.6: Number of completed and ongoing trials was updated (same update was applied in Section 1.1). Statement is included regarding the benefit/risk due to COVID-19 as described above.

[redacted]

- Section 4: The study is conducted in approximately 125 centers. The number of centers have increased with the increase in sample size that was implemented with Protocol Amendment 02.
- Section 4.2:
  - Exclusion criterion #8 and #19 were updated to include reference to SVR12.
  - Exclusion criterion #25 was removed (patients at risk of cardiac arrythmia, see rationale above).
  - Exclusion criterion #31 was added (body weight, see rationale above).
- Section 5.1.1: Once daily tacrolimus formulations have been added to control study treatment, as they are allowed since Protocol Amendment 02 in Cohort 2 and were previously missed.
- Section 5.5.2.1:
  - Instructions were added if during the COVID-19 pandemic that limits or prevents on-site study visits, delivery of IMP directly to a patient's home are required.
  - The in-home health provider may also be contracted on a global level.
- Section 5.5.4.1 and Section 5.5.4.2:
  - Clarified that screening weight is also acceptable for dose calculation if not longer than 2 weeks prior to baseline visit. Furthermore, a 10% deviation from calculated dose is allowed (as described above, same change was applied in Section 6.5.3).
  - The in-home health provider may also be contracted on a global level.
- Section 5.5.5:
  - Wording regarding missed doses of CFZ533 has been revised to improve clarity. In addition, in case more than the allowed doses are missed, investigator should contact the sponsor immediately to discuss if the patient can remain on treatment or should be permanently discontinued from randomized study treatment and managed as per local practice.
  - Flexibility was increased to allow a delayed dosing of a maximum of 7 days.
  - For patients randomized to TAC the management of over-immunosuppression should first start with a reduction of MMF/EC-MPS dose by 50% or more and secondly (if required), TAC reduction as per local practice
  - Leucopenia has been added as potential symptome of MMF intolerance.
  - Information related to EC-MPS has been included.
- Section 5.5.5.1:
  - Recently released guidance was included for the treatment of borderline rejections.
  - Additional guidance on tapering of methylprednisolone (for treatment of BPAR) has been included.
  - Patients weighing <50 kg who receive additional CFZ533 compensatory doses on the same day should receive these at least 1 h apart.
  - A PK and PD sample should be collected at the visit after IV-Ig infusion.
- Section 5.5.7:

[redacted]

  - Recommendation added to follow newest guideline of the American Society of Transplantation Infectious Diseases Community of Practice to treat CMV in solid organ transplant recipients.
  - Recommendation for treatment of BKV infections added based on a recent publication.
  - Information regarding COVID-19 treatment based on local policies added.
- Section 5.6.1 and Section 5.6.2.1: Patients who discontinue CFZ533 regimen should not initiate a new immunosuppressive treatment as per SoC prior to 4 weeks after the last dose of CFZ533 to avoid the risk of over-immunosuppression (see rationale above).
- Section 5.6.2.1:
  - Section title has been updated to clarify the guidance is for study treatment and study discontinuations.
  - Early discontinued patients will be asked if they would be willing to consent for follow-up phone calls every 6 months until Month 60 to determine their survival status, potential graft loss, changes in immunosuppressive treatment and SAE related to study treatment.
  - To align the number of follow-up visits for all discontinued patients, patients discontinuing between Month 6 and 12 will also have a second follow-up visit at Month 18.
  - Biopsy collections post-discontinuation have been clarified to be consistent with Table 6-3.
- Section 5.6.2.2.1: Clarification was added regarding stopping rule for hospitalizations due to viral loads (see above). In addition, ABMR will also be included in the BPAR stopping rule (same change was applied in Section 9.8.1). Titel was updated to align with changes implemented in protocol amendment 02.
- Section 6:
  - Instructions were added how patient care should continue if during the COVID-19 pandemic, on-site study visits are limited or prevented.
  - Addition of information for unscheduled visits.
  - Clarified that a study Month is defined as 28 calendar days.
  - Clarification was added which visits are applicable to patients randomized to the tacrolimus arm and it was clarified Month 5 TAC dose administration record is not required.
  - Additional weight assessments have been included to gain additional safety data. Weight will be measured every 2 months until Month 12 and every 3 months thereafter.
  - Included additional transcriptomics samples to be collected.
  - PROs will be collected at all sites (same change was incorporated in Section 6.6.4).
  - Removed DSA assessment from Baseline visit, as DSA is not expected to change between Baseline and Screening (also updated in Section 6.5.4.4 and Section 9.5.3.2).
  - MMF trough levels are measured as MPA levels (same change was applied in Section 6.5.4).

[redacted]

  - Clarification added that local labs may only be allowed to assess eligibility in Cohort 1 for deceased donors. A sample should also be sent for central lab.
  - Footnotes for viral serology have been expanded to include SVR12. In addition, it was clarified that CMV, EBV and BKV serology at screening is only required based on local standard of care. Same change was applied in Section 6.5.4.4.
  - In Cohort 2 Assessment Schedule, TAC trough levels have been removed at visits not applicable for patients randomized to TAC.
  - In Cohort 2 Assessment Schedule, dosing at Months 19 and 41 can be done by in home nurse.
  - Assessment schedule for discontinuations: Follow-up phone calls for graft survival every 6 months have been included and a new row to collect "Death". For the follow-up phone calls (after FU-2) only SAEs considered to be related and immunosuppressive regimen changes should be included and no other SAEs/AEs/concomitant medication. Collection time point for biopsies after early discontinuation has been revised. If FU-1 or FU-2 are at Month 12, DSA should be assessed. A visit window for follow-up visits has been added.
- Section 6.1: Clarification that a new ICF will need to be signed if the investigator chooses to re-screen a patient.
- Section 6.2: Clarification that subject's race and ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors, as well as to assess the diversity of the study population as required by Health Authorities.
- Section 6.4: Instructions were added if, during the COVID-19 pandemic or other exceptional cases that limits or prevents on-site study visits or kidney biopsies, Month 12 assessments could be collected up to Month 15.
- Section 6.5: Instructions were added if during the COVID-19 pandemic that limits or prevents on-site study visits, regular phone calls will occur for safety monitoring.
- Section 6.5.4: Clarification added that local labs may only be allowed to assess eligibility in Cohort 1 for deceased donors. A sample should also be sent for central lab. Local labs may also be assessed if central labs are not available due to the COVID-19 pandemic. Every effort must be made to obtain central lab samples at the time of biopsy for the Month 12 visits.
- Section 6.5.4.4:
  [redacted]
  - In addition to the local sample, a sample for central DSA analysis will be collected at Month 12 (also updated in the assessment schedules).
- Section 6.6.3: Other biomarker samples for transcriptomics analysis will be collected for newly enrolled patients in addition to the use of residual samples.
- Section 6.6.4: If electronic devices are not available, paper PROs might be used as back-up solution.
- Section 7.2.2: Follow-up duration after the last CFZ533 dose was increased to 14 weeks (see rationale above). Due to this change the follow-up phone call was moved from 60

[redacted]

days to 12 weeks after end of study visit at Month 60. This change has been incorporated throughout the document (Section 3.1, Section 5.6.1 and Section 6).

- Section 7.6: Additional guidance was included on how to manage a female patient that becomes pregnant. In addition, more guidance on the timing of the follow-up was included to align with the consent for pregnancy follow-up.
- Section 8.4: The responsibility for monitoring the stopping rules lie within Novartis; therefore, the sentence that "DMC provides guidelines for stopping rules" was removed. Enrollment period is prolonged due to COVID; hence, the number of DMC meetings was removed to allow to follow the defined frequency.
- Section 9.3.2: Listing for dose of antibodies for the treatment of acute rejections was removed.
- [redacted]
- Section 9.4.3: The missing data plan was updated to a joint multivariate normal imputation approach for the [redacted], eGFR, and proteinuria. Same change was done in Section 9.5.1.2 and Section 9.5.3.1.
- Section 9.4.4: New section was created for supportive analyses.
- Section 9.5.1.1: Significance level was corrected.
- Section 9.5.3.1: eGFR formula was updated to align with the MDRD-4 as implemented with Protocol Amendment 02. Additional information on supportive analyses and imputation included.
- Section 10.2: Additional information on the informed consent procedure was included to improve clarity.
- Section 12: Reference list was updated.
- Appendix 4: Blinding table was corrected to reflect that the Global Trial Director, Study Monitor and unblinded physician are unblinded at the treatment level but not the individual patient level during treatment administration, safety emergency event, and DMC report.
- Appendix 5a: Sample numbers for DSA samples have been added. Information regarding dose reference IDs for unscheduled CFZ533 administrations has been included.
- Appendix 5b: Unscheduled sample numbers for PD and immunogenicity samples have been added.
- Other minor wording changes were done throughout the protocol.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

[redacted]

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 02 (Dec-2019)

This amendment version 02 implements major changes related to the primary and secondary objectives, sample size, stopping rules and plans for interim analysis. At the time of this amendment release, the study has started and approximately 250 patients are randomized.

[redacted]

- The non-inferiority objectives based on composite efficacy failure have been moved to secondary objectives. Assessment of non-inferiority of the established kidney transplant trial endpoint is not well correlated with long-term outcomes in the modern transplant era, as few graft losses or deaths occur in the first year post-treatment. However, they are retained as secondary endpoints to allow comparison to literature.
- To maintain the family-wise Type I overall error rate for testing at an alpha-level of 5%, a hierarchical testing scheme was introduced including [redacted] eGFR, and composite efficacy failure.
- Based on the above stated changes, the overall sample size has been increased to 681 patients as follows:

  Cohort 1 – from 200 de novo renal transplant patients to 496 patients

  Cohort 2 – from 125 maintenance renal transplant patients to 185 patients

  [redacted]
- The stopping rule based on BPAR was proportion of BPAR with Banff ≥ 1B greater than 20% with probability > 90%. This has been corrected to proportion of BPAR with Banff ≥ 1B greater than 30% with probability > 90%. The objective for the composite endpoint is to demonstrate non-inferiority against SoC with a non-inferiority margin of 20%. However,

[redacted]

the rate of BPAR in clinical trials of TAC+MMF are 14-28% (Silva et al 2007, Kramer et al 2010). Hence evaluating a stopping rule for BPAR based on an absolute rate of 20% is not consistent with these results or with evaluating non-inferiority with a 20% NI margin. In addition, the BPAR rate seen in the CCFZ533X2201 Study was 24%, hence an absolute rate of 20% for the stopping rule was too conservative.

- The plans for interim analyses were removed. Planning of subsequent studies in a de novo population will be based on the primary Month 12 analysis, so formal interim analysis for internal purposes is not needed anymore.
- [redacted]
- It is clarified that the primary Month 12 analysis for each study cohort may be conducted separately, depending on the enrollment rates.
- PK data will be unblinded following the primary Month 12 analysis, to allow CSR completion for submission purpose.
- To decrease the burden of a baseline biopsy on maintenance patients in Cohort 2, the retrospective biopsy data collection has been extended from 1 Month to up to 12 weeks prior to enrollment. This is also consistent with other inclusion/exclusion criteria that are also assessed within 12 weeks prior to enrollment. Most of the factors that may affect the graft and cause histological changes or damage are controlled during this 12-week timeframe, and we do not expect any changes or differences in histology parameters.
- Specific to Cohort 2: once daily tacrolimus formulations (Advagraf, Envarsus, etc.) are permitted. In case a patient is switched from Myfortic® to MMF for medical reasons (not protocol driven), this switch must have occurred at least 2 weeks prior to baseline visit.

The minor modifications are:

- Specific to Cohort 1: The 50% cap applied to the percentage of randomized patients on each induction therapy is changed to a range between 40-60% for each induction therapy. This range will still allow meaningful subgroup analyses across the two stratification factors while increasing the flexibility for recruitment.
- Specific to Cohort 2: The 50% cap applied to the percentage IRT of randomized patients in each time since transplant stratum (6-≤12, > 12-24 months) is changed to a range between 40-60% for each time stratum with the same rationale as stated above.
- Statement added that, in case treatment with plasmapheresis is required, patient should be discontinued from CFZ533 and switched to SoC. This is because the plasma concentrations are difficult to estimate following plasmapheresis.
- Clarification added to state end of study visit assessments are completed at time of premature treatment discontinuation
- Figure 3-1 updated to reflect increase in number of patients and remove interim analyses.
- Clarification added to Table 5.5 that IV-Ig administration, post-transplant, may include Day 1.

[redacted]

Changes to assessment schedule:

- Correction made to administration of CFZ533 to allow optional in home dosing at Month 29, 38 and 47 for cohort 1 patients.
- Clarification that kidney allograft biopsy to be collected as per local practice throughout the duration of the trial.
- Removed assessments of temperature and blood pressure from months 20 and 38 for Cohort 2, these were included accidently at time of amendment version 01.
- MMF trough sample and TAC trough sample added to Month 39 for Cohort 1 and removed from Month 38 and added to Month 39 for Cohort 2. Correction to change made at time of amendment v01.
- Removal of urine pregnancy tests at months when serum pregnancy tests are taken, Cohort 1.
- Addition of patient reported outcomes for both Cohort 1 and Cohort 2.

Clarifications for consistency:

- eGFR calculation is clarified throughout the protocol as MDRD-4.
- Inclusion 8, sentence pertaining to variances in lab results is removed as not applicable to this criterion.
- Exclusion 8, HBc was included accidently at the time of amendment version 01 and removed again.
- Exclusion 12, clarified that for eGFR decline, this should be assessed using results from the same laboratory up to time point of enrollment.
- Exclusion criteria 19, clarified that results obtained within 28 days prior to baseline are acceptable.
- Exclusion 30 clarified that patient should not receive a live vaccine within four weeks before enrollment rather than date of transplant.
- Clarified that the stopping rules apply until enrollment is completed and that BPAR rates are based on adjudicated biopsies and not locally read biopsies.
- Change ‘central pathologist’ to ‘adjudication committee’ as this is correct terminology for assessment of biopsies.
- Addition of assessment table clarifying visits and assessments needed if patient prematurely discontinues treatment.
- Duration of SAE reporting clarified for patients discontinuing treatment early.

Typographical and grammatical corrections

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font~~ for deletions and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) for approval prior to implementation.

The changes herein affect the Informed Consent Form (ICF).

[redacted]

Amendment 01 (May-2019)

This amendment version 01 implements two major changes related to the study duration and collection of biopsy samples. At the time of this amendment release, the study has started and approximately 73 patients are randomized.

The major modifications to the protocol are:

- Length of study is extended by 48 months to 60 months to allow patients to continue further treatment following the 12 month primary treatment period. Furthermore, this will enable the Sponsor to collect long-term efficacy, safety, PK/PD [redacted] and immunogenicity data, in Cohort 1 (de novo patients) and Cohort 2 (maintenance patients).
  - Additional visits were added,
  - Corticosteroids (CS) will be tapered off, as per local standard practice after 12 months of treatment,
  - Yearly data analysis once all patients reach months 24, 36 and 48 to monitor efficacy and safety and assess long term overall benefit risk. Final analysis will be once all patients reach Month 60 or discontinue from the study.
  - Study treatment will be unblinded following primary analysis when all patients complete Month 12.
  - Allow patients who consented under the original protocol, the option of remaining in the study to Month 12 in case they do not want to re-consent to Month 60
- Kidney biopsies at Baseline and at Month 12 are now mandatory in both Cohort 1 and 2 and biopsy specimens should be sent to the central blinded reader for assessment. In addition, any biopsies taken according to routine local practice, in case of suspected rejection and in case of premature discontinuation prior Month 12 should also be sent to the central blinded reader for assessment. For Cohort 1 de novo patients, a back table biopsy should be performed at baseline. Any back table biopsies taken according to routine practice prior to the introduction of this amendment will be sent to the central pathologist for blinded review. For Cohort 2 maintenance patients, a biopsy at Baseline is not required in case a biopsy was performed within 1 month prior to enrollment. In this case, the biopsy reading data will be retrospectively collected and biopsy specimens if available, should be sent to the central blinded reader for assessment.

  The rationale for making biopsies mandatory is that renal allograft biopsies are performed mainly in the setting of acute graft dysfunction and, consequently, the possibility of graft failure is suspected only when a continued and irreversible fall in renal function has become apparent. By the time the clinical diagnosis is confirmed histologically by biopsy, irreversible graft damage may have occurred. Surveillance or protocol biopsies, which are performed during the first post-transplantation year irrespective of graft function, may be clinically useful by allowing the early identification of subclinical rejection or chronic allograft nephropathy (CAN) at a point when they are amenable to treatment.

  Furthermore, the histology exploratory objective relating to the evaluation of differences in kidney histopathology for patients on CFZ533 regimens compared to a TAC-based regimen has now been upgraded to a secondary objective. It will be broadened to include,

[redacted]

but not limited to, analysis of histologic assessments like [redacted] The detailed histological subscore parameters required to calculate these scores will only be available through the central pathology assessment of the protocol biopsies.

The minor modifications to the protocol are:

- Introduction of International Nonproprietary Name (INN) name, iscalimab.
- Increase in number of participating sites to 65.
- Continuous quantitative viral serology test for Epstein Barr virus (EBV) to be performed over the duration of the study by the central laboratory. The EBV viral plasma load in patients treated with CFZ533 and mycophenolate mofetil (MMF)/CS will be compared with viral loads from the concurrent standard of care (SoC) arms with TAC and MMF/CS in order to reveal potential differences and how they relate to long-term outcome with respect to post-transplant lymphoproliferative disease (PTLD).
- Addition of extra dose(s) of CFZ533 administered sub-cutaneous if patient is treated for Antibody Mediated Rejection (ABMR) or BK viremia with intravenous infusion of immunoglobulin (IV-Ig), to compensate for accelerated elimination of CFZ533 after IV-Ig, in order to maintain CFZ533 plasma concentration within target ranges.
- Cohort 2, estimated glomerular filtration rate (eGFR), creatinine and proteinuria measurements will be collected retrospectively from 0 – 1 month prior to enrollment.
- Exclusion criterion 8, now made applicable only to Cohort 1 to exclude patients if they are a recipient of a kidney from a donor who tests positive for anti-HIV, HBsAg or HCV.
- An exclusion criterion 30 is added to ensure that patients who have received a live vaccine within four weeks before transplantation cannot participate in the study (to align with recent updates in the CFZ533 Investigator Brochure (IB)).
- Appendix 4, remove blinded status from designated Sponsor personnel as internal systems such as the Clinical Trial Management System (CTMS) reveal treatment arm, previously blinded information.

- Mandatory condom use is removed as there is no longer a requirement to use condoms when treated with MMF per EMA (CHMP 2017) and FDA guidelines 2018.
  - 24 hour window added to Day 5 for Cohort 1 and Day 15 for both cohorts. CFZ533 is a 146 kDa IgG1-type mAb and distributes slowly into the tissues. No major difference in peak plasma concentration is expected if 15 mg/kg intravenous (IV) dose is administered between Day 4 and Day 6.
  - In the event of persistent MMF intolerance patients are permitted to switch to mycophenolic acid (MPA) (e.g., Myfortic®) or permanently discontinue MMF and remain in the study on their randomized study treatment.
  - Changes in the assessment schedule and blood log:
    - To add PK, [redacted] immunogenicity blood samples during the 4 year extension period (blood sampling every 3 months)

[redacted]

- For patients experiencing IV-Ig administrations, additional PK blood samples are to be collected immediately prior IV-Ig.
- MMF trough samples added as separate row for clarity as previously hidden within the safety laboratory tests

Clarifications and corrections to the protocol as per Health Authority/Independent Review Boards (IRBs) and Investigators requests are:

- Cohort 1, exclusion criterion 7, additional wording to clarify that donor-specific antibodies (DSA) assessment within 12 weeks prior to enrollment is acceptable if no blood transfusion or abortion during this period.
- Cohort 2, exclusion 10, clarification that multi-organ transplantation includes en bloc and dual kidney transplantation.
- Cohort 2, exclusion criterion 14, clarification added that no severe humoral and/or cellular rejection is within 12 weeks prior to enrollment.
- Cohort 2, exclusion criterion 12, increase in allowance of eGFR decline to allow for a better identification of patients with declining and/or fluctuating renal function.
- Cohort 2 exclusion criterion 15, clarification specifying volume of urine to protein creatinine ratio (UPCR) in relation to proteinuria.
- Exclusion criterion 17 is reworded to clearly specify exclusion of patients with a known hypersensitivity to any constituent of the study regimen.
- Exclusion criteria 19 and 20 are reworded to clearly specify whether recipient or donor is referred to.
- Exclusion 20, clarification added to allow EBV results up to 28 days prior to baseline visits.
- Exclusion 21, additional wording stating appropriate documentation be available for after anti-tuberculosis (TB) treatment, so patients with history of latent TB are eligible.
- Exclusion criteria 27, corrected from Hbg < 8 mg/dL to Hbg < 8 g/dL.
- Exclusion criterion 29, pertaining to contraception to be used by female participants in case the vasectomized male partner is not the sole partner. For those female patients, a highly effective method of contraception have to be applied with increased duration to 14 weeks after study medications are stopped.
- For Cohort 2 clarification provided that patients may switch from Myfortic® to MMF at least 2 weeks prior to baseline visit.
- For Cohort 1, clarification that MMF may be initiated prior to transplant according to local practice.
- Rabbit anti-thymocyte globulin (rATG) induction therapy, dosing guidance changed to comply with US and EU SmPC.
- Section 3.1. rATG should be administered on day of transplantation, to be consistent with section 5.5.4.1.
- Section 5.5.2.1 Interactive Response Technology (IRT) can be contacted up to two days in advance of study visit if required, to allow pharmacist to prepare medication in advance e.g., for weekend visits.

[redacted]

- Section 5.5.4.1 updated to clarify that first dose (IV) of CFZ533 will be administered within 1 hour of unclamping to avoid loss of the drug through blood loss.
- Section 5.5.8, guidance on administration of live vaccines added.
- Section 5.5.9, clarification for non-protocol immunosuppressants allowed for those patients in follow up who discontinued from the randomized study treatment and switched to standard of care treatment as per local practice.
- Section 6.1, additional information provided for completion of CRF and that patients may be re-screened only once.
- Section 6.5.3.4, evaluation of viral serology clarified.

Changes to assessment schedule for consistency with body text.

- Section 6.5.2 updated to clarify that dry weight of patient (if dialyzed or in case of fluid retention after surgery) will be used for calculation of CFZ533 dose on Day 1 and Day 5.
- Section 6.5.4 Electrocardiogram (ECG) to be recorded after 5 minutes rest to be consistent with section 6 assessment schedule.
- Clarification in relation to serum and urine pregnancy testing and reporting.
- Updated Banff 2017 will be used for classification of kidney allograft pathology.
- Appendix 4, addition of unblinded physician to ensure study physician remains blinded in case of questions from investigator.
- Appendix 5a/5b, blood log updated for dose, PK, PD and Immunogenicity samples.
- Section 5.5.4.1 and Appendix 6, addition of guidance for injecting the study drug
- Power calculations were updated to use a binomial model instead of a Poisson model to correctly account for patients discontinuing therapy who still have biopsy information.

Typographical and grammatical corrections.

[redacted]

Protocol summary

Protocol number	CCFZ533A2201
Full Title	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.
Brief title	Study of efficacy, safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) of an anti-CD40 monoclonal antibody, CFZ533, in *de novo* and maintenance kidney transplant recipients.
Sponsor and Clinical Phase	Novartis Phase 2b
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to investigate the safety, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) of: • two CFZ533 dose regimens in *de novo* kidney transplant recipients (Cohort 1), in combination with mycophenolate mofetil (MMF) and corticosteroids, compared to a standard of care control arm of tacrolimus (TAC), MMF and corticosteroids (CS). • one CFZ533 dose regimen started 6-24 months post-transplantation in maintenance kidney transplant recipients (Cohort 2), in combination with either MMF or enteric-coated mycophenolate sodium (EC-MPS) with or without corticosteroids, compared to a standard of care control arm of TAC and MMF or EC-MPS with or without corticosteroids. This study will allow the assessment of the ability of CFZ533 to replace Calcineurin inhibitors (CNIs) as the standard of care by potentially improving long term outcome (reduced graft loss) while maintaining comparable short term anti-rejection efficacy and providing better renal function with an adequate safety and tolerability profile, in *de novo* and maintenance renal transplant patients.
Primary Objective(s)	**Cohort 1:** • To demonstrate that CFZ533 600 mg and/or 300 mg bi-weekly (Q2W) subcutaneous (SC) is non-inferior to a TAC-based regimen with respect to the proportion of patients who experience composite efficacy failure event (biopsy proven acute rejection (BPAR), graft loss, or death) over 12 months post-transplantation **Cohort 2:** • 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 composite efficacy failure event (biopsy proven acute rejection (BPAR), graft loss, or death) over 12 months post-conversion
Secondary Objectives	**Cohort 1:** • 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 • To assess the safety and tolerability of CFZ533 regimens compared to a TAC based regimen

[redacted]

	• To assess the pharmacokinetics of CFZ533 and explore the dose-exposure relationship during the 60 months treatment period • To assess the immunogenicity of CFZ533 during the 60 months treatment period. **Cohort 2:** • To demonstrate that CFZ533 450 mg Q2W SC is superior to a TAC-based regimen with respect to the 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 • To assess the pharmacokinetics of CFZ533 during the 60 months treatment period and explore the dose-exposure relationship (together with PK data from Cohort 1) • To evaluate the immunogenicity of CFZ533 during the 60 months treatment period
Study design	Study CCFZ533A2201 is a randomized, 60-month (5 year) study comprising of 12-months treatment for the primary analysis plus an additional 48-month treatment period. The study is active-controlled, partially-blinded for the initial 12 months of treatment, multicenter, dose range finding study to evaluate the efficacy, safety, tolerability, PK and PD of CFZ533 in 2 different cohorts: adult *de novo* kidney transplant recipients and maintenance kidney transplant population (6-24 months post-transplant).
Population	The study population will consist of 2 Cohorts: **Cohort 1:** adult male and female *de novo* renal transplant recipients of a primary graft from a deceased or living donor. It is planned to randomize approximately 200 patients. **Cohort 2:** adult male and female maintenance renal transplant recipients of a primary graft received 6 to 24 months prior enrollment. It is planned to randomize approximately 125 patients.
Key Inclusion criteria	**Both cohorts**: • Written informed consent obtained before any assessment. • Male or female patient ≥ 18 years old. • Up to date vaccination as per local immunization schedules. **Inclusion criteria specific to Cohort 1:** • Recipients of a primary kidney transplant from a brain-dead donor (DBD), living unrelated or non-HLA identical living related donors. • Recipients of a kidney with a cold ischemia time (CIT) < 24 hours. **Inclusion criteria specific to Cohort 2:** • Recipients of a primary graft received 6 to 24 months prior enrollment, on a regimen containing TAC+MMF/EC-MPS±CS. • Patients with an actual eGFR according to Modification of Diet in Renal Disease (MDRD-4) ≥ 45 mL/min/1.73m^2.
Key Exclusion criteria	**Exclusion criteria specific to Cohort 1:** • Multi-organ transplant recipients, including en bloc and dual kidney transplantation, or prior kidney transplant • Recipients of an organ from a donor after cardiac death (DCD). • Recipient of an organ from an HLA identical living related donor.

[redacted]

	• ABO incompatible or complement-dependent lymphocytotoxic (CDC) crossmatch positive transplant (isolated positive B cell crossmatches are not an exclusion criterion). • Recipients of kidneys from donors who are older than (>) 65 years. • Recipients of kidneys from donors with terminal serum creatinine > 2 mg/dL. • Patients at high immunological risk for rejection as determined for assessment of anti-donor reactivity: - high Panel Reactive Antibodies (PRA) > 20% or - presence of pre-formed DSA. Results 12 weeks prior to enrollment are acceptable if no blood transfusion or abortion occurred during this period. • Recipient of a kidney from a donor who tests positive for HIV, HBsAg or HCV. **Exclusion criteria to Cohort 2:** • Recipients of a kidney re-transplant. • Recipient of a multi-organ transplant, including en bloc and dual kidney transplantation. • DSA within 12 weeks prior enrollment. • eGFR decline ≥10.0 mL/min within 12 weeks prior enrollment. • Ongoing rejection or rejection that required treatment within 12 weeks prior enrollment. • Severe humoral and/or cellular rejection (BANFF ≥ IIb) within 12 weeks before enrollment. • Proteinuria > 1 g/day or urine protein creatine ratio (UPCR) >1.2 mg/mg at time of enrollment. **Key exclusion criteria applicable to both Cohorts:** • Recipient who tests positive for anti-HIV, HBsAg or anti-HCV (without proof of sustained viral response (SVR12) after anti-HCV treatment) within 28 days prior to baseline visit. • Recipient who tests negative for Epstein Barr virus (EBV) within 28 days prior to baseline visit. • Evidence of advanced liver disease (Child-Pugh C), or any sign of liver decompensation. • Patient with severe systemic infections, current or within the two weeks prior to randomization. • History of malignancy of any organ system, treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases, with the exception of localized excised non-melanomatous skin lesions. • Patients who weigh less than 30 kg or more than 180 kg.
Study treatment	**Cohort 1 – *de novo* patients:** • **Arm 1:** CFZ533 30 mg/kg IV (Day 1), CFZ533 15 mg/kg IV (Day 5), then CFZ533 600 mg SC Q2W (from Day 15) + MMF + corticosteroids (n=75) • **Arm 2:** CFZ533 30 mg/kg IV (Day 1), CFZ533 15 mg/kg IV (Day 5), then CFZ533 300 mg SC Q2W (from Day 15) + MMF + corticosteroids (n=75) • **Arm 3**: TAC + MMF + corticosteroids (n=50)

[redacted]

	All patients will receive induction therapy: Basiliximab or Thymoglobulin (rATG). In Cohort 1, randomization will be stratified by donor category (deceased vs. living donors) and induction therapy. **Cohort 2 – maintenance patients:** • **Arm 1:** CFZ533 30 mg/kg IV (Day 1) then CFZ533 450 mg SC Q2W (from Day 15) + MMF/EC-MPS ± corticosteroids (n=75) • **Arm 2:** TAC + MMF/EC-MPS ± corticosteroids (n=50) In Cohort 2, randomization will be stratified by corticosteroid use (yes/no) and time since transplant (6 - ≤ 12 months, > 12-24 months).
Efficacy assessments	• Composite efficacy (BPAR, Graft Loss or Death) [redacted]
Key safety assessments	• renal function (eGFR) • Proportion of patients with AEs, SAEs, AEs related to study drug • AEs of special interest: infections, malignancies, including PTLD, thromboembolic events, MACE, new onset diabetes mellitus (NODM)
Other assessments	• CFZ533 plasma concentrations over time (Cmax, Ctrough, AUC) • Semi-quantitative analysis of anti-CFZ533 antibodies in plasma (immunogenicity) [redacted] • Biomarkers
Data analysis	An interim analysis is planned with all data available for the cut-off on 12-Mar-2021. Evaluation of safety and efficacy 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 analysis will occur when all patients in each Cohort have completed Month 12 or discontinued prematurely. Additional analyses will be performed when all patients have completed Year 2, 3, 4, and 5 to monitor long term efficacy and safety as described in the SAP. The primary analysis is a non-inferiority (NI) evaluation of CFZ533 arm(s) to the control arm with respect to composite efficacy failure events (BPAR, graft loss, or death) will be evaluated in the *de novo* (Cohort 1) and maintenance (Cohort 2) cohorts. The estimand definition for the primary objective in each Cohort to demonstrate non-inferiority of CFZ533 vs. TAC control is as follows: • **Population:** defined through appropriate inclusion/exclusion criteria to reflect the targeted population; adult male and female *de novo* renal

[redacted]

	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 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 • **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 failures between the CFZ533 arm(s) and control The number of composite efficacy failure events in each arm is assumed to follow a Poisson distribution and the probability of a composite event occurring can then be derived as $\theta_i = 1 - \exp(-\lambda_i T)$ where λ_i is the event rate for arm i and T = (12 months) is the evaluation time. The pre-defined success criteria for each cohort is considered to be a composite rate difference between at least one of the CFZ533 arms and the control group with a non-inferiority (NI) margin of less than 20% for the *de novo* cohort (Cohort 1) and 12% for the maintenance cohort (Cohort 2), and certainty greater than 90% defined as $\Pr(\theta_{CFZ533} - \theta_{SoC} < NI \mid data) > 0.90.$ The required posterior probabilities will be estimated from simulations of the posterior distributions of $\theta_{CFZ533} - \theta_{SoC}$ and compared to the thresholds for the levels of certainty. The prior distributions will be assumed to be a non-informative Beta (1,1) for both the CFZ533 and the control arms. The posterior mean composite rates for each treatment group and for the difference in mean response rates between treatments will be presented together with 95% credible intervals.
Key words	Renal transplantation, *de novo* patients, maintenance patients, CFZ533, CNI-free immunosuppression.

1 Introduction

1.1 Background

Over the past decades, kidney transplantation has become a recognized medical procedure with considerable impact on extending and improving the quality of life of patients with end stage renal failure as compared to renal replacement therapy such as dialysis (5 year survival rate of 68% vs 36%, respectively) (Hart et al 2017).

The introduction of the calcineurin inhibitors (CNI) in human kidney transplantation revolutionized transplantation medicine, and made transplantation a preferable therapeutic intervention for end-stage renal diseases.

[redacted]

Current immunosuppressive regimens are usually based on combinations of 2 or 3 immunosuppressive drugs. CNIs, such as cyclosporine (CsA) or tacrolimus (TAC), and mycophenolates are the most widely used. In particular, the combination of TAC and mycophenolate mofetil continues to rise and is considered the standard of care immunosuppressant (SoC) regimen (Hart et al 2017).

The current SoC regimen provides excellent short-term efficacy with very low rates of acute rejection and a graft survival in the first-year post-transplant of approximately 95% (Hart et al 2017). However, considerable side effects that accompany treatment with CNIs hamper long-term kidney graft and patient survival, and cause major additional morbidity; at 5 years post-transplant graft survival declines to 68% and continues to decline to 53.4% at 10 years post-transplant (Hart et al 2017).

The major and most frequent side effects of CNIs is nephrotoxicity which is directly associated with irreversible renal function deterioration. Kidney allograft function is an important predictor of graft survival. In addition, CNIs are also associated with the development of diabetes, hypertension, dyslipidemia, neurotoxicity, gastrointestinal and hematological toxicity. All these adverse effects may be minimized or eliminated in the setting of a CNI-free regimen. Therefore, there is a high medical need for new immunosuppressant agents with the potential to prolong patient and graft survival with an improved safety profile over CNIs-based immunosuppressive regimens while maintaining antirejection efficacy.

In the search for novel therapies, there has been an increasing interest in the role that co-stimulation, B cells, plasma cells and antibodies play in the immune response to an allograft, specifically acute cellular rejection and chronic antibody mediated rejection (Clatworthy 2011). By developing a specific treatment that decreases the priming of T -and B-cells and the subsequent production of *de novo* donor specific antibodies and by eliminating CNIs, it is hypothesized that chronic rejection can be minimized, and long-term graft survival may be increased.

Recently, a CTLA-4-Fc fusion protein was approved for use in renal transplant immunosuppression without a CNI (Nulojix® PI 2017). Belatacept targets the CD80/86-CD28 pathway responsible for T-cell activation, and, when used without a CNI, results in better renal function and decreased cardiovascular risk in comparison to CNI based regimens. Although the benefit in renal function is significant, belatacept-based treatment regimens have also been found to result in a higher rate of acute rejection (17-22%) compared to the current SoC and have been associated with untoward side effects such as post-transplant lymphomas (PTLD) and progressive multifocal leukoencephalopathy (PML) (Vincenti et al 2010).

CD40 signaling is implicated in the pathology of transplant rejection as well as a range of autoimmune diseases. CFZ533, (INN: iscalimab), is a fully human, IgG1 anti-CD40 antibody that blocks recombinant CD154 (rCD154)-induced activation of CD40 pathway signaling in vitro and in vivo. The Fc-portion of CFZ533 has a single amino acid mutation which eliminates the cell-depleting ability of the antibody via antibody-dependent cell mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). It is able to block T cell-dependent antibody responses in humans and prolongs allograft survival in a preclinical transplantation model.

[redacted]

Targeting both CD40 and CD154 has shown promise in non-human transplant models, including models for solid organs (liver and kidney), pancreatic islets and graft versus host disease (GVHD). Similarly, the fully human IgG4 anti-CD40 antibody ASKP1240 (4D11) prolonged renal allograft survival in cynomolgus monkeys for up to 180 days when given as maintenance therapy and 50 days as induction therapy (Imai et al 2007, Aoyagi et al 2009). Non-human primate (NHP) studies with CFZ533 are in agreement with these results with survival times of up to 100 days (end of experiment) and normal graft morphology when administered as a monotherapy.

Recently, in an Astellas clinical Phase 2 study in renal transplantation, ASKP1240 was shown to be unable to prevent rejections in a CNI-free setting. However, the doses used in the study are assumed to have been insufficient to achieve full tissue CD40 occupancy (particularly during the first weeks of treatment), due to high target-mediated drug disposition (Harland et al 2015). These results, taken together with data from studies in non-human primates and analysis of the ASKP1240 data by Novartis (see Section 3.3), reinforce the approach of targeting the CD40-CD154 axis with sufficient exposure of the CD40 blocking agent both in tissues and periphery to adequately inhibit this pathway for efficacy (Ma et al 2014, Cordoba et al 2015).

Targeting CD40 with CFZ533 in *de novo* renal transplant patients may provide an opportunity to develop a treatment regimen that avoids CNI toxicities with similar anti-rejection effect, better renal function, a longer kidney-graft functional time, a better long term survival, an improved cardiovascular and metabolic profile (less hyperlipidemia and new onset diabetes mellitus), and prevention of *de novo* donor specific antibody formation. Also, maintenance transplanted patients are expected to benefit from such a CNI-free regimen after conversion to CFZ533.

CFZ533 is currently in Phase 2 evaluation in various indications, using intravenous infusions and subcutaneous injections of multiple doses (6 clinical trials were completed and 7 are ongoing as of 15-Nov-2020). A Proof of Concept trial (CCFZ533X2201-PoC) that evaluated the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of multiple doses of CFZ533 in combination with MMF and corticosteroid, compared to a TAC-based regimen, in *de novo* renal transplant recipients is completed. The CFZ533 patients received a loading regimen of 10 mg/kg IV on Day 1, 3, 7, 15, 29, 43 and 57, followed by a maintenance regimen at 10 mg/kg IV every four weeks, up to 12 months post-transplantation. The final data analysis showed that this regimen was well tolerated, and specifically not associated with increased risks of over-immunosuppression such as infection or neutropenia, and supported the transition to the CCFZ533A2201 dose range finding study (refer to the actual IB for more details).

Long-term graft survival is a complex and multifactorial process that depends on individual risk factors such as functional outcomes, immunological parameters and histological findings. A drug with a novel MoA that influences most of these individual risk factors, should therefore have the potential to improve relevant long-term outcomes compared to the current SoC (e.g., TAC).

1.2 Purpose

The purpose of this study is to investigate the safety, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) of:

[redacted]

- two CFZ533 dose regimens in *de novo* kidney transplant recipients, in combination with mycophenolate mofetil (MMF) and corticosteroids, compared to a standard of care control arm of TAC, MMF and corticosteroids.
- one CFZ533 dose regimen started 6-24 months post-transplantation in maintenance kidney transplant recipients, in combination with MMF/EC-MPS with or without corticosteroids, compared to a standard of care control arm of TAC and MMF/EC-MPS with or without corticosteroids.

This study will allow the assessment of the ability of CFZ533 to replace CNIs in terms of anti-rejection efficacy, while providing better renal function with a better safety and tolerability profile, in *de novo* and maintenance renal transplant patients. Overall, results of this study will be used to inform the CFZ533 dose and regimen selection for investigation in later phases of clinical development.

2 Study objectives and endpoints

2.1 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

Cohort 1 – *de novo* patients

Objectives	Endpoints
Primary Objective	**Endpoint for 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.	• Proportion of patients with composite efficacy failure event (BPAR, Graft Loss or Death) over 12 months post-transplantation
Secondary Objectives	**Endpoints for secondary objectives**
• 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
• 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 -Serious adverse events -AEs related to study drug -AEs of special interest: o Infections, including opportunistic infections

[redacted]

Objectives	Endpoints
	○ Malignancies, including post-transplant lymphoproliferative disorder (PTLD) ○ Thromboembolic events ○ Major adverse cardiovascular events (MACE) ○ 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 60 months treatment period and explore the dose-exposure relationship.	• Free CFZ533 plasma concentrations over time
• To evaluate the immunogenicity of CFZ533 during the 60 months treatment period	• Semi-quantitative analysis of anti-CFZ533 antibodies in plasma (CFZ533-treated patients only)

Exploratory Objectives	Endpoints for exploratory objectives
[redacted]	

Objectives	Endpoints
[redacted]	

Cohort 2 – maintenance patients

Objectives	Endpoints
Primary Objective	**Endpoint for primary objective**
• 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	• Proportion of patients with composite efficacy failure event (BPAR, Graft Loss or Death) over 12 months post-conversion
Secondary Objectives	**Endpoints for secondary objectives**
• To demonstrate that CFZ533 450 mg Q2W SC is superior to a TAC-based regimen with respect to the mean change in eGFR from baseline to 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 - Serious adverse events - AEs related to study drug - AEs of special interest:

[redacted]

	○ Infections, including opportunistic infections ○ Malignancies, including post-transplant lymphoproliferative disorder (PTLD) ○ Thromboembolic events ○ Major adverse cardiovascular events (MACE) ○ 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 60 months 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 60 months treatment period	• Semi-quantitative analysis of anti-CFZ533 antibodies in plasma (CFZ533-treated patients only)

Exploratory Objectives	**Endpoints for exploratory objectives**
[redacted]	

3 Investigational plan

3.1 Study design

Study CCFZ533A2201 is a randomized, phase 2b, 60-month study comprising of 12-months treatment for the primary analysis plus an additional 48-month open-label treatment period. The study is active-controlled, partially-blinded for the initial 12 months of treatment, multicenter, dose range finding study to evaluate the efficacy, safety, tolerability, PK and PD of CFZ533 in 2 different cohorts:

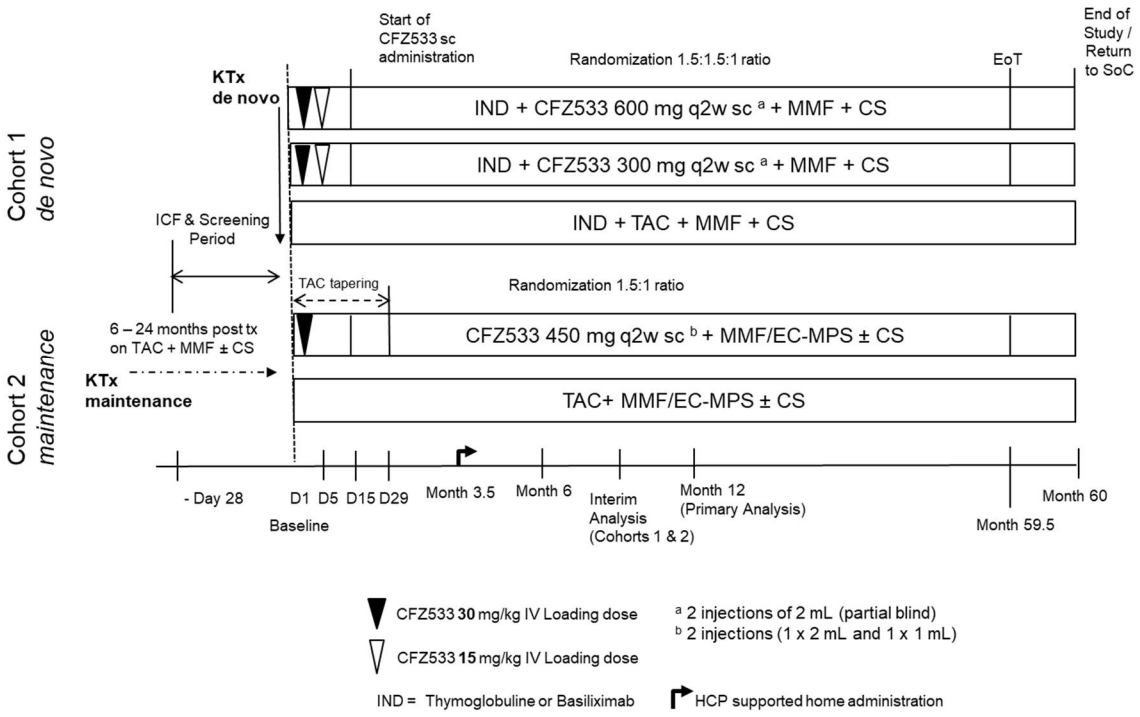
- In adult *de novo* kidney transplant recipients, CFZ533 in combination with MMF and corticosteroids as compared to standard of care comprised of TAC, MMF and corticosteroids.
- In a maintenance kidney transplant population (6-24 months post-transplant), CFZ533 in combination with MMF/EC-MPS with or without corticosteroids, compared to a standard of care control arm of TAC and MMF/EC-MPS with or without corticosteroids.

All *de novo* transplant patients will receive induction therapy, either basiliximab or rabbit anti-thymocyte globulin (rATG). No other induction therapy is allowed.

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 Informed Consent Form (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.

Figure 3-1 Study design



Tx: transplant; KTx: kidney transplant; D: day; EOT: end of treatment; ICF: informed consent form; HCP: health care provider; IND: induction.

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

Cohort 1 – *de novo* kidney transplant patients:

Patients will be consented and screened for eligibility prior to kidney transplantation. A total of 200 patients who meet the inclusion criteria and none of the exclusion criteria will be randomized prior to transplant surgery, at a ratio of 1.5:1.5:1 to CFZ533 600 mg SC Q2W (Arm 1), CFZ533 300 mg SC Q2W (Arm 2) or TAC control (Arm 3) (Figure 3-1).

For all patients, induction therapy, either basiliximab or rATG, must be started on the day of transplantation. No other induction therapy is allowed. The choice of the induction therapy is at the investigator's discretion, however, the percentage of randomized patients on each

induction therapy will be set as a range of 40-60% driven by the rate of recruitment into each individual stratum.

Control arm: patients randomized to the TAC control arm will be initiated on a TAC-based regimen with MMF and corticosteroids.

CFZ533 arms: patients randomized to both CFZ533 arms will be administered the first dose of CFZ533 at 30 mg/kg IV pre- or intra-operatively (Day 1) with completion of the infusion within one hour of unclamping and prior graft revascularization, in combination with MMF and corticosteroids. MMF and corticosteroids may be initiated prior to surgery according to local practice. A second IV dose of CFZ533 at 15 mg/kg will be infused at Day 5 post-transplant.

Subsequent doses starting at Day 15 (subcutaneously):

- Arm 1 (600 mg): 600 mg SC (2 injections of 2 mL CFZ533 at 150 mg/mL) Q2W, up to Month 59.5 visit.
- Arm 2 (300 mg): 300 mg SC (1 injection of 2 mL CFZ533 at 150 mg/mL, and 1 injection of 2 mL of the generic placebo) SC, Q2W, up to Month 59.5 visit. After completion of the primary endpoint analysis at Month 12, placebo will be removed once unblinded treatment kits are available.

The last dose of CFZ533 will be administered at Month 59.5 visit. Considering the half-life and elimination characteristics of CFZ533, and achieved trough plasma levels at the end of the treatment period, in the 600 mg arm (de novo patients), the median CFZ533 plasma concentration is expected to drop below 20 μg/mL at about 14 weeks after the last dose, with no expected pharmacodynamic activity in target tissues (e.g., germinal centers; data from non-human primates in CFZ533 Investigator Brochure (IB)).

CFZ533 SC will be administered by authorized Investigator/staff at each of the study visits or, as from Month 3.5, in-home by a health care provider. Pre-filled syringes (PFS) will be used upon availability once patients have completed all their Month 12 visit assessments required for the primary endpoint analysis (see Section 5.5.2.1).

Concomitant immunosuppression: MMF and corticosteroids will be initiated at the time of transplant and maintained throughout the treatment period. MMF and corticosteroids may be initiated prior to surgery as per local practice. Corticosteroids may be tapered off, as per local standard practice and investigator discretion, only after 12 months of treatment.

Cohort 2 – maintenance patients:

A total of 125 maintenance patients, who meet the inclusion criteria and none of the exclusion criteria, on a stable 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 3-1). 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 set as a range of 40-60% driven by the rate of recruitment into each individual stratum.

Control arm: patients will continue to receive the same immunosuppressive regimen (same drugs) as before entering the trial. Patients on a once daily TAC formulation can continue with this regimen.

[redacted]

CFZ533 arm: On Day 1, patients randomized to Arm 1 will be administered the first dose of CFZ533 at 30 mg/kg IV, concomitantly with MMF/EC-MPS and 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 reduced by a further 50%. By Day 29, patients will be fully tapered off their TAC. Subsequent doses of 450 mg SC Q2W, will be administered by authorized Investigator/staff at each of the study visits or as from Month 3.5, in-home by a health care provider, in combination with MMF/EC-MPS with or without corticosteroids, up to Month 59.5 visit. PFS will be used upon availability once patients have completed all their Month 12 visit assessments required for the primary endpoint analysis (see Section 5.5.2.1).

Randomized patients in both cohorts will remain on CFZ533 treatment until the Month 59.5 visit and undergo Study Completion evaluations at the Month 60 visit. After this visit, patients will have a further 12 weeks safety follow-up period. At the study completion visit (Month 60 or earlier), the patients will be switched to local standard of care regimen. In case a patient is switched to a TAC-based immunosuppression, TAC should be introduced at the lowest dose (0.5 mg b.i.d.), and increased progressively after trough level measurement.

Note that in Cohort 1 only MMF is allowed. Corticosteroid doses will be administered according to local practice. Corticosteroids may be tapered off, as per local standard practice and investigator's discretion, only after 12 months of treatment.

3.2 Rationale for study design

The controlled parallel group study design is well-established in renal transplant trials to evaluate a new immunosuppressive drug regimen versus current standard treatment. This approach will allow the comparison with data from previous published study results conducted in kidney and liver transplantation.

As this trial uses drugs requiring different modes of administration (oral, intravenous infusions and subcutaneous injections), as part of the investigational or the control arm, complete blinding is not possible due to the unnecessary placebo burden for patients.

However, in order to minimize bias between high and low CFZ533 doses in the *de novo* Cohort 1, patients, investigators and site staff, persons performing the assessments, and Novartis Clinical Research Associate teams will remain blinded to CFZ533 doses, from the time of randomization until completion of the primary analysis. Designated Sponsor personnel will remain blinded to the complete treatment group assignments until the primary analysis in Cohort 1 (see Appendix 4) to minimize bias to potential changes to the protocol and analysis.

Use of PFS will be allowed only once patients have completed their Month 12 visit assessments required for the primary endpoint analysis to avoid any impact on the main study analysis. PFS will be supplied as a blinded kit until completion of the Month 12 primary endpoint analysis to keep blinding to the dose.

The patient population will be described in more detail in Section 4 below.

[redacted]

3.3 Rationale for dose/regimen, route of administration and duration of treatment

3.3.1 *De novo* kidney transplant patients (Cohort 1)

In *de novo* patients (Arm 1 and Arm 2), the treatment starts with a **loading** regimen where CFZ533 is administered at 30 mg/kg IV on Day 1, and at 15 mg/kg IV on Day 5, followed by a **maintenance** regimen starting from Day 15 where CFZ533 is administered bi-weekly (Q2W) at **600 mg SC** (Arm 1) or **300 mg SC** (Arm 2) up to Month 59.5. In both arms CFZ533 will be given with MMF and corticosteroids.

3.3.1.1 Loading regimen (Cohort 1)

The level of CD40 receptor expression has the potential to affect exposure to CFZ533 and target engagement (receptor occupancy) in target tissues. High CD40 expression (as compared to healthy conditions) may be associated with high elimination rate of CFZ533 and loss of CD40 pathway blockade, if CD40 receptors are not fully saturated.

The **loading regimen** is intended to achieve, at start of treatment, full CD40 receptor saturation and minimal CD40-mediated elimination, in conditions where CD40 expression in target tissues has been enhanced (e.g., just after kidney transplantation, as illustrated below with ASKP1240).

ASKP1240 in kidney transplantation

The risk associated with underdosing in conditions where CD40 expression is enhanced is illustrated through the program ASKP1240 (Astellas), an anti-CD40 blocking antibody with similar PK and pharmacology properties as CFZ533 that was previously investigated in kidney transplant patients (Phase 2 trial data presented at the American Transplant Congress in 2015; Harland et al 2015).

In the CNI-free and low CNI arms a fixed dose of 200 mg IV ASKP120 (corresponding to about 2.9 mg/kg for a 70 kg bodyweight patient) was administered on Days 0, 7, 15, then Q2W and Q4W (every 4 weeks). The cumulative dose for ASKP1240 up to Day 29 and 57 was 800 and 1200 mg, respectively. Most of the rejections in the CNI-free arm occurred before Day 60. It is hypothesized that ASKP1240 failed in the CNI-free regimen likely due to under dosing that failed to fully saturate increased levels of CD40 expression in tissues during the first 1 or 2 months, leading to an enhanced CD40 mediated clearance of ASKP1240, sub-optimal tissue exposure and high rates of rejection.

This hypothesis is further supported by preclinical data with ASKP1240 in transplanted monkeys (Ma et al 2014). After receiving the allograft kidneys, the recipient's immune system was rapidly activated, resulting in an increase in CD40 expression in B cells, dendritic cells, or macrophages as well as on selected allograft parenchymal cells. As a result of the immune response against allo-antigens, the number of activated cells and unoccupied CD40 sites increased and would have required higher doses or more frequent administration of ASKP1240, a notion borne out by the increased clearance of ASKP1240 observed in transplanted animals (Ma et al 2014).

[redacted]

Previous experience with CFZ533 in kidney transplant patients

In the Part 2 of the proof of concept study CCFZ533X2201, evaluating the safety, tolerability, PK/PD and efficacy of multiple doses of CFZ533 in combination with MMF and corticosteroids, compared to a TAC-based regimen, in *de novo* renal transplant recipients, a **loading regimen** was also implemented (10 mg/kg IV on Day 1, 3, 7, 15, 29, 43 and 57), followed by a **maintenance** regimen at 10 mg/kg IV Q4W. Treatment with CFZ533 was well tolerated, and not associated with an increased risk for over-immunosuppression such as infection or neutropenia.

Assuming a BW of 70 kg, the cumulative dose of CFZ533 was 3500 and 4900 mg up to Day 29 and 57 post-transplant, respectively.

In this study, with the exception of the first week post transplantation, the above mentioned loading regimen led to CFZ533 plasma concentrations that were generally > 200 µg/mL for up to 3 months.

Similarly, in study CCFZ533A2201, assuming an absolute bioavailability of 75% for CFZ533 doses administered subcutaneously (preliminary data from the first-in-human study CCFZ533X2101), the cumulative dose for CFZ533 in *de novo* patients are expected to be 4050 and 4950 mg up to Day 29 and 57, respectively.

As shown in Figure 3-2, for Cohort 1 Arm 1 and Arm 2, the proposed IV loading regimen during the first week, followed by the proposed Q2W SC maintenance regimen (Section 3.3.1.2 for more details) is expected to provide similar plasma exposure levels during the first 3 months, as compared to study CCFZ533X2201-Part 2.

In the First-in-human Phase 1 clinical study (CCFZ533X2101) in rheumatoid arthritis patients, the administration of CFZ533 at 30 mg/kg IV (single dose: mean Cmax of about 848 µg/mL and 16 weeks of target engagement as measured through PK/PD data in whole blood) showed a favorable safety and tolerability profile.

The IV loading doses in CCFZ533A2201 will be administered during the first week post-transplant while the patient is at the hospital. This is expected to be more convenient for the patient as compared to multiple IV administrations during the first or second month (as in study CCFZ533X2201-Part 2), and not expected to translate into safety concerns.

Conclusion

Collectively, PK/PD data for CFZ533 in renal transplant patients (Study CCFZ533X2201-Part 2), as well as data from ASKP1240 in transplanted non-human primates and transplant patients, support the idea that an efficient dosing regimen in renal transplant patients requires a **loading** regimen, providing early full CD40 saturation and minimal CD40-mediated elimination of CFZ533 in conditions were the recipient immune system is rapidly activated, resulting in an increase in CD40 expression. The risks associated with underdosing include a high elimination rate of CFZ533, a loss of CD40 pathway blockade in target tissues, and increased rejection rates in conditions were CD40 expression is elevated.

3.3.1.2 Maintenance regimen (Cohort 1)

In *de novo* patients, 2 SC **maintenance dosing regimens** are proposed after initial IV loading.

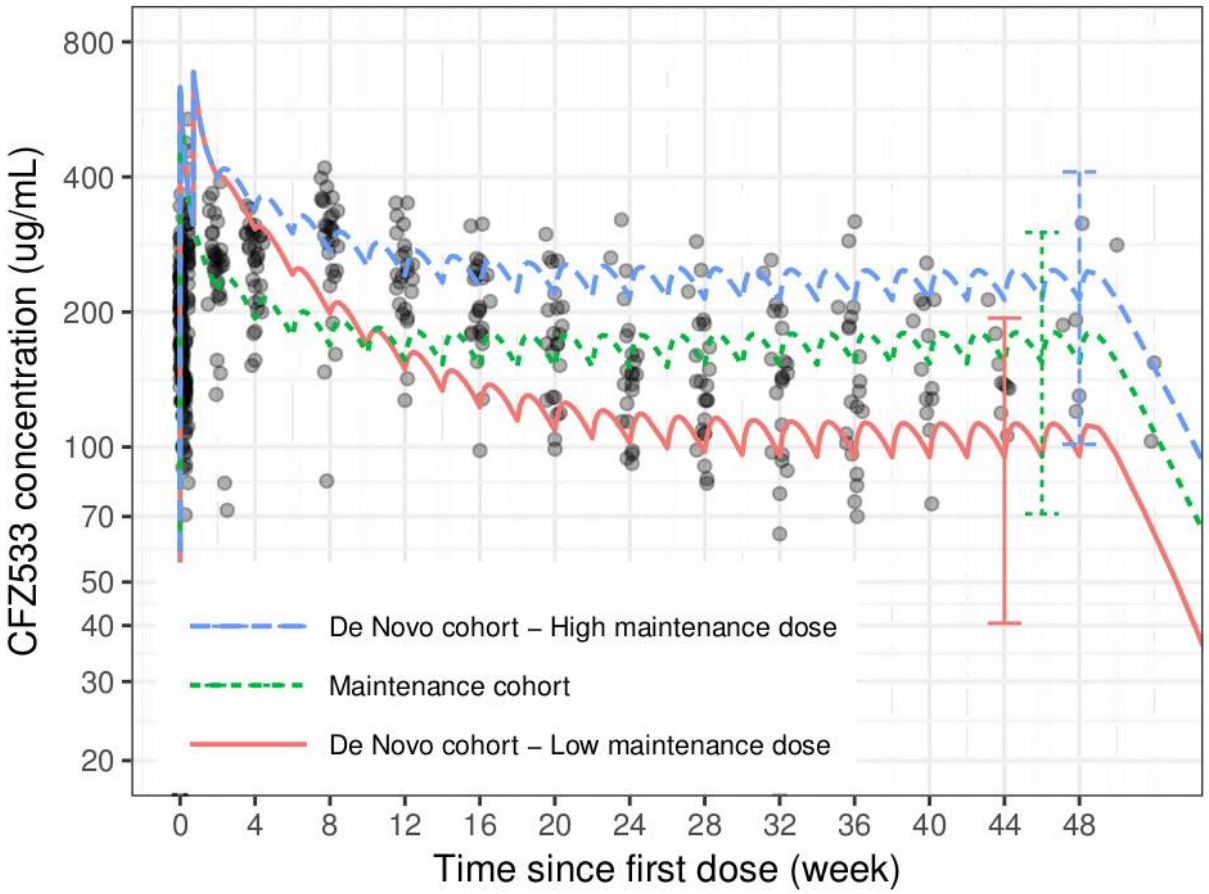
[redacted]

In **Arm 1**, the **600 mg SC Q2W** maintenance regimen is expected to provide steady state median trough CFZ533 plasma concentrations of about 200 µg/mL, which are in the upper range of the CFZ533 trough concentrations measured in study CCFZ533X2201-Part 2 (Figure 3-2). In that study, preliminary efficacy data suggest comparable treated biopsy proven acute rejection (tBPAR) rates up to Day 180 in the CFZ533 and Standard of Care arms.

The half-life of CFZ533 is about 2 weeks when full CD40 saturation (minimal contribution of CD40 receptors to the overall clearance) is obtained, therefore supports the bi-weekly SC regimen. Also, the Q2W SC regimen in this study is expected to provide less between-subject variability as compared to the Q4W IV regimen in study CCF533X2201-Part 2.

In **Arm 2**, the **300 mg SC Q2W** maintenance regimen is expected to provide steady state median trough CFZ533 plasma concentrations of about 100 µg/mL, which are in the lower range of the CFZ533 trough concentrations measured in study CCFZ533X2201-Part 2 (Figure 3-2).

Figure 3-2 **Predicted plasma concentration-time profiles for CFZ533 in *de novo* kidney transplant patients and in maintenance kidney transplant patients plotted together with actual CFZ533 plasma concentrations from study CCFZ533X2201-Part 2 in kidney transplant patients**



The lines represent the predicted time-course of the CFZ533 plasma concentrations for the typical transplant patient in Cohort 1 (*de novo* transplant patients; 600 mg SC Q2W maintenance regimen - **blue long-dash line**, or 300 mg SC Q2W maintenance regimen – **red solid line**) and Cohort 2

[redacted]

(maintenance transplant patients; 450 mg SC Q2W maintenance regimen - **green short-dash line**). For each of these regimens, the 90% prediction intervals for the trough CFZ533 plasma concentration at steady state are displayed. Those predictions are for patients with body weight ranging from 50 to 120 kg. The CFZ533 plasma concentrations measured in Study CCFZ533X2201-Part 2 are displayed as **grey dots** (PoC part with *de novo* transplant patients where after a loading IV regimen, the maintenance regimen for CFZ533 was 10 mg/kg IV Q4W; 6-month Interim Analysis data). Predictions are based on a model fit to the data from the single ascending dose/First-in-human study (CCFZ533X2101) and the transplant study (CCFZ533X2201-Part 2).

Both SC maintenance regimens are expected to provide trough plasma concentrations that are above 40 µg/mL for 90% of the transplant patients with a body weight (BW) of 50 to 120 kg. Plasma concentrations above 40 µg/mL are predicted to result in complete CD40 pathway blockade in 'healthy' conditions. This threshold was guided by preclinical data in non-human primates (see Investigator Brochure for more details):

- In a PK/PD study, rhesus monkeys were immunized with keyhole limpet hemocyanin (KLH) approximately 3 weeks prior to CFZ533 administration. A second immunization was administered 2 weeks after dosing and a third after complete wash-out of CFZ533. The loss of CFZ533-CD40 occupancy correlates with the ability to mount a partial recall and memory immune response to the second KLH vaccination. CD40 occupancy by CFZ533 at plasma concentrations >40 µg/mL at the time of the second KLH vaccination completely prevented recall antibody responses.
- In the 26-week toxicology study in cynomolgus monkey, 3 animals dosed at 1 mg/kg SC weekly had average steady state plasma concentrations ≥38 µg/mL. These concentrations were associated with complete suppression of germinal center development in cortical B cell areas of lymph nodes. Incomplete or no suppression of germinal centers was observed in lymphatic tissues in 3 animals with an average steady state plasma concentration <20 µg/mL.

3.3.2 Maintenance kidney transplant patients (Cohort 2)

In maintenance transplant patients enrolled 6 to 24 months post-transplantation, an IV **loading dose** of CFZ533 at 30 mg/kg IV will be administered on Day 1, concomitantly with MMF/EC-MPS and 50% of the baseline TAC dose. From Day 15, the **maintenance regimen** for CFZ533 is **450 mg Q2W SC** concomitantly with MMF/EC-MPS and TAC reduced to 25% of the baseline dose. By Day 29, patients will be fully tapered off their TAC. At Day 29 and subsequent doses of CFZ533 at 450 mg SC Q2W will be administered in combination with MPA with or without corticosteroids.

3.3.2.1 Loading regimen (Cohort 2)

In Cohort 2, the CFZ533 loading regimen is lower as compared to the loading regimens in Cohort 1. This is justified based on the expectation that, after 6 months (or more) under TAC and especially under MMF/EC-MPS, CD40 expression would be down modulated and would require less drug to achieve full target saturation in target tissues. This is supported by literature data on the effect of MMF on CD40 expression:

- In Colic et al (Colic et al 2003), human monocyte-derived dendritic cells (MDDC) were generated *in vitro* with granulocyte macrophage-colony stimulating factor (GM-CSF) and

[redacted]

interleukin (IL)-4 in the presence or absence of MMF. MMF reduced the number of immature MDDC in culture, dose-dependently, by inducing apoptosis and inhibited their stimulatory activity on allogeneic lymphocytes. These changes correlated with down-regulation of costimulatory and adhesion molecules such as CD40, CD54, CD80 and CD86. These results suggest that MMF impairs differentiation, maturation and function of human MDDC *in vitro*, which is an additional mechanism of its immunosuppressive effect.

- In Mehling et al (Mehling et al 2000), MMF decreased the ability of dendritic cells (DC) to stimulate allogeneic T cells in mixed lymphocyte reaction assays. Accordingly, flow cytometric analyses revealed a dose-dependent reduction of the expression of CD40, CD80, CD86, I-A, and ICAM-1 on DC with a concurrent reduction of IL-12 production. These data suggest that MMF, in addition to affecting T lymphocytes, directly affects Antigen Presenting Cells, resulting in an impairment of immune responses.

3.3.2.2 Maintenance regimen (Cohort 2)

The 450 mg SC Q2W regimen was selected to provide data at an intermediate dose level from those tested in *de novo* transplant patients, which enables an assessment of the dose (exposure)-response relationship to support the choice of an adequate dosing regimen in Phase 3 studies.

In maintenance kidney transplant patients, the 450 mg SC Q2W maintenance regimen is expected to achieve steady state median trough CFZ533 plasma concentrations of about 150 µg/mL, which are in the mid-range of the CFZ533 trough concentrations measured in study CCFZ533X2201-Part 2 (Figure 3-2), and also well above 40 µg/mL for >90% of the patients (for a bodyweight range of 50 to 120 kg).

The immunosuppressant drugs, TAC and MMF, are marketed drugs and their dosage and administration will be based on their product labeling and standard of care. EC-MPS administration will be based on local standard of care.

3.4 Rationale for choice of comparator

The choice of the control arm for this study was based upon the predominance of TAC use in *de novo* kidney transplantation worldwide in combination with MMF and corticosteroids (Hart et al 2017). The combination of TAC and MMF is as well the most commonly used regimen in maintenance transplant population. Corticosteroid use however, is progressively decreased over time after transplantation, and in many patients fully stopped. For this population, the protocol does not mandate the reintroduction of corticosteroids.

Two MPA (mycophenolic acid) formulations are currently used in clinical transplantation as part of the maintenance immunosuppressive regimen in combination with TAC with or without corticosteroids. Mycophenolate mofetil (MMF) was the first MPA agent to be approved for the prevention of acute rejection following renal transplantation, in combination with cyclosporine and steroids. EC-MPS is an alternative MPA formulation available in clinical transplantation developed to try to improve the upper gastrointestinal tolerability of mycophenolate.

The KDIGO (2009) clinical practice guideline suggests as the first line of antiproliferative agent (grade 2b level of recommendation), the use of mycophenolate (either MMF or EC-MPS) along with TAC with or without corticosteroids for initial maintenance of immunosuppression. EC-

[redacted]

MPS and MMF have shown to be similar in both efficacy and safety (Salvadori et al 2004; Budde et al 2004; Budde et al 2006; Salvadori et al 2006; Johnston et al 2006). One randomized controlled trial compared MMF 2 g daily vs. EC-MPS 1.44 g daily with CsA-ME, corticosteroids, with or without induction (Salvadori et al 2004). There were no significant differences in BPAR (24% MMF vs. 23% EC-MPS), patient or graft survival or rates of malignancy or infection. There was no difference in rates of gastrointestinal disorders (80% MMF vs. 81% EC-MPS), despite the fact that the potential reduction of gastrointestinal adverse events has been the incentive for the development of EC-MPS. Another study (Budde et al 2004) tested the crossover between the two formulations and also found no differences in any of the outcome parameters. Recently data using TAC with either EC-MPS or MMF also showed the same efficacy and safety (Budde et al 2007).

3.5 Purpose and timing of interim analyses/design adaptations

An interim analysis is planned for data which is collected up to a data cut-off date of 12-Mar-2021. Evaluation of safety and efficacy 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.

Additional analyses will be performed when all patients complete Year 2, 3, 4, and 5 to monitor long term efficacy and safety as described in the SAP.

With the change in the development strategy of iscalimab, the purpose of this interim analysis is to obtain efficacy and safety data in both *de novo* and maintenance cohorts, to inform dose selection and design of the future Phase 3 program. Consequently, this study will be considered a Phase 2b dose finding study with the sample size currently achieved considered sufficient to support these objectives.

3.6 Risks and benefits

CFZ533 is a new biological entity currently in Phase 2 evaluation in various indications, using intravenous infusions and subcutaneous injections of multiple doses (6 clinical trials were completed and 7 are ongoing as of 15-Nov-2020).

Risks: the potential safety concerns in humans and the investigator guidance are based on data from the available clinical program with CFZ533, preclinical and toxicological data, as well as experience with other compounds of the same class (refer to the current investigator's brochure).

Beyond the potential risks described in the Investigators' Brochure (IB), there may be risks which may be serious and unforeseen with the use of CFZ533.

The risk to patients in this trial will be minimized by adherence to the eligibility criteria; close clinical monitoring and adherence to the protocol defined stopping rules (refer to Section 5.6.2.2). The risks of insufficient efficacy will be minimized by frequent monitoring of clinical laboratory data, signs and symptoms suggesting rejections and the early discontinuation of any treatment arm that is ineffective according to the Stopping Rules (see details in Section 5.6.2.2).

The list of potential risks related to CFZ533 administration, in the current Investigator's Brochure, include those generally associated with administration of a monoclonal antibody in

humans. These include the possibility of a hypersensitivity reaction (characterized by acute or delayed allergic reaction, anaphylaxis, urticaria, rash, dyspnea, hypotension, fever, chills), immunogenicity, infections (e.g., caused by polyomavirus or cytomegalovirus), therapeutic failure of vaccination during CFZ533 treatment, changes in lymphoid structure, loss of efficacy or allergic/immune-mediated inflammatory reactions due to development of anti-CFZ533 antibodies, thrombophilia, systemic inflammation and lymphoproliferative disorders (refer to the actual IB for more details).

Novartis has performed a study-specific medical and safety risk assessment and concluded that based on the current data, the benefit/risk of iscalimab due to COVID-19 pandemic remains unchanged in the target population. Please note, that infections are already a risk in transplanted patients, are described as potential risk in this protocol, and will need to be actively monitored by investigators and managed in study participants. In new patients, SARS-Cov-2 testing should be performed per investigator discretion in accordance with local practice.

A serious infusion reaction that results in anaphylaxis could happen in monoclonal antibody therapy.

As with any therapeutic protein, immunogenicity is always a risk, although it is important to note that CFZ533 is a fully human monoclonal antibody with lower risk of immunogenicity compared to humanized or chimeric antibodies.

In Study CCFZ533X2101 (FIH), one subject at 1 mg/kg IV (1 week full CD40 occupancy) developed specific antibodies to CFZ533, which were detected 6 weeks after CFZ533 plasma concentrations were below the limit of quantification. The presence of anti-drug antibodies (ADA) in this subject did not compromise exposure and was not associated with an immune related safety signal. This corresponds to an ADA incidence of 2% in this study.

No immunogenicity was reported in Japanese healthy volunteers (Ethnicity Sensitivity Study CCFZ533X1101).

No ADAs were detected in any of the 15 patients enrolled in Study CCFZ533X2205 (myasthenia gravis) during the 12-week treatment and 24-week follow up period after the last dose of CFZ533.

Anti-CFZ533 antibodies are being assessed in all CFZ533-treated subjects, in all clinical studies with CFZ533.

Benefits:

Study CCFZ533X2201 was a two-part, randomized, multiple dose, open-label, study evaluating safety, tolerability, pharmacokinetics/pharmacodynamics (PK/PD) and efficacy of CFZ533, in combination with MMF and CS, with and without TAC, in de novo renal transplant recipients.

Primary objective for Part 1 of this trial (n=7 subjects enrolled) was to assess the safety, tolerability and PK of multiple IV and SC CFZ533 doses at 3mg/kg dose in combination with MMF, CS and TAC (standard exposure) in de novo renal transplant patients over the treatment and follow-up period. The review of PK/PD data confirmed expected exposure.

Primary objective for Part 2 of the trial was to assess the potential for CFZ533 to act as the primary immunosuppressant in a CNI-free regimen with MMF and corticosteroids in de novo renal

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transplant patients. All patients received basiliximab induction therapy and were followed for up to 12 months.

A total of 52 patients were screened and randomized of which 51 received a kidney transplant (34 received CFZ533 and 18 patients TAC). A total of 30 (88.2%) patients in the CFZ533 group and 13 (72.2%) patients in the control group completed the study as per protocol. The reasons for study discontinuation in the CFZ533 group were physician decision (3 patients) and lack of efficacy (1 patient), while the reason for study discontinuation in the control group were graft loss (2 patients), subject/guardian decision (2 patients), and lost to follow-up (1 patient).

A blinded external independent Adjudication Committee (AC) was implemented to centrally read all biopsies taken for suspected rejections, delayed graft function and other kidney disease related events in an unbiased, standardized and blinded manner.

CFZ533 regimen demonstrated comparable efficacy as compared to TAC-based regimen. The adjudicated treated BPAR (tBPAR) was reported in 7 (21.2%) patients of the CFZ533 group and 3 (16.7%) patients of the control group over the treatment period of 12 months. The majority of the tBPAR incidences in the CFZ533 (6/7) and control (2/3) groups occurred within the first 3 months of transplantation.

The K-M estimate of the probability of first event of adjudicated tBPAR was comparable in both groups, (83% for CFZ533 vs 78% for the control group).

The adjudicated BPAR (BPAR) was reported in 8 (24.2%) patients of the CFZ533 group and 6 (33.3%) patients of the control group over the treatment period of 12 months, majority of which occurred within the first 3 months of transplantation (7/8 in the CFZ533 and 5/6 in the control arm).

Adjudicated composite efficacy failure (tBPAR or graft loss or death) was reported in 7 (21.2%) patients in the CFZ533 group and 4 (22.2%) patients in the control group.

Overall, patients in the CFZ533 arm had significantly better renal function throughout the study; the mean eGFR was consistently higher in the CFZ533 group than in the control group from Day 2 through Day 337. The mean eGFR at Days 1, 29, 337 was 9.9, 57.1, and 61.2 mL/min/1.73m^2, respectively in the CFZ533 group versus 9.6, 45.5, and 52.6 mL/min/1.73m^2 in the TAC-control group, respectively.

Two grafts were lost in the TAC-control arm (11.1%), but none in the CFZ533 group.

Overall, safety data from the CCFZ533X2201-Part2 study indicates that CFZ533 has a favorable safety and tolerability profile. More than 60% patients in both treatment groups reported serious adverse events (SAEs) with a 61.8% (21 patients) incidence in the CFZ533, and a 66.7% (12 patients) incidence in the TAC-control group. The number of study drug-related SAEs was comparable between the CFZ533-, (12 patients, 35.3%) and the TAC-control group (6 patients, 33.3%).
The incidence of new-onset diabetes mellitus (NODM) was lower in the CFZ533 group (3/24 patients, 12.5%) than in the TAC-control group (3/10 patients, 30.0%). Only 1 patient out of 3 patients in CFZ533 group was reported with NODM while on CFZ533 and the other 2 patients had NODM while on TAC regimen after switching from CFZ533.

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There was no death, no thromboembolic event in the CFZ533 arm (1 in the TAC-control arm), no case of PTLD and no case of progressive multifocal leukoencephalopathy (PML).

The incidence of infections was comparable between the treatment groups with 85.3% in the CFZ533 group and 88.9% in the control group, and fewer infection complications (58.8% vs 83.3%) with no increase of opportunistic infections. Viral infections had comparable incidence in the CFZ533 (58.8%) and control (55.6%) groups; bacterial infections had as well a similar incidence (50%) in both treatment groups.

The incidence of BK virus infections was comparable among the treatment groups with 29.4% (10 patients) in the CFZ533 group and 27.8% (5 patients) in the TAC-control group. The incidence of cytomegalovirus (CMV) infection reported as adverse event (AE) was higher in the CFZ533 group (10 patients, 29.4%) as compared with the control group (4 patients, 22.2%) (Refer to CFZ533 IB for more details).

In the CCFZ533X2201 study, Month 12 allograft biopsies were not required as per protocol. After study completion at Month 12 post-transplantation, biopsies were performed on a subset of study patients to assess if Tac-free therapy with CFZ533 preserves the quality of transplanted kidney grafts. At two participating sites in the Post Trial Access study with NCC code CCFZ533X2401M, five patients treated with CFZ533 and 7 patients treated with TAC had surveillance renal graft biopsies taken at Month 12 or Month 24. All biopsies taken were reviewed based on the Banff criteria 2017 and scored by a pathologist blinded to therapy. The chronic allograft damage index (CADI) was calculated and a CADI of 1 or less was considered as ‘normal renal histology’.

Three of five patients (60%) on CFZ533 had ‘normal renal histology’ versus none of seven on TAC. The average CADI score (± SE) at final biopsy was 1.6 (±0.6) for CFZ533 and 5.1 (±0.8) for TAC. One patient on CFZ533, with a CADI score 3, had significant BK viremia, 20 000 copies/ml. In addition, two patients were excluded from the analysis, since they switched therapy as per protocol after only 2 months. (Farkash et al 2019, Abstract 19-LB-4719, accepted at ATC 2019).

Compared to current standard of care, CFZ533 appears to be associated with lower CADI scores, with close to normal histology maintained in a high proportion of kidney allografts. These findings confirm observations in nonhuman primates (Cordoba et al 2015). Lower CADI scores are associated with better graft outcomes up to 3 years (Yilmaz et al 2003). In the ongoing CCFZ533A2201 study, the collection of biopsies at baseline and Month 12 will allow to further understand the potential impact of CFZ533 on preserving graft morphology.

The expected benefit profile of CFZ533 from its mechanism of action and its use in a CNI-free setup in de-novo transplant patients is anticipated to provide long term graft survival without compromising short term efficacy, with a better renal function, less development of *de novo* DSA and an improved cardiovascular and metabolic profile with less hyperlipidemia, hypertension and NODM, and less neurotoxicity.

Same benefits are also expected in the maintenance transplant population.

Based on the overall risk-benefit assessment, and because there is a large unmet need for new immunosuppressive treatment with less severe side effects and improved long-term graft and

[redacted]

patient survival, the current study evaluating CFZ533 in both *de novo* and maintenance transplant patients is justified.

3.7 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

4 Population

The study population will consist of 2 Cohorts as described below:

Cohort 1: consists of adult male and female *de novo* renal transplant recipients of a primary graft from a deceased or living donor. It is planned to randomize approximately 200 patients.

Cohort 2: consists of adult male and female maintenance renal transplant recipients of a primary graft received 6 to 24 months prior enrollment. It is planned to randomize approximately 125 patients.

Both cohorts of this multicenter study will be conducted in approximately 125 centers worldwide.

It is expected that the screen failure rate will be around 25% therefore approximately 434 patients may need to be screened in order to complete recruitment.

The Investigator must ensure that all patients being considered for the study meet the following eligibility criteria. Deviation from **any** entry criterion excludes a patient from enrollment into the study.

4.1 Inclusion criteria

Patients eligible for inclusion **in both cohorts** must fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male or female patient ≥ 18 years old.
3. Up to date vaccination as per local immunization schedules.
4. Able to communicate well with the Investigator, to understand and comply with the requirements of the study.

Inclusion criteria specific to *de novo* Cohort 1:

5. Recipients of a primary kidney transplant from a brain-dead donor (DBD), living unrelated or non-HLA identical living related donor.
6. Recipients of a kidney with a cold ischemia time (CIT) < 24 hours.

Inclusion criteria specific to maintenance Cohort 2:

[redacted]

7. Recipients of a primary graft received 6 to 24 months prior enrollment, on a regimen containing TAC+MMF/EC-MPS±CS.
8. Patients with an actual eGFR (MDRD-4) ≥ 45 mL/min/1.73m^2.

4.2 Exclusion criteria

Patients fulfilling **any** of the following criteria are not eligible for inclusion in this study:

Exclusion criteria specific to *de novo* Cohort 1:

1. Multi-organ transplant recipients, including en bloc and dual kidney transplantation, or prior kidney transplant.
2. Recipients of an organ from a donor after cardiac death (DCD).
3. Recipient of an organ from an HLA identical living related donor.
4. ABO incompatible or complement-dependent lymphocytotoxic (CDC) crossmatch positive transplant (isolated positive B cell crossmatches are not an exclusion criterion).
5. Recipients of kidneys from donors who are older (>) than 65 years.
6. Recipients of kidneys from donors with terminal serum creatinine > 2 mg/dL.
7. Patients at high immunological risk for rejection as determined for assessment of anti-donor reactivity:
    - high PRA > 20% or
    - presence of pre-formed DSA. Results 12 weeks prior to enrollment are acceptable if no blood transfusion or abortion occurred during this period.
8. Recipient of a kidney from a donor who tests positive for HIV, HBsAg or HCV (without at least Sustained Viral Response after 12 weeks of HCV treatment (SVR 12)).

Exclusion criteria to maintenance Cohort 2:

9. Recipients of a kidney re-transplant.
10. Recipient of a multi-organ transplant, including en bloc and dual kidney transplantation.
11. DSA within 12 weeks prior enrollment.
12. eGFR decline ≥10.0 mL/min within 12 weeks prior enrollment.

    In order to account for variances between laboratories, it is recommended to assess any change in eGFR using results from one laboratory and avoid comparing results from different laboratories. The eGFR should be calculated using the MDRD-4 formula (MDRD-4 formula is more sensitive to relatively small changes in the serum creatinine).
13. Ongoing rejection or rejection that required treatment within 12 weeks prior enrollment.
14. Severe humoral and/or cellular rejection (BANFF ≥ IIb) within 12 weeks before enrollment.
15. Proteinuria > 1 g/day or UPCR >1.2 mg/mg at time of enrollment.

Exclusion criteria applicable to both Cohorts:

[redacted]

16. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer.
17. History of hypersensitivity to any constituent of the study regimen, and of any drugs of similar chemical classes.
18. Any additional contraindication to the use of TAC or mycophenolate mofetil according to the national labeling information of these products (see local product label).
19. Recipient who tests positive for anti-HIV, HBsAg or anti-HCV (without proof of sustained viral response (SVR) after anti HCV treatment, defined as at least SVR12) within 28 days prior to baseline visit.
20. Recipient who tests negative for Epstein Barr virus (EBV) within 28 days prior to baseline visit.
21. Evidence of active tuberculosis (TB) infection with appropriate documentation (after anti-TB treatment, patients with history of latent TB may become eligible according to national guidelines).
22. Evidence of advanced liver disease (Child-Pugh C), or any sign of liver decompensation.
23. Patient with severe systemic infections, current or within the two weeks prior to randomization.
24. Patient with any history of coagulopathy or medical condition requiring long-term anticoagulation which would preclude renal biopsy after transplantation (low dose aspirin treatment or interruption of chronic anticoagulant is allowed).
26. History of malignancy of any organ system, treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases, with the exception of localized excised non-melanomatous skin lesions.
27. Patient with Hbg < 8 g/dL, WBC count ≤ 2,000/mm^3 or with platelet count ≤ 50,000/mm^3.
28. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
29. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception during dosing and for 14 weeks after the study medications have been stopped. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient, otherwise highly effective methods to be applied.

[redacted]

- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

  In case of use of oral contraception women should have been stable on the same brand (or generic equivalent) for a minimum of 3 months before taking study treatment.

  Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential (see additional instructions in Section 6.5.6).

  If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

30. Patients who have received a live vaccine within four weeks before enrollment.

31. Patients who weigh less than 30 kg or more than 180 kg at screening or baseline.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

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, which would be 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.

[redacted]

- 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 (see details in Section 5.5.2.1)

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. After completion of the primary endpoint analysis at Month 12, placebo will be removed once unblinded study treatment kits are available. Patients will continue to receive their randomized dose.

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.

5.1.2 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.

5.2 Treatment arms

Patients will be randomized across 3 treatment arms in a 1.5:1.5:1 ratio to CFZ533 or SoC in Cohort 1 and across 2 treatment arms in a 1.5:1 ratio to CFZ533 or SoC in Cohort 2.

[redacted]

Cohort 1 – *de novo* patients:

Patients will be randomized at baseline to one of the following 3 arms:

- **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 will be randomized at Baseline to one of the following 2 arms:

- **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.

5.3 Treatment assignment and randomization

At baseline and prior to surgery, all eligible patients will be randomized via an Interactive Response Technology (IRT) system to one of the treatment arms within a cohort. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient,

[redacted]

which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be administered to the patient.

The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and that the randomization of CFZ533 doses assigned to CFZ533 arms in Cohort 1 is concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

For Cohort 1: randomization will be stratified by:

- Donor category (deceased versus living donor kidneys); and
- Induction therapy (basiliximab versus rATG).

Furthermore, the IRT will cap the randomization in each induction therapy stratum (basiliximab and rATG) to a range of 40-60%.

For Cohort 2: randomization will be stratified by:

- Corticosteroids use (yes/no); and
- Time since transplant: 6 - ≤ 12M and > 12-24M.

Furthermore, the IRT will cap the randomization in each time since transplant stratum (6 - ≤12, > 12-24 months) to a range of 40-60%.

The randomization scheme for patients will be reviewed and approved by a member of the Randomization Group and a member of the Biostatistics Quality Assurance Group.

5.4 Treatment blinding

Details of the level of blinding for each study role (patient, investigator, Novartis staff, etc.) are provided in Appendix 4. Some specific considerations are below.

This is a randomized, partially-blinded study of CFZ533 versus active standard of care (TAC+ MMF+CS), in which the CFZ533 arms in Cohort 1 (*de novo* patients) are blinded to dose for minimum of 12 months treatment and will only be unblinded following the primary 12-month analysis.

The partial-blinding will include:

- Patients, investigators, site personnel, persons performing the assessments and the monitors will be aware of whether the patient is receiving CFZ533 or SoC. Patients will get 2 x 2 mL injections, either 2 injections of 2 mL CFZ533 at 150 mg/mL or 1 injection of 2 mL CFZ533 at 150 mg/mL and 1 injection of 2 mL of the generic placebo.
- Patients, investigators, site personnel, persons performing the assessments, monitors and the Sponsor will remain blinded to the CFZ533 dose (600 mg versus 300 mg). Following data base lock for the interim analysis, the dose level will be unblinded for Sponsor and following

[redacted]

completion of the primary analysis at Month 12, the dose level will be unblinded for the patients, investigators, site personnel, persons performing the assessments and monitors.

- Designated Sponsor personnel will remain blinded to the complete treatment group assignments to minimize bias to potential changes to the protocol and analysis until data base lock for the interim analysis of Cohort 1 and Cohort 2.

The Adjudication Committee (AC) will remain blinded to the CFZ533 and SoC treatment for the duration of the study.

Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study (see Appendix 4 for details); the identity of the CFZ533 treatments will be concealed by the use of study drug that are all identical in schedule of administration and appearance.

Trough CFZ533 plasma concentrations will not be shared with the investigators and site staff at the patient level so that the CFZ533 dose administered is not revealed.

The laboratory bioanalyst will receive a copy of the randomization schedule to facilitate analysis of the PK samples. The laboratory bioanalyst may provide concentration data to the PK expert under blinded conditions and will keep unblinding information confidential until the clinical database lock for IA of Cohort 1 and Cohort 2. Unblinding of site and patient will only occur in the case of patient emergencies (see Section 5.6) and at completion of the primary analysis at Month 12.

5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

5.5.1 Patient numbering

Each patient is uniquely identified by a Subject Number assigned by Novartis. The subject number is composed of a site number and a sequential number. Once assigned to a patient, the Subject Number will not be re-used.

Upon signing the ICF, the patient is assigned the next sequential number available in the electronic data capture (EDC) system. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site must select the CRF book with a matching Subject Number in the EDC system to enter data.

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the appropriate CRF.

5.5.2 Dispensing the study drug

5.5.2.1 Investigational drug

The investigational drug, CFZ533 will be supplied by Novartis to the Investigators as double-blind supplies for Cohort 1 and open-labeled supplies for Cohort 2. After completion of the primary endpoint analysis at Month 12, Cohort 1 supplies will be open-label.

[redacted]

For preparation of CFZ533, the pharmacist or designee at the Investigator's site will need to log into the IRT system to receive the treatment code. IRT may be contacted up to two days in advance of study visit for dispensing medication. In addition, the pharmacist or designee at the Investigator's site will prepare the medication for administration to patients based on a separate pharmacy manual.

Appropriate documentation of the patient specific dispensing process must be maintained.

The study drug outer packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the "n" treatment arms. Investigator staff will identify the study drug package(s) to be used for a single dose administration by contacting the IRT and obtaining the medication number(s). Immediately before drug administration or dispensing the package to the in-home health care provider or patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

During a Public Health emergency that may limit on-site study visits, delivery of IMP directly to a patient's home is generally permitted in the event the Investigator has decided that an on-site visit by the patient is no longer appropriate or possible, and that it is in the interest of the patient's health to administer the study treatment even without performing an on-site visit. Implementation will need to be discussed with Novartis. The dispatch of IMP from the site to the patient's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 3-month's supply. In this case, regular phone calls will occur between the site and the patient for instructional purposes, safety monitoring, and discussion of the patients' health status until the patients can again visit the site.

Optional in-home drug administration

At protocol specified time points (see Table 6-1) and during a Public Health emergency, if in-home administration of CFZ533 supported by a health care provider has been opted for, the investigator or delegated site staff will dispense, via the IRT, an appropriate number of investigational treatment packages to the home health care provider. The investigator staff will detach the outer part of the label and affix it to the source documentation (Drug Label Form) and issue a Patient Drug Dosing Record form for the in-home health care provider to complete. Detailed instructions on the in-home administration of the study treatment will be described in the information for use (IFU) provided to each health care provider and made available to the site staff and investigator. These instructions should be reviewed in detail by the site personnel.

Home health care provider will be contracted on a per country basis or by a global vendor, depending on local regulations and Novartis organization decision. The in-home health care provider will be trained by Novartis on the protocol and the instructions for use (IFU). This will be documented in a training log and stored appropriately.

Use of PFS

Once available, and after completion of all their Month 12 visit assessments required for the primary endpoint analysis, patients will receive SC injections using CFZ533 PFS instead of LIVI. PFS will be administered by eligible patients themselves, caregivers or investigator/staff. Dosing will continue to be administered every 2 weeks.

The decision to allow for a patient or caregiver to administer CFZ533 via PFS is left to the discretion of the investigator and/or site staff, and should be based on clinical judgement and evaluation of factors that include the patient's prior history of safety and tolerability to iscalimab, indication of hypersensitivity or other acute reactions to previous doses of CFZ533, etc. Starting from Month 12, the Investigator will determine if a patient or caregiver is able to appropriately self-inject or inject the study drug following completion of the self-administration training and first two PFS treatments self-administered on site. Site must document training completion and decision.

If patient/caregiver is authorized to perform the injection at home, only visits with other assessments beside the study drug injections will mandate patients to come to site (e.g., Month 15, Month 18, Month 21, etc.). Between the on-site visits, the investigator or delegated site staff will telephone the patient at least monthly to check on their status (e.g., AEs, concomitant medications, pregnancy status). It is highly recommended that the investigator or delegated site staff contact the patient on each scheduled dosing day.

Site will dispense all necessary material for self-injection such as PFS kits and cooler bags for transportation. Site will dispense CFZ533 from the IRT according to the patient's cooled storage capacity at home and investigator discretion, with a maximum stock to cover administration up to the next scheduled on-site visit (5 treatments). The site will instruct the patient that on the day of clinic visits, CFZ533 dosing will be done at the site, after collection of PK samples which are required before dosing.

The study medication transportation, home-storage, preparation and administration guidelines are described in separate instructions for use (IFU) provided to the patient. The patient will be provided with a form to record each CFZ533 dose administration, the location, and who performed it. The site will use the recorded data from the form to complete the dosing record in the eCRF.

5.5.2.2 Control and other study treatment

Each patient will be supplied by the study site with commercial drugs. Commercial Novartis drugs and/or 3rd party drugs used for this trial will be locally purchased and supplied either by the local CPO or by the clinical site per local regulations.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

[redacted]

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients will be asked to return all unused study treatment and packaging at the next site visit or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site. Destruction of unused drug should be done according to local requirements and after the approval by the Novartis Clinical Team.

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

5.5.4.1 Cohort 1 –*de novo* patients

CFZ533 administration – Arms 1 and 2

CFZ533 will be administered by IV infusion or SC injection to the patient by authorized Investigator staff at each visit specified in the Assessment schedule.

The first dose of CFZ533 (30 mg/kg) will be administered intravenously pre- or intra-operatively and must be completed within one hour of unclamping and before graft revascularization. If administered pre-operatively this should be done no longer than 4 hours prior to surgery.

The study medication preparation and administration guidelines are described in a separate pharmacy manual. The patient will be weighed at the Baseline visit and preferably the baseline weight value will be used for the initial study medication preparation and the calculation of the dose. If screening is less than 2 weeks prior to Day 1, screening weight may also be used.

The second dose of CFZ533 15 mg/kg will be administered IV on Day 5. Preferably, most recent actual weight will serve as basis for the second IV dose calculation.

A variation of the total administered amount of CFZ533 on Day 1 or Day 5 of up to +/- 10% from the calculated dose (e.g., due to the fluctuation of body weight or due to rounding of the final required volume) is acceptable.

Patients randomized to **Arm 1** will receive maintenance doses every 2 weeks as 2 SC injections of 2 mL of CFZ533 at 150 mg/mL (4 CFZ533 vials, 1 mL each, or after completion of Month 12 visit assessments, 2 CFZ533 PFS 300 mg/2 mL), in combination with MMF and corticosteroids.

Patients randomized to **Arm 2** will receive every 2 weeks 1 SC injection of 2 mL of CFZ533 at 150 mg/mL (2 CFZ533 vials, 1 mL each, or after completion of Month 12 visit assessments - 1 CFZ533 PFS 300mg/2mL), and 1 SC injection of 2 mL generic placebo (2 placebo vials, 1 mL each, or after completion of Month 12 visit assessments - 1 Placebo PFS 2 mL), in combination

[redacted]

with MMF and corticosteroids. After completion of the primary endpoint analysis at Month 12, placebo PFS will be removed.

When administering CFZ533 the injection site must be rotated each time to keep the skin healthy and both syringes should never be applied at the same injection site. For detailed instruction see Appendix 6.

Starting at Month 3.5, the patient may be offered the option for CFZ533 in-home administration (at protocol specified time points, see Table 6-1), supported by a home health care provider or to continue with administration at the site.

Starting after the Month 12 visit assessments, CFZ533 SC dosing using PFS will be administered once available by authorized patients/ their caregivers at home or by the investigator/delegated site staff at site. The Investigator should promote compliance by instructing the patient to take the study drug exactly as prescribed and highlight that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the Investigator if they are unable for any reason to take the study drug as prescribed.

Administration of CFZ533 should occur after sample collection for PK assessments at visits specified in Table 6-1 (see Section 6.6.1).

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

All dosages prescribed and dispensed to the patients during the study must be recorded on the appropriate CRF.

Table 5-1 CFZ533 liquid in vial (LIVI) treatment until Month 12 in Cohort 1:

Treatment Arm	Active kit	Placebo kit	Comment
CFZ533 600 mg q2w	Two kits of: 2 x CFZ533 150mg/1mL vials	NA	Appropriately blinded kits
CFZ533 300 mg q2w	One kit of: 2x CFZ533 150mg/1mL vials	One kit of: 2x CFZ533 Placebo 1mL vials	Appropriately blinded kits

Table 5-2 CFZ533 prefilled syringe (PFS) treatment after Month 12 in Cohort 1:

Treatment Arm	IMP kit	Comment
CFZ533 600mg q2w	2x CFZ533 300mg/2mL PFS	Appropriately blinded kit - each kit contains 2 PFS which are bandrolled to constitute 1 kit for dispensation
CFZ533 300mg q2w	1x CFZ533 300mg/2mL PFS + 1x CFZ533 Placebo 2mL PFS	Appropriately blinded kit - each kit contains 2 PFS which are bandrolled to constitute 1 kit for dispensation

After the unblinding of the study, placebo PFS will be removed and all patients will receive open-label PFS supplies.

The last dispensing visit for CFZ533 in the trial for every patient occurs at Month 59.5.

[redacted]

MMF administration – All arms

Mycophenolate mofetil will be given as tablets of 500 mg or capsules of 250 mg b.i.d. For *de novo* transplant patients who remain intubated >24 hours post-transplant and/or who are otherwise unable to swallow oral medication, IV MMF may be substituted until oral conversion is possible.

The first dose of MMF may be administered prior to surgery or immediately after randomization and no later than 24 hours after graft reperfusion.

All MMF doses and changes must be recorded on the appropriate CRF.

Dose adjustment/interruption guidance for MMF is provided in Section 5.5.5.

Tacrolimus administration – Arm 3

After transplantation, all patients randomized in Control Arm 3 will receive TAC, in combination with MMF and corticosteroids which should be initiated no later than 24 hours post transplantation. Initiating TAC before transplantation is permitted.

TAC will be administered as p.o. capsules b.i.d. according to local label.

Every effort should be made to keep the patients within target trough levels as per local label. TAC dose adjustments will be based on local laboratory trough level results.

In case a patient temporarily cannot take oral TAC (e.g., in case of a surgical intervention), TAC intravenous administration is allowed as per local practice. TAC granules for oral suspension are also allowed to be used for patients who cannot swallow tablets.

In the event of TAC intolerance, dose reduction of TAC may be necessary. If this occurs, the change in TAC regimen should be recorded on the appropriate CRF.

Dose adjustment/interruption guidance for TAC is provided in Section 5.5.5.

TAC dosing will be recorded on the appropriate CRF at each visit.

Corticosteroids administration – All arms

Corticosteroids will be administered with dosing according to local standard practice in a way that is consistent across all patients enrolled at each site. Corticosteroids may be tapered off, as per local standard practice and investigator discretion, only after 12 months of treatment. Corticosteroids doses should be recorded on the appropriate CRF.

Induction therapy – All arms

Basiliximab

Patients will receive 2 x 20 mg doses of basiliximab administered IV. The first dose should be given within 2 hours prior to transplant surgery, and the second dose should be administered 4 days post-transplant. The second dose should be withheld if complications such as severe hypersensitivity reaction to basiliximab or graft loss occur.

All basiliximab doses (2 doses) and changes must be recorded on the appropriate CRF under the Immunosuppressive category.

[redacted]

Rabbit anti-thymocyte globulin (rATG) induction therapy

Thymoglobuline, used for antibody induction therapy should be administered on the day of transplantation.

Thymoglobuline should be given at 1 to 1.5 mg/kg/day as per approved local labeling. This dosing guidance is for Thymoglobuline, where other rATG products are used, usage should be consistent with local practice and approved labeling.

Close attention should be paid to hematological parameters (e.g., lymphocytes, WBC and platelets) when administering rATG. Refer to manufacturer's product labeling for additional safety information.

Dosing of rATG should be recorded on the appropriate CRF under the Immunosuppressive category.

5.5.4.2 Cohort 2 – maintenance patients

CFZ533 administration – Arm 1

CFZ533 will be administered by IV infusion or SC injection to the patient by authorized Investigator staff at each visit specified in the Assessment schedule.

The first dose of CFZ533 30 mg/kg will be administered IV on Day 1. The patient will be weighed at the Baseline visit and preferably the baseline weight value will be used for the initial study medication preparation and the calculation of the dose. If screening is less than 2 weeks prior to Day 1, screening weight may also be used.

A variation of dose (e.g., due to rounding of the final required volume and body weight fluctuation) of up to +/- 10% on Day 1 will be acceptable.

Patients randomized to Arm 1 will receive maintenance doses every 2 weeks as 1 SC injection of 2 mL + 1 SC injection of 1 mL CFZ533 at 150 mg/mL (3 CFZ533 vials, 1 mL each, or after completion of Month 12 visit assessments, 1 CFZ533 PFS 300 mg/2mL and 1 CFZ533 PFS 150mg/1mL), in combination with MMF/EC-MPS with or without corticosteroids.

Starting at Month 3.5, the patient may be offered the option for CFZ533 home administration (at protocol specified time points, see Table 6-1), supported by a home health care provider.

Starting after the Month 12 visit assessments, CFZ533 SC dosing using PFS will be administered by authorized patients/ their caregivers at home or by the investigator/delegated site staff at the site. The Investigator should promote compliance by instructing the patient to take the study drug exactly as prescribed and highlight that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if they are unable for any reason to take the study drug as prescribed.

Administration of CFZ533 should occur after sample collection for PK assessments at visits specified in Table 6-1.

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

All dosages prescribed and dispensed to the patients during the study must be recorded on the appropriate CRF.

[redacted]

Table 5-3 CFZ533 liquid in vial (LIVI) treatment until Month 12 in Cohort 2:

Treatment arm	Active kit	Placebo kit	Comment
CFZ533 450mg q2w	Three vials of:CFZ533 150mg/1mL	NA	Open-label kits

Table 5-4 CFZ533 prefilled syringe (PFS) treatment after Month 12 in Cohort 2:

Treatment Arm	Active kit	Comment
CFZ533 450mg q2w	1x CFZ533 300mg/2mL PFS + 1x CFZ533 150mg/1mL PFS	Open-label kit – each kit contains 2 PFS which are bandrolled to constitute 1 kit for dispensation

The last dispensing visit for CFZ533 in the trial for every patient occurs at Month 59.5.

Tacrolimus administration

Arm 1

On Day 1, patients randomized to Arm 1 will be administered 50% of the current TAC dose, concomitantly with the first dose of CFZ533 30 mg/kg IV and with MMF/EC-MPS. At Day 15, TAC dose will be reduced by a further 50%. By Day 29, patients will be fully tapered off their TAC.

Arm 2

Patients randomized in Control Arm 2 will continue to receive the same TAC dose as before entering the trial.

If patients were receiving once daily TAC formulations (Advagraf, Envarsus, etc.), they are permitted to remain and continue on their current regimen.

All TAC doses and changes must be recorded on the appropriate CRF.

MMF/EC-MPS administration – Arms 1 and 2

Patients must continue to take MMF/ EC-MPS as part of the regimen they were taking prior enrollment. It will continue to be administered daily, up to Month 60, and according to local standard practice.

All MMF/EC-MPS doses and changes must be recorded on the appropriate CRF.

Dose adjustment/interruption guidance for MMF/EC-MPS is provided in Section 5.5.5.

Corticosteroids administration Arms 1 and 2

In case corticosteroids were part of the immunosuppressive regimen the patient was taking prior enrollment, they will continue to be administered. Corticosteroids may be tapered off, as per local standard practice and investigator's discretion, only after 12 months of treatment.

Corticosteroids doses should in that case be recorded on the appropriate CRF.

The investigator must promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient must also be instructed to contact the investigator if he/she is unable for any reason to take any of the study medications.

[redacted]

5.5.5 Permitted dose adjustments and interruptions of study treatment

CFZ533

During the first 12 months of treatment period, only 1 dose of CFZ533 can be missed. In case more than one dose of CFZ533 is missed during the first 12 Months in the study, the investigator should contact the Sponsor immediately to discuss if the patient can remain on treatment or be permanently discontinued from randomized study treatment and managed as per local practice.

After 12 months, 1 omitted dose within a 3-month period is allowed. The investigator will contact the Novartis team if more than 1 dose in 3 months is missed to discuss further management of this patient.

In case of medical or operational need, CFZ533 SC administration may be delayed by a maximum of 7 days. The subsequent dose must be administered as per original schedule (not recalculated from the time of the last delayed dosing).

CFZ533 dose adjustments are not permitted except when IV immunoglobulin (IV-Ig) is used to treat Antibody Mediated Rejections (ABMR) and BK virus infection.

Tacrolimus

For control patients who are unable to tolerate the protocol-specified dosing scheme, dose adjustments and temporary interruptions of TAC are permitted in order to keep the patient on study drug. Temporary interruptions of TAC should not exceed 21 consecutive days.

If TAC is discontinued for more than 21 consecutive days, and the study regimen cannot be maintained, the patient must be permanently discontinued from the randomized regimen and managed per local practice.

MMF (Cohort-1)

For both CFZ533 and Control patients who are unable to tolerate the protocol-specified dosing scheme of MMF, dose adjustments and interruptions of MMF are permitted in order to keep the patient on study drug. The following guidelines must be followed:

-In the event of MMF intolerance (e.g., gastrointestinal disorders, bronchiectasis, leucopenia), temporary dose adjustment or interruption may be necessary. It is recommended to reduce the actual dose by 50%, for approximately 15 consecutive days.

-In case of persistent intolerance, MMF can be discontinued and patient may be switched to other mycophenolates formulations (e.g., Myfortic® mycophenolic acid) and remain in the study on randomized study treatment. Alternatively, MMF may be discontinued completely and patients may remain in the study on randomized study treatment.

EC-MPS (Cohort 2 only)

For both CFZ533 and Control patients who are unable to tolerate the protocol-specified dosing scheme of EC-MPS, dose adjustments and interruptions of EC-MPS are permitted in order to keep the patient on study drug. The following guidelines must be followed:

-In the event of EC-MPS intolerance (e.g., gastrointestinal disorders, bronchiectasis, leucopenia), temporary dose adjustment or interruption may be necessary. It is recommended to reduce the actual dose by 50%, for approximately 15 consecutive days.

[redacted]

-Alternatively, EC-MPS may be discontinued completely and patients may remain in the study on randomized study treatment.

Management of signs of over-immunosuppression

In case of suspected over-immunosuppression, reducing the CFZ533 dose is not permitted, since under-dosing of CFZ533 may trigger loss of immunosuppression. It is recommended to reduce the MMF/EC-MPS dose by 50 % or more

If there still are signs of over-immunosuppression, MMF/EC-MPS may be permanently discontinued and/or corticosteroids dosage reduced. Corticosteroids can be completely tapered off only after Month 12.

Patients on CFZ533 with signs of over-immunosuppression, or who have side effects of MMF/ EC-MPS, may continue on their randomized regimen without MMF/EC-MPS therapy, as per PI discretion.

In case of persistent signs of over-immunosuppression despite MMF /EC-MPS discontinuation, or if the symptoms are severe, patient should be discontinued from CFZ533 and switched to SoC.

For patients randomized to TAC, the management of over-immunosuppression should firstly start with a reduction of MMF/EC-MPS dose by 50% or more and secondly if further reduction of immunosuppression is required, TAC reduction as per local practice.

All immunosuppressive therapy administered post discontinuation of study regimen should be recorded on the appropriate CRF.

5.5.5.1 Treatment of Acute Rejection Episodes/Biopsy proven acute reaction (BPAR)

In all suspected acute rejection episodes, regardless of initiation of anti-rejection treatment, an allograft biopsy must be performed **preferably** within 24 hours, latest within 48 hours. Whenever possible, anti-rejection therapy should be postponed until a histological diagnosis of rejection is confirmed. These biopsies will be read by the local pathologist as well as a central reader, and the histological lesions will be graded according to the updated 2017 Banff criteria (Appendix 2). Determination of the need for treatment will be according to the local pathologist's findings and the investigator judgment.

All episodes of acute rejection should be treated as per local practice, for example bolus steroids, increased dose of oral steroids or TAC (for Control patients) as first line and anti-T-cell antibody for steroid-resistant rejection. Although there is no consensus to treat borderline rejections, 5-year follow-up data shows that treatment of borderline rejection did not significantly affect progression to death, graft loss or acute rejection (Wilson et al 2019). Therefore, a benefit-risk assessment of treating patients for borderline rejection must be made on a case-by-case basis. Prior to discontinuing a patient for borderline rejection, a discussion with the Novartis unblinded clinical team is encouraged.

Recommended treatment with bolus methylprednisolone is with at least 3 boluses of IV methylprednisolone with a minimal dose of 250 mg/bolus or at least 2 boluses of IV methylprednisolone with a minimal total dose of 750 mg followed by 7 days taper, especially

[redacted]

for treatment of Banff 1a/1b. Other anti-rejection therapies (i.e., antibody therapy with rATG) should only be used in cases of steroid resistant rejections, vascular rejections or rejections with a Banff grade ≥ 2a.

Patients experiencing a BPAR should be treated in a consistent manner, for all patients in the treatment arms and cohorts.

The specific anti-rejection treatment must be recorded on the appropriate CRF; steroids and anti-T-cell antibody treatment (e.g., rATG) will be recorded on the corresponding concomitant medications page under the immunosuppressive category whereas anti-rejection increases of TAC will be recorded on the corresponding dose administration record.

Patients requiring cyclosporine, or azathioprine or TAC (if the patient is on a CFZ533 arm) or any other agents for anti-rejection treatment with the exception of rATG will be discontinued from the randomized study regimen, but followed until the end of the current 12 month treatment period, i.e., attend the next 2 scheduled visits per the assessment schedule (Table 6-1). Any patient requiring anti-Tcell antibody therapy for rejection should be discontinued from CFZ533 and should continue in the study follow-up on standard of care immunosuppression.

The CFZ533 dose will not be modified; no extra dosing will be administered due to the occurrence of a rejection episode, with the exception of antibody mediated rejections treated with IV-Ig.

Handling of biopsies is addressed in a separate manual. All episodes of acute rejection must be entered on the corresponding eCRF (e.g., Acute Rejection page, Kidney Allograft Biopsy page) preferably within 24 hours.

Treating antibody mediated rejections (ABMR)

In case of unsuccessful treatment with corticosteroids or rATG, patient may be treated with IV immunoglobulin (IV-Ig). To compensate for the loss of CFZ533 due to accelerated elimination of CFZ533 after IV-Ig, additional doses of CFZ533 SC will be administered to the patient in order to maintain CFZ533 plasma concentration within target ranges as per Table 5-5.

As it is not possible to propose a CFZ533 extra dose(s) dosing strategy that matches every possible IV-Ig application in clinical practice, we would recommend the following:

- The cumulative IV-Ig dose should be approximately 2 g/kg (maximum), split in 2 to 3 administrations (maximum) over 1 or 2 weeks (maximum)
- Every effort should be made to align the IV-Ig infusions with a planned per protocol dosing visit (Q2W regimen). If not possible, an unscheduled visit may be scheduled.
- Prior to the IV-Ig infusion(s) a pharmacokinetic blood sample will be taken to assess the CFZ533 concentration in plasma (visit x).
- PK and PD samples should also be collected at the next scheduled visit after IV-Ig infusion (visit x+1) before the next administration of CFZ533.

The extra doses administered correspond to the randomized CFZ533 dose.

[redacted]

Table 5-5 Administration schedule for extra subcutaneous dose(s) of CFZ533 due to IV-Ig administration

Applicable for all CFZ533 arms in Cohort 1 and Cohort 2	**Timing of IV-Ig relative to closest planned dosing visit**	**Planned and extra doses of CFZ533 to be administered on the day of IV-Ig[a] and/or at next per protocol planned dosing visit** **Route: SC**
IV-Ig administration occurring post-transplant/Day 1 and up to Month 1 (Day 29 included) **<u>General rule</u>:** **3 extra doses of CFZ533 SC**	IV-Ig administered **at** a scheduled dosing Visit x	• **Day of IV-Ig[a] = Visit x** [b]: 1 scheduled dose + 2 extra doses after IV-Ig administration • **Visit (x + 1)** [b]: 1 scheduled dose + 1 extra dose
	IV-Ig administered **at unscheduled visit** within **1 week FOLLOWING** a scheduled dosing Visit x	• **Day of IV-Ig[a]** [b]: 2 extra doses after IV-Ig administration • **Visit (x + 1)** [b]: 1 scheduled dose + 1 extra dose
	IV-Ig administered (**at unscheduled visit**) Within 1 week **PRIOR** a scheduled dosing Visit x	• **Day of IV-Ig[a]** [b]: 2 extra doses after IV-Ig administration • **Visit x**: 1 scheduled dose (no extra dose) • **Visit (x + 1)** [b]: 1 scheduled dose + 1 extra dose
IV-Ig administration occurring after Month 1 (Day 29) and up to Month 2 (Day 57 included) **<u>General rule</u>:** **2 extra doses of CFZ533 SC**	IV-Ig administered **at a scheduled dosing visit**	• **Day of IV-Ig[a]** [b]: 1 scheduled dose + 2 extra doses after IV-Ig administration
	IV-Ig administered **at an unscheduled visit**	• **Day of IV-Ig[a,]** [b]: 2 extra doses after IV-Ig administration
IV-Ig administration occurring after Month 2 (Day 57) **<u>General rule</u>:** **1 extra dose of CFZ533 SC**	IV-Ig administered **at a scheduled dosing visit**	• **Day of IV-Ig[a,]** [b]: 1 scheduled dose + 1 extra dose after IV-Ig administration
	IV-Ig administered **at an unscheduled visit**	• **Day of IV-Ig[a]**: 1 extra dose after IV-Ig administration

[a] The 'Day of IV-Ig' is defined as the **first day** corresponding to the administration of a cumulative IV-Ig dose of approximately 2 g/kg (max.)

[b] Patients weighing <50 kg who receive additional CFZ533 compensatory doses on the same day should receive these at least 1 h apart.

In case treatment with plasmapheresis is required, patient should be discontinued from CFZ533 and switched to SoC.

[redacted]

5.5.5.2 Treatment of Delayed Graft Function (DGF)

In case of DGF, treatment will be according to local practice, but the randomized study regimen cannot be interrupted for more than 2 weeks for CFZ533 (i.e., one SC dose) and 21 consecutive days for TAC and MMF (see Section 5.5.5 for more details).

If a patient with DGF is not able to return to or maintain their randomized study regimen as per protocol, the patient should be discontinued from the study. If a patient is placed on permanent dialysis (or re-transplanted) the Graft Loss, and Adverse Event CRFs should be completed, as well as an SAE report of Graft Loss submitted.

Dialysis treatments should be recorded on the appropriate CRF. Re-transplantation should be recorded under the surgical and medical procedures on the appropriate CRF.

5.5.6 Rescue medication

Not applicable.

5.5.7 Concomitant medication

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the appropriate CRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started.

CMV prophylaxis

Cytomegalovirus (CMV) pre-emptive therapy and/or prophylaxis is recommended for all donor CMV positive/recipient CMV negative cases and considered for all recipients who are CMV positive. It is highly recommended to follow the guideline of the American Society of Transplantation Infectious Diseases Community of Practice to treat cytomegalovirus in solid organ transplant recipients (Razonable and Humar 2019). Such prophylaxis should be recorded on the appropriate CRF.

Hepatitis B Virus (HBV) prophylaxis

Prophylaxis for recurrent hepatitis B during the course of this study is allowed and will be administered at the discretion of the Investigator. Prophylaxis should be recorded on the appropriate CRF.

BK virus

Patients with BK viremia or viruria should be treated according to local practice. If treatment is given it should be recorded on the appropriate CRF.

In case a patient is treated with IV-Ig, additional doses of CFZ533 SC will be administered immediately following IV-Ig. Refer to Table 5-5 Administration schedule for extra subcutaneous dose(s) of CFZ533 due to IV-Ig administration for further guidance.

[redacted]

Treatment guideline for BK viremia from the American Society of Transplantation Infectious Diseases Community of Practice (Hirsch and Randhawa 2019) recommend doing a benefit-risk assessment in the individual patient and using stepwise immunosuppression reduction for kidney transplant patients with plasma BKV DNAemia of >1000 copies/mL sustained for 3 weeks or increasing to >10 000 copies/mL reflecting probable and presumptive BKV associated nephropathy, respectively. Reducing immunosuppression is the primary recommended intervention for patients with biopsy proven BKV associated nephropathy. Return to routine maintenance immunosuppression after successful clearance of BKV DNAemia should be considered under careful monitoring plasma viral loads to counteract rejection.

Consistent with the above, immunosuppressives can be adjusted as follows for patients with BK viremia ongoing in the trial:

For patients treated with CFZ533:

It is recommended to keep the patient on the current CFZ533 dosage. MMF/EC-MPS can be discontinued and may be done so permanently if deemed necessary. Corticosteroid dosages can be adjusted but can be completely tapered off only after Month 12.

For patients treated with TAC:

It is recommended to avoid high concentrations of TAC and consider reducing the MMF/EC-MPS dose by 50% for approximately 4 weeks and thereafter check the BK viremia again. If no improvement, everolimus can be introduced after discontinuation of the randomized treatment.

COVID-19

The epidemiology of COVID-19 is continuously evolving, and currently, there are no universally agreed treatment protocols for patients with SARS-CoV-2 infections. The investigator should use clinical judgement and adhere to local policies for testing and treatment of coronavirus infections.

Oral Candida treatment

For oral thrush (Candida), Nystatin may be used in a swish and swallow regimen; alternatively, clotrimazole (Mycelex®) lozenges/troches may be used. Systemic therapy is to be based on center practice and at the Investigator's discretion. Treatment should be recorded on the appropriate CRF.

Pneumocystis jirovecii (Pneumocystis carinii) pneumonia (PCP) prophylaxis

All patients should be treated according to local practice, as part of standard of care practice for transplanted patients. If treatment is given it should be recorded on the appropriate CRF.

5.5.8 Vaccination

For subjects participating in clinical studies, all vaccinations at time of randomization should be up to date based on most recent local Guidelines.

Vaccination of subjects during treatment with CFZ533 and prior to clearance of the antibody from the tissues is likely to result in therapeutic failure (i.e., non-protective antibody titers) due

[redacted]

to the pharmacologic activity of CFZ533. Administration of live attenuated vaccines should be avoided while receiving CFZ533 treatment and for at least 14 weeks thereafter, depending on the dose and time for reconstitution of humoral immune function. Based on predicted median plasma concentration-time profile at the highest investigated dose regimen (600 mg SC bi-weekly), at least 14 weeks are needed after the last dose to drop CFZ533 plasma concentration below 20 µg/mL with no expected pharmacodynamic activity in target tissues (e.g., germinal centers) (refer to CFZ533 IB).

5.5.9 Prohibited medication

Use of the treatments displayed in Table 5-6 is NOT allowed in order to avoid potential confounding factors or interaction with investigational or control treatment medication.

Immunosuppressants other than those specified in the protocol are NOT allowed after informed consent up to the end of study. If the use of any non -protocol immunosuppressants is discovered prior to randomization, the patient must not be randomized and will be recorded as a screen failure. If discovered after randomization, no further doses of non-protocol immunosuppressants are to be given, and the patient should continue on the study treatment regimen, noting the protocol deviation.

These non-protocol immunosuppressants are allowed for those patients in follow up who discontinued from the randomized study treatment and switched to standard of care treatment as per local practice.

Table 5-6 Prohibited medication

Treatment group	Medication	Action to be taken
All	Azathioprine, sirolimus, Everolimus, Once a day TAC formulations in Cohort 1 only (e.g., Advagraf, Envarsus), belatacept, EC-MPS (e.g., Myfortic)*, cyclosporine, alemtuzumab, Rituximab, Induction treatment with any antibody (except rATG and basiliximab), complement inhibitors, proteasome inhibitors, live vaccines	Discontinue the prohibited medication immediately Keep the patient in the study Report the protocol deviation

* With the exception of patients in Cohort 2 and in case of persistent MMF intolerance in Cohort 1, patients are permitted to switch to EC-MPS (e.g., Myfortic®) and remain in the study on their randomized study treatment.

5.5.10 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the

[redacted]

requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name
- patient number

In addition, oral and written information to the patient must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that unblinding can be performed at any time.

If study drug discontinuation occurs because of treatment unblinding, it does not require the patient to be discontinued from the study and all ongoing visit assessments. Refer to Section 6 for the visit schedule and assessments.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol i.e., last patient last visit at Month 60.

Information on the patient's completion or discontinuation of the study and the reason for discontinuation of the study will be recorded on the appropriate CRF.

In any case, the investigator or site staff must contact the IRT as soon as possible to record the subject's study completion (Month 60) and/or discontinuation.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care. This care may include initiating another immunosuppressive treatment outside of the study as deemed appropriate by the investigator.

Initiation of another immunosuppressive treatment will be required for all patients randomized to the CFZ533 arms. In case a CFZ533 patient is switched to a TAC-based regimen, TAC should be initiated at the lowest daily dose, e.g., 0.5 mg b.i.d., starting 4 weeks after last CFZ533 administration. TAC trough levels will be measured 2 weeks after TAC initiation and dosage appropriately adjusted to reach and maintain a trough level at approximately 5 ng/mL.

For all patients, a safety follow-up should be conducted (e.g., by telephone) 12 weeks after last visit (Month 60). The information to be collected at this follow up visit includes any serious adverse events, pregnancy, and patient and graft survival status.

[redacted]

5.6.2 Discontinuation of study treatment

5.6.2.1 Study treatment and study discontinuation

Possible reasons for study treatment discontinuation are:

- Adverse Event
- Lack of efficacy
- Technical problems
- Patient/Guardian Decision
- Lost to follow-up
- Death
- Graft Loss
- Pregnancy
- Treatment unblinding
- Received CFZ533 and transplant not performed
- For patients already enrolled at the time protocol amendment v01 is introduced: Patient unwilling to continue in study until Month 60. In this case patient will remain on study treatment until Month 12 and complete assessments as per protocol amendment v01, after which they will be discontinued from the study.

The investigator should discontinue a patient from their randomized treatment regimen if, on balance, he/she believes that continuation would be detrimental to the patient's well-being. The Dosage administration records for CFZ533, MMF/EC-MPS and TAC will be used to record when a patient has discontinued study treatment. Appropriate CRF for treatment and/ or study disposition should also be completed, giving the date and primary reason for stopping study treatment or the study.

Patients who discontinue CFZ533 regimen should not initiate a new immunosuppressive treatment as per SoC prior to 4 weeks after the last dose of CFZ533 to avoid the risk of over-immunosuppression.

Discontinuation prior to Month 12

Patients who discontinue study treatment prior to Month 12 should NOT be considered withdrawn from the study. At the time of treatment discontinuation, patients will complete the end of study (EOS) visit and patient status will remain as 'subject continuing' in subject status form, located in the EOS visit, in Rave EDC. They should remain in study on local standard of care. Patients will come to the clinical sites for 2 Follow-up visits (FU-1 and FU-2) after discontinuation from randomized treatment. Patients who are discontinued from treatment prior to Month 6 should return to site for their scheduled Months 6 and 12 visits to obtain follow-up information. Patients who are discontinued from treatment between Months 6 and 12 should return to site for their scheduled Month 12 (FU-1) and Month 18 (FU-2) visits to obtain follow-up information. Information will be collected on graft loss/re-transplant, rejection episodes, vital signs, hospitalizations, central lab samples (proteinuria and serum creatinine), AEs/SAEs, concomitant medications, malignancies, opportunistic infections (especially CMV, BKV and EBV), DSA (at Month 12 only) and immunosuppressive therapy.

[redacted]

A Month 12 biopsy should be done in all patients who discontinued the study as follows :

- If premature study drug discontinuation occurs between Day 1 and Month 11, a biopsy should be collected at Month 12 (FU-1 or FU-2).
- If discontinuation occurs between Month 11 and Month 15 visits, a biopsy should be collected at time of discontinuation. If biopsy was collected at Month 12, no additional biopsy collection is required (please also see Table 6-3 for full details).

After completion of follow-up visits (FU-1 and FU-2), patients will be contacted by the investigator every 6 months (at Month 18, 24, 30, 36, 42, 48, 54 and 60) for follow-up phone calls to determine their survival status, potential graft loss, changes in immunosuppressive treatment and SAE related to study treatment.

Discontinuation following Month 12

Patients who discontinue treatment following Month 12, will complete the EOS visit at time of treatment discontinuation and patient status will remain as 'subject continuing' in subject status form, located in the EOS visit, in Rave EDC. Patient should remain in the study on local standard of care. All patients who discontinue the study medication after the 12 months treatment period should return for the two on-site follow up visits. The first follow-up visit will be the following 6 monthly visit (Month 18, 24, 30, 36, 42, 48 or 54). The next visit will be 6 months following this visit. For example: when discontinuation occurs after Month 12, patient shall return for Month 18 and Month 24 follow-up visits or, if discontinuation occurs after Month 22 , patient shall return for Month 24 and Month 30 follow-up visits and so forth. Finally, if discontinuation occurs after Month 54, patient shall return for Month 60 follow-up visit to obtain the follow-up information outlined in Table 6-3. After completion of follow-up visits (FU-1 and FU-2), patients will be contacted every 6 months (at Month 18, 24, 30, 36, 42, 48, 54 and 60) for follow-up phone calls to determine their survival status, potential graft loss, changes in immunosuppressive treatment and SAE related to study treatment.

If patients refuse to return for the on site follow-up visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the information on survival status, graft loss/re-transplant, rejection episodes, malignancies, opportunistic infections, and immunosuppressive therapies. Since patients will be followed even after discontinuation of study medication, the appropriate CRF for Study Completion should only be completed at month 60 or earlier if the patient can no longer be followed, e.g., death, lost to follow-up, withdrawal of consent.

No study drug will be provided for patients who discontinue study treatment.

If study drug discontinuation occurs because of treatment unblinding, it does not require the patient to be discontinued from the study and all ongoing visit assessments. Refer to Section 6 for the visit schedule and assessments.

Patients who become pregnant while in the study must be discontinued from the study medication and from the study.

If transplantation is not performed after the administration of a single IV CFZ533 loading dose, patient will be discontinued from the study. A safety follow-up should be conducted (e.g., by

[redacted]

telephone) up to 20 weeks after single IV CFZ533 administration. The information to be collected at this follow up includes any serious adverse events, including infections.

5.6.2.2 Study "Stopping rules"

Following a review of the AE(s), a decision to either hold or permanently discontinue enrollment in a CFZ533 study arm will be made by the Sponsor.

The stopping rules apply until enrollment is completed. With amendment 04 the enrollment is considered complete therefore the stopping rule evaluation will no longer be applicable to define further enrollment. Patient safety will continue to be monitored by the DMC throughout the duration of the trial.

5.6.2.2.1 Stopping rules applicable for the CFZ533 arms in the *de novo* cohort (Cohort 1):

1. Three (3) patients experiencing PTLD **OR**
2. Two (2) patients with PML **OR**
3. Serious* infection proportion greater than 30% with a probability > 90% **OR**
4. Proportion of BPAR with Banff ≥1B or ABMR greater than 30% with a probability > 90%.

* SAEs reported due to any hospitalization related to pre-emptive treatment for asymptomatic viral loads (e.g., CMV, BKV, EBV) will be excluded from the stopping rule analysis.

BPAR rates are based on adjudicated biopsy readings and not biopsy readings by local pathologist. Based on these stopping rules, a table containing the maximum number of patients with BPAR with Banff ≥1B and the maximum number of patients with serious infections for various different illustrative sample sizes can be found in the Appendix 3. The stopping rules 3 and 4 above should be applied to a treatment arm only after at least 10 patients are enrolled in that arm.

5.6.2.2.2 Stopping rules applicable for the CFZ533 arm in the maintenance cohort (Cohort 2):

If the BPAR rejection proportion with a BANFF ≥ 1B or ABMR exceeds 30% with a probability >90%.

BPAR rates are based on adjudicated biopsy readings and not biopsy readings by local pathologist. Based on this stopping rule, the maximum number of patients with BPAR for various different illustrative sample sizes is provided in Appendix 3 based on a non-informative prior (beta distribution). The stopping rule above should be applied to a treatment arm only after at least 10 patients are enrolled in that arm.

5.6.3 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

[redacted]

In this situation, the investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment Table 6-1 and Table 6-2.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a patient's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the ICF.

For EU and rest of world: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

5.6.4 Loss to follow-up

For patients whose status is unclear because they fail to appear for study visits or are not reachable for phone visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her planned end of study visit has passed.

5.6.5 Replacement of early withdrawals or discontinuations

Patients who are prematurely withdrawn from study medication or from the study will not be replaced. These patients will NOT be considered lost to follow-up.

Patients who are randomized and not treated for any reason will be replaced.

5.6.6 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit-risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrollment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely discontinued patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

[redacted]

6 Visit schedule and assessments

Table 6-1 and Table 6-2 list all of the assessments and indicates with an 'X' when the visits are performed at site. An 'S' indicates the data for the assessment which are recorded in the source documents at the site. An 'x' indicates study drug dosing which may be performed at an optional in-home visit or self administration at home of PFS post Month 12 visit assessments.

If a Public Health emergency limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Phone calls or visits by site staff/home nursing service to the patient´s home depending on local regulations and capabilities, can replace on-site study visits, for the duration of the pandemic until it is safe for the patient to visit the site again.

In case of premature treatment discontinuation

At the time of premature treatment discontinuation, patients will complete the end of study (EOS) visit and patient status will remain as 'subject continuing' in subject status form, located in the EOS visit, in Rave EDC. They should remain in study on local standard of care. Patients will come to the clinical sites for 2 Follow-up visits (FU-1 and FU-2) after discontinuation from randomized treatment. Patients who are discontinued from treatment prior to Month 6 should return to site for their scheduled Months 6 and 12 visits to obtain follow-up information. Patients who are discontinued from treatment between Months 6 and 12 should return to site for their scheduled Month 12 (FU-1) and Month 18 (FU-2) visits to obtain follow-up information as outlined in Section 5.6.2.1. Visits and assessments are detailed in the assessment Table 6-3. If they refuse to return for these assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the patient and graft status.

Patients who discontinue treatment following Month 12, will complete the EOS visit at time of treatment discontinuation and patient status will remain as 'subject continuing' in subject status form, located in the EOS visit, in Rave EDC. Patient should remain in the study on local standard of care. All patients who discontinue the study medication after the 12 months treatment period should return for the two follow up visits. The first follow-up visit will be the following 6 monthly visit (Month 18, 24, 30, 36, 42, 48 or 52). The next visit will be 6 months following this visit. For example: if discontinuation occurs after Month 12, patient shall return for Month 18 and Month 24 follow-up visits. If discontinuation occurs after Month 22, patient shall return for Month 24 and Month 30 follow-up visits and so forth. Finally, if discontinuation occurs after Month 54, patient shall return for Month 60 follow-up visit to obtain the follow-up information as outlined in Section 5.6.2.1. Visits and assessments are detailed in the assessment Table 6-3.

After completion of follow-up visits (FU-1 and FU-2), all patients will be contacted every 6 months (at Months 18, 24, 30, 36, 42, 48, 54 and 60) for follow-up phone calls to determine their survival status, potential graft loss, changes in immunosuppressive treatment and SAE related to study treatment.

[redacted]

Assessment schedule

Every effort will be made to take the PK sample at the protocol specified time. Other assessments (e.g., ECG, vital signs) will be taken prior to or after the PK sample.

ECGs must be recorded after 5 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is: ECG collection first, followed by vital signs, and blood sampling.

At Month 60 visit (last study visit), patients will be initiated on a local standard of care treatment. At a minimum, patients will be contacted for safety evaluations (e.g., SAEs) up to 12 weeks after this last visit. Documentation of attempts to contact the patient should be recorded in the source documentation.

A Study Month is defined as 28 calendar days.

In case the investigator deems an unscheduled visit necessary, some or all of the following assessments may be conducted: vital signs, ECGs, safety lab samples, DSA and collection of PK/immunogenicity/PD samples.

[redacted]

Table 6-1 Assessment schedule – Cohort 1

Assessment schedule – Cohort 1: Screening to Month 5

Period	**Screening** (3)	**Baseline** (4)	**Treatment Cohort 1**															
Month		**1**								**1.5**	**2**	**2.5**	**3**	**3.5**	**4**	**4.5**	**5**	
Day	**D-28 to 1**	**BL/D1**	**D1**			**5 (± 24 hours)**			**15 (± 24 hours)**	**29**								
Hour (h)			**Pre**	**0**	**EOI +1h**	**Pre**	**0**	**EOI + 1h**										
Visit for TAC patients	Y	Y	Y	Y					Y	Y		Y		Y		Y		
Demography	X																	
Inclusion / Exclusion criteria	X#	X#																
Informed Consent (1)	X																	
Kidney transplant background recipient/donor		X																
Kidney transplant procedure		X																
Medical history	X																	
Physical examination	S#	S#									S				S			
Pregnancy test Serum (2)	S#	S#											S					
Pregnancy test Urine (2)										S		S				S		S
Randomization via IRT		S																
Viral serology (5) recipient/donor	X#	X#																
Contact IRTo	S			S		S			S	S	S	S	S	S	S	S	S	S
Administration of CFZ533 IV Arms 1 and 2 (6) (6a)				X			X											
Administration of CFZ533 300mg or 600mg S.C. study treatment (6b)									X	X	X	X	X	X	x	X	x	x

[redacted]

Period	**Screening** (3)	**Baseline** (4)	**Treatment Cohort 1**															
Month		**1**								**1.5**	**2**	**2.5**	**3**	**3.5**	**4**	**4.5**	**5**	
Day	**D-28 to 1**	**BL/D1**	**D1**			**5**			**15**	**29**								
Hour (h)			**Pre**	**0**	**EOI +1h**	**Pre**	**0**	**EOI + 1h**										
TAC (Arm 3 only) / MMF / CS Dosage Administration Record (7)				X					X	X		X		X		X		
Serum for donor specific antibodies (8)	X													X				
ECG evaluation	X#	X#																
Safety laboratory tests (9)	X#	X#					X		X	X		X		X		X		
Vital Signs:																		
-Height	X																	
-Weight	X#	X#					X					X				X		
-Temperature (10)	X#	X#	X				X		X	X	X	X	X	X		X		
-Blood pressure/pulse (10)	X#	X#	X				X		X	X	X	X	X	X		X		
EBV viral load		X												X				
EBV, CMV & BK viral load (11)	Ongoing																	
CFZ533 Pharmacokineticso (12)			X		X	X		X	X	X	X	X	X	X		X		
MPA trough levels										X		X		X		X		
Tacrolimus trough levels (13)						X(13)			X	X		X		X		X		
[redacted]																		
CFZ533 Immunogenicity (15)			X							X		X		X				
[redacted]																		
Kidney Allograft Biopsy(16)		X	As per local practice															

[redacted]

AE, SAE [17]	Ongoing
Concomitant medications	Ongoing
Surgical & medical procedures	As required
Malignancies	As required
Infections	As required
Withdrawal of Informed Consent	As required
Kidney allograft rejection	As required
Dialysis	As required
Graft loss	As required
Hospitalizations	As required

Assessment schedule – Cohort 1: Month 5.5 to 14

Period	**Treatment Cohort 1**																	
Month	**5.5**	**6**	**6.5**	**7**	**7.5**	**8**	**8.5**	**9**	**9.5**	**10**	**10.5**	**11**	**11.5**	**12**	**12.5**	**13**	**13.5**	**14**
Visit for TAC patients		Y				Y				Y				Y				
Physical examination		S				S				S				S				
Pregnancy test Serum [2]		S								S				S				
Pregnancy test Urine [2]				S		S		S				S				S		S
Contact IRT[o]	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Administration of CFZ533 300mg or 600mg S.C. study treatment[6b]	x	X	x	x	x	X	x	x	x	X	x	x	x	X	x	x	x	x
TAC (Arm 3 only) / MMF / CS Dosage Administration Record [7]		X				X				X				X				
Serum for donor specific antibodies[#] [8]		X												X				
ECG evaluation		X												X				
Safety laboratory tests [9]		X				X				X				X				

[redacted]

Period	Treatment Cohort 1																	
Month	**5.5**	**6**	**6.5**	**7**	**7.5**	**8**	**8.5**	**9**	**9.5**	**10**	**10.5**	**11**	**11.5**	**12**	**12.5**	**13**	**13.5**	**14**
Vital Signs:																		
-Weight		X				X				X				X				
-Temperature [10]		X				X				X				X				
-Blood pressure/pulse [10]		X				X				X				X				
EBV viral load		X												X				
EBV, CMV & BK viral load [11]	Ongoing																	
CFZ533 Pharmacokinetics[o] [12]		X				X				X				X				
MPA trough levels		X				X				X				X				
Tacrolimus trough levels [13]		X				X				X				X				
[redacted]																		
CFZ533 Immunogenicity[o] [15]		X				X				X				X				
[redacted]																		
Dose record for PFS for patients															x	x	x	x
Kidney Allograft Biopsy [16]	As per local practice													X	As per local practice			
AE, SAE [17]	Ongoing																	
Concomitant medications	Ongoing																	
Surgical & medical procedures	As required																	
Malignancies	As required																	
Infections	As required																	
Withdrawal of Informed Consent	As required																	
Kidney allograft rejection	As required																	
Dialysis	As required																	
Graft loss	As required																	
Hospitalizations	As required																	

[redacted]

Assessment schedule - Cohort 1: Month 14.5 to 23

Period	Treatment Cohort 1																	
Month	**14.5**	**15**	**15.5**	**16**	**16.5**	**17**	**17.5**	**18**	**18.5**	**19**	**19.5**	**20**	**20.5**	**21**	**21.5**	**22**	**22.5**	**23**
Visit for TAC patients		Y						Y						Y				
Physical examination		S						S						S				
Pregnancy test Serum (2)		S						S						S				
Pregnancy test Urine (2)				S		S				S		S				S		S
Contact IRTº	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Administration of CFZ533 300mg or 600mg S.C. study treatment(6b)	x	X	x	x	x	x	x	X	x	x	x	x	x	X	x	x	x	x
TAC (Arm 3 only) / MMF / CS Dosage Administration Record		X						X						X				
Serum for donor specific antibodies# (8								X										
ECG evaluation																		
Safety laboratory tests (9)		X						X						X				
Vital Signs:																		
-Weight		X						X						X				
-Temperature (10)		X						X						X				
-Blood pressure/pulse (10)		X						X						X				
EBV viral load																		
EBV, CMV & BK viral load (11)	Ongoing																	
CFZ533 Pharmacokineticsº (12)		X						X						X				
MPA trough levels		X						X						X				
Tacrolimus trough levels (13)		X						X						X				
[redacted]																		
CFZ533 Immunogenicity (15)		X						X						X				
[redacted]																		

[redacted]

Period	Treatment Cohort 1																	
Month	**14.5**	**15**	**15.5**	**16**	**16.5**	**17**	**17.5**	**18**	**18.5**	**19**	**19.5**	**20**	**20.5**	**21**	**21.5**	**22**	**22.5**	**23**
Dose record for PFS for patients	x		x	x	x	x	x		x	x	x	x	x		x	x	x	x
Kidney allograft Biopsy (16)	As per local practice																	
AE, SAE (17)	Ongoing																	
Concomitant medications	Ongoing																	
Surgical & medical procedures	As required																	
Malignancies	As required																	
Infections	As required																	
Withdrawal of Informed Consent	As required																	
Kidney allograft rejection	As required																	
Dialysis	As required																	
Graft loss	As required																	
Hospitalizations	As required																	

[redacted]

Assessment schedule - Cohort 1: Month 23.5 to 32

Period	Treatment Cohort 1																	
Month	**23.5**	**24**	**24.5**	**25**	**25.5**	**26**	**26.5**	**27**	**27.5**	**28**	**28.5**	**29**	**29.5**	**30**	**30.5**	**31**	**31.5**	**32**
Visit for TAC patients		Y						Y						Y				
Physical examination		S						S						S				
Pregnancy test Serum (2)		S						S						S				
Pregnancy test Urine (2)				S		S				S		S				S		S
Contact IRTº	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Administration of CFZ533 300mg or 600mg S.C. study treatment(6b)	x	X	x	x	x	x	x	X	x	x	x	x	x	X	x	x	x	x
TAC (Arm 3 only) / MMF / CS Dosage Administration Record		X						X						X				
Serum for donor specific antibodies (8)		X												X				
ECG evaluation		X												X				
Safety laboratory tests (9)		X						X						X				
Vital Signs:																		
-Weight		X						X						X				
-Temperature (10)		X						X						X				
-Blood pressure/pulse (10)		X						X						X				
EBV viral load		X																
EBV, CMV & BK viral load (11)	Ongoing																	
CFZ533 Pharmacokineticsº (12)		X												X				
MPA trough levels		X						X						X				
Tacrolimus trough levels (13)		X						X						X				
[redacted]																		
CFZ533 Immunogenicity (15)		X												X				

[redacted]

Period	Treatment Cohort 1																	
Month	**23.5**	**24**	**24.5**	**25**	**25.5**	**26**	**26.5**	**27**	**27.5**	**28**	**28.5**	**29**	**29.5**	**30**	**30.5**	**31**	**31.5**	**32**
[redacted]																		
Dose record for PFS for patients	x		x	x	x	x	x		x	x	x	x	x		x	x	x	x
Kidney allograft Biopsy[16]	As per local practice																	
AE, SAE [17]	Ongoing																	
Concomitant medications	Ongoing																	
Surgical & medical procedures	As required																	
Malignancies	As required																	
Infections	As required																	
Withdrawal of Informed Consent	As required																	
Kidney allograft rejection	As required																	
Dialysis	As required																	
Graft loss	As required																	
Hospitalizations	As required																	

[redacted]

Assessment schedule - Cohort 1: Month 32.5 to 41

Period	Treatment Cohort 1																	
Month	**32.5**	**33**	**33.5**	**34**	**34.5**	**35**	**35.5**	**36**	**36.5**	**37**	**37.5**	**38**	**38.5**	**39**	**39.5**	**40**	**40.5**	**41**
Visit for TAC patients		Y						Y						Y				
Physical examination		S						S						S				
Pregnancy test Serum (2)		S						S						S				
Pregnancy test Urine (2)				S		S				S		S				S		S
Contact IRTº	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Administration of CFZ533 300mg or 600mg S.C. study treatment(6b)	x	X	x	x	x	x	x	X	x	x	x	x	x	X	x	x	x	x
TAC (Arm 3 only) / MMF / CS Dosage Administration Record		X						X						X				
Serum for donor specific antibodies (8)								X										
ECG evaluation								X										
Safety laboratory tests (9)		X						X						X				
Vital Signs:																		
-Weight		X						X						X				
-Temperature (10)		X						X						X				
-Blood pressure/pulse (10)		X						X						X				
EBV viral load								X										
EBV, CMV & BK viral load (11)	Ongoing																	
CFZ533 Pharmacokineticsº (12)								X										
MPA trough levels		X						X						X				
Tacrolimus trough levels (13)		X						X						X				
CFZ533 Immunogenicity (15)								X										
[redacted]																		
Dose record for PFS for patients	x		x	x	x	x	x		x	x	x	x	x		x	x	x	x
Kidney allograft Biopsy(16)	As per local practice																	

[redacted]

AE, SAE [17]	Ongoing
Concomitant medications	Ongoing
Surgical & medical procedures	As required
Malignancies	As required
Infections	As required
Withdrawal of Informed Consent	As required
Kidney allograft rejection	As required
Dialysis	As required
Graft loss	As required
Hospitalizations	As required

Assessment schedule - Cohort 1: Month 41.5 to 50

Period	**Treatment Cohort 1**																	
Month	**41.5**	**42**	**42.5**	**43**	**43.5**	**44**	**44.5**	**45**	**45.5**	**46**	**46.5**	**47**	**47.5**	**48**	**48.5**	**49**	**49.5**	**50**
Visit for TAC patients		Y						Y						Y				
Physical examination		S						S						S				
Pregnancy test Serum [2]		S						S						S				
Pregnancy test Urine [2]				S		S				S		S				S		S
Contact IRT[o]	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Administration of CFZ533 300mg or 600mg S.C. study treatment[6b]	x	X	x	x	x	x	x	X	x	x	x	x	x	X	x	x	x	x
TAC (Arm 3 only) / MMF / CS Dosage Administration Record		X						X						X				
Serum for donor specific antibodies [8]		X												X				
ECG evaluation		X												X				
Safety laboratory tests [9]		X						X						X				
Vital Signs:																		

[redacted]

Period	Treatment Cohort 1																	
Month	**41.5**	**42**	**42.5**	**43**	**43.5**	**44**	**44.5**	**45**	**45.5**	**46**	**46.5**	**47**	**47.5**	**48**	**48.5**	**49**	**49.5**	**50**
-Weight		X						X						X				
-Temperature [10]		X						X						X				
-Blood pressure/pulse [10]		X						X						X				
EBV viral load														X				
EBV, CMV & BK viral load [11]	Ongoing																	
CFZ533 Pharmacokinetics[o] [12]		X												X				
MPA trough levels		X						X						X				
Tacrolimus trough levels [13]		X						X						X				
CFZ533 Immunogenicity [15]		X												X				
[redacted]																		
Dose record for PFS for patients	x		x	x	x	x	x		x	x	x	x	x		x	x	x	x
Kidney allograft Biopsy [16]	As per local practice																	
AE, SAE [17]	Ongoing																	
Concomitant medications	Ongoing																	
Surgical & medical procedures	As required																	
Malignancies	As required																	
Infections	As required																	
Withdrawal of Informed Consent	As required																	
Kidney allograft rejection	As required																	
Dialysis	As required																	
Graft loss	As required																	
Hospitalizations	As required																	

[redacted]

Assessment schedule - Cohort 1: Month 50.5 to End of Study

Period	Treatment Cohort 1																			Study Completion (18)
																				EOS
Month	**50.5**	**51**	**51.5**	**52**	**52.5**	**53**	**53.5**	**54**	**54.5**	**55**	**55.5**	**56**	**56.5**	**57**	**57.5**	**58**	**58.5**	**59**	**59.5**	
Visit for TAC patients		Y						Y						Y						Y
Physical examination		S						S						S						S
Pregnancy test Serum (2)		S						S						S						S
Pregnancy test Urine (2)				S		S				S		S				S		S		
Contact IRTº	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	X
Administration of CFZ533 300mg or 600mg S.C. study treatment(6b)	x	X	x	x	x	x	x	X	x	x	x	x	x	X	x	x	x	x	x	
TAC (Arm 3 only) / MMF / CS Dosage Administration Record		X						X						X						X
Serum for donor specific antibodies (8)								X												X
ECG evaluation								X												X
Safety laboratory tests (9)		X						X						X						X
Vital Signs:																				
-Weight		X						X						X						X
-Temperature (10)		X						X						X						X
-Blood pressure/pulse (10)		X						X						X						X
EBV viral load																				X
EBV, CMV & BK viral load (11)	Ongoing																			
CFZ533 Pharmacokineticsº (12)								X												
MPA trough levels		X						X						X						X
Tacrolimus trough levels (13)		X						X						X						X
CFZ533 Immunogenicity (15)								X												
[redacted]																				

[redacted]

Period	Treatment Cohort 1																			Study Completion (18)
																				EOS
Month	**50.5**	**51**	**51.5**	**52**	**52.5**	**53**	**53.5**	**54**	**54.5**	**55**	**55.5**	**56**	**56.5**	**57**	**57.5**	**58**	**58.5**	**59**	**59.5**	
Dose record for PFS for patients	x		x	x	x	x	x		x	x	x	x	x		x	x	x	x	x	
Kidney allograft Biopsy(16)	As per local practice																			
AE, SAE (17)	As required																			
Concomitant medications	As required																			
Surgical & medical procedures	As required																			
Malignancies	As required																			
Infections	As required																			
Withdrawal of Informed Consent	As required																			
Kidney allograft rejection	As required																			
Dialysis	As required																			
Graft loss	As required																			
Hospitalizations	As required																			

S = assessment to be recorded in source documentation but not in CRF
X = Clinic visit. Assessment to be recorded in CRF
x = Optional in-home visit or starting from Month 12.5 self administration at home with PFS. Dosing to be recorded in CRF
Y = Visit is applicable to patients randomized to TAC treatment arms.
° = as applicable based on randomization treatment
# = only need to be performed once in a 24-hour period if Screening, Baseline and Day 1 occur in close proximity
D = Day
BL+ Baseline
EOI = end of infusion (IV administration)
EOT: end of treatment
EOS: end of study
(1) Informed consent should be obtained prior to performing any study related procedures.

[redacted]

(2) Pregnancy tests should be carried out according to local practice. Testing is performed locally and results must be available and negative prior to randomization. Patient will perform monthly urine test in the home if not attending for visit.

(3) Screening may extend up to 4 weeks prior to transplant (e.g., for scheduled living donor transplants) and ends when the patient is either randomized or becomes a screening failure.

(4) Baseline covers the transplant period from up to 24 hours prior to surgery until randomization/enrollment or its failure.

(5) Qualitative viral serology test results for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), and hepatitis C virus (anti-HCV) antibodies must be negative for both recipient and donor. Recipients with positive anti-HCV can be included after anti-HCV treatment, if SVR12 was confirmed with a negative HCV-RNA qualitative/ quantitative test (historical results are acceptable). At baseline, qualitative IgG and IgM cytomegalovirus (CMV), Epstein Barr virus (EBV), and BK virus (BKV) per local standard of care should be assessed. Recipient should test IgG positive for Epstein Barr virus (EBV) to be eligible (historical positive EBV-IgG tests are acceptable).

(6) First dose (30 mg/kg) of CFZ533 will be administered intravenously pre- or intra-operatively and must be completed within one hour of unclamping and before graft revascularization. Pre-transplant immunosuppression such as induction therapy should be recorded on the concomitant medication page under the immunosuppressive category. Other study drugs (e.g., MMF, CS) must be started within 24 hours post-transplantation.

(6a) Second dose (15 mg/kg) of CFZ533 will be administered intravenously at site.

(6b) 300/600 mg subcutaneously bi-weekly (Q2W) by authorized investigator staff at each of the study visits (X) or optional in-home dosing by in home vendor or self-administration at home (starting Month 12.5) (x) until Month 59.5 visit.

(7) Arm 3 only: TAC will be administered as soon as possible and no later than 24 hours after reperfusion of the graft. TAC trough levels should be measured at each study visit, TAC dose adjustment should be used to ensure that TAC trough levels remain within the target ranges as per local label. For all arms: Pre-transplant immunosuppression such as induction therapy should be recorded on the concomitant medication page under the immunosuppressive category. Other study drugs (e.g., MMF, CS) must be started within 24 hours post-transplantation.

(8) HLA antibodies (Donor Specific Antibodies) will be assessed locally, preferably by Luminex® single antigen assay, at screening to rule out the existence of pre-formed DSA, at the defined time points as well as when a renal biopsy is performed in the event of suspected rejection.

(9) Central laboratory tests include: hematology, urinalysis, serum chemistries, renal function, quantitative EBV, MPA trough levels and coagulation parameters. For baseline evaluation (hematology, blood chemistry, urinalysis and special analyses), blood samples should be drawn prior to transplantation and can be analyzed at the local laboratory for inclusion of the patients who received a transplant from a deceased donor; in such instances, a sample should also be sent for assessment to the central lab for all parameters assessed at screening. Living donor transplanted patients should have their inclusion / exclusion criteria checked by Central laboratory tests. For patients discontinued from treatment, samples will be taken at next scheduled 6 month and 12 month visits for testing of proteinuria and creatinine.

(10) Obtained every 15 minutes for 2 hours after the start of the CFZ533 IV infusion. Otherwise taken at every on-site visit.

(11) EBV, CMV, BKV viral load will be assessed locally if active infection is suspected. It is highly recommended to quantify the BKV, EBV and CMV viremia and record the results on the corresponding CRF pages (number of copies/mL) as well as method used.

(12) PK blood collection at Day 1 and Day 5 (Arms 1 and 2): should be taken pre-dose and 1-hour after the end of infusion. For remaining visits: Pre-dose only. Samples will also be taken immediately prior to IV-Ig and should also be collected at the next scheduled visit after IV-Ig infusion (visit x+1) before the next administration of CFZ533 (see details in Section 5.5.5.1).

[redacted]

(13) Arm 3 only: TAC C0 blood levels will be measured locally for TAC dose adjustments. A TAC trough level will be measured 4-7 days after the treatment initiation (first TAC dose). Trough levels will be measured after any dose adjustment to ensure that a trough level as per local label is maintained. Levels should also be obtained at the time of any suspected acute rejection.

[redacted]

(15) Immunogenicity (anti-CFZ533 antibodies): all blood samples are taken pre-dose. Blood samples are obtained from all patients treated with CFZ533 (Arms 1 and 2).

(16) A biopsy will be performed at Baseline (back table), at Month 12 post-transplant and in case of suspected rejection. Please refer to Table 6-3 for biopsies in case of premature treatment discontinuation. Back table biopsies taken per routine practice prior to the introduction of amendment 01 will be sent to the adjudication committee for blinded review.

(17) All serious adverse events, serious infections and pregnancies must be reported from informed consent until 12 weeks following the end of study visit (Month 60). For patients who prematurely discontinue study or study treatment, SAEs should be captured until completion of last follow up visit or 14 weeks following the last administration of CFZ533 treatment and until 12 weeks for TAC subjects (whichever is later).

(18) If patients prematurely discontinue study treatment, patients will complete EOS visit. Patients should continue in the study on SoC per local practice and return for the two follow up visits. Any permanent discontinuation of the randomized study regimen should be recorded on the appropriate CRF pages. After discontinuation of study regimen, the immunosuppressive regimen prescribed should be recorded on the appropriate CRF under the Immunosuppressive category. Follow-up phone calls will be conducted every 6 months after follow-up visits until Month 60.

[redacted]

[redacted]

Table 6-2 Assessment schedule – Cohort 2

Assessment schedule – Cohort 2: Screening to Month 5.5

Period	Screening (3)	Baseline	Treatment Cohort 2												
Month			1					1.5	2	2.5	3	3.5	4	4.5	5
Day	**D-28 to 1**	**BL/D1**	**D1**			**15**	**29**								
Hour (h)			**Pre**	**0**	**EOI +1h**										
Visit for TAC patients	Y	Y	Y	Y			Y				Y		Y		
Demography	X														
Inclusion / Exclusion criteria	X#	X#													
Informed Consent (1)	X														
Retrospective eGFR, creatinine and proteinuria (1a)	X														
Retrospective Kidney transplant background recipient/donor		X													
Medical history	X														
Physical examination	S#	S#							S				S		
Pregnancy test Serum (2)	S#	S#									S				
Pregnancy test Urine (2)							S		S				S		S
Randomization via IRT		S													
Viral serology recipient (4)		X													
Contact IRTº		S				S	S	S	S	S	S	S	S	S	S
Administration of CFZ533 30 mg/kg IV study treatment (5)				X											
Administration of CFZ533 450mg S.C. study treatment (6)						X	X	X	X	X	X	x	X	x	x
Administration of TAC (CFZ533 arm) (7)				X		X	X								

[redacted]

Period	Screening (3)	Baseline	Treatment Cohort 2												
Month			1					1.5	2	2.5	3	3.5	4	4.5	5
Day	**D-28 to 1**	**BL/D1**	**D1**			**15**	**29**								
Hour (h)			**Pre**	**0**	**EOI +1h**										
TAC (control arm) / MMF/EC-MPS/CS Dosage Administration Record (8)				X			X				X		X		
Serum for donor specific antibodies (9)	X										X				
ECG evaluation	X#	X#													
Safety laboratory tests (10)	X#	X#				X	X		X		X		X		
Vital Signs:															
-Height	X														
-Weight	X#	X#							X				X		
-Temperature (11)	X#	X#		X		X	X	X	X	X	X		X		
-Blood pressure/pulse (11)	X#	X#		X		X	X	X	X	X	X		X		
EBV viral load		X									X				
EBV, CMV & BK viral load (12)			Ongoing												
CFZ533 Pharmacokineticso (13)			X		X	X	X	X	X	X	X		X		
MPA trough levels							X		X		X		X		
Tacrolimus trough levels (14)							X				X		X		
[redacted]															
CFZ533 Immunogenicity (16)			X				X		X		X				
[redacted]															
Kidney Allograft Biopsy(17)		X	As per local practice												
AE, SAE (18)	Ongoing														
Concomitant medications	Ongoing														

[redacted]

Period	Screening (3)	Baseline	Treatment Cohort 2											
Month			1					1.5	2	2.5	3	3.5	4	4.5	5
Day	**D-28 to 1**	**BL/D1**	**D1**			**15**	**29**								
Hour (h)			**Pre**	**0**	**EOI +1h**										
Surgical & medical procedures	As required														
Malignancies	As required														
Infections	As required														
Withdrawal of Informed Consent	As required														
Kidney allograft rejection	As required														
Dialysis	As required														
Graft loss	As required														
Hospitalizations	As required														

Assessment schedule – Cohort 2: Month 5.5 to 14

Period	Treatment Cohort 2																	
Month	**5.5**	**6**	**6.5**	**7**	**7.5**	**8**	**8.5**	**9**	**9.5**	**10**	**10.5**	**11**	**11.5**	**12**	**12.5**	**13**	**13.5**	**14**
Visit for TAC patients		Y				Y				Y				Y				
Physical examination		S				S				S				S				
Pregnancy test Serum (2)		S								S				S				
Pregnancy test Urine (2)				S		S		S				S				S		S
Contact IRT°	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Administration of CFZ533 450mg S.C. study treatment° (6)	x	X	x	x	x	X	x	x	x	X	x	x	x	X	x	x	x	x
TAC / MMF/EC-MPS Dosage Record Administration° (8)		X				X				X				X				
Serum for donor specific antibodies# (9)		X												X				
ECG evaluation		X												X				

[redacted]

Period	Treatment Cohort 2																	
Month	**5.5**	**6**	**6.5**	**7**	**7.5**	**8**	**8.5**	**9**	**9.5**	**10**	**10.5**	**11**	**11.5**	**12**	**12.5**	**13**	**13.5**	**14**
Safety laboratory tests (10)		X				X				X				X				
Vital Signs:																		
-Weight		X				X				X				X				
-Temperature (11)		X				X				X				X				
-Blood pressure/pulse (11)		X				X				X				X				
EBV viral load		X												X				
EBV, CMV & BK viral load (12)	Ongoing																	
MPA trough levels		X				X				X				X				
CFZ533 Pharmacokinetics° (13)		X				X				X				X				
Tacrolimus trough levels (14)°		X				X				X				X				
[redacted]																		
CFZ533 Immunogenicity° (16)		X				X				X				X				
[redacted]																		
Dose record for PFS for patients															x	x	x	x
Kidney Allograft Biopsy (17)	As per local practice													X	As per local practice			
AE, SAE (18)	Ongoing																	
Concomitant medications	Ongoing																	
Surgical & medical procedures	As required																	
Malignancies	As required																	
Infections	As required																	
Withdrawal of Informed Consent	As required																	
Kidney allograft rejection	As required																	
Dialysis	As required																	
Graft loss	As required																	
Hospitalizations	As required																	

[redacted]

Assessment schedule – Cohort 2: Month 14.5 to Month 23

Period	Treatment Cohort 2																	
Month	**14.5**	**15**	**15.5**	**16**	**16.5**	**17**	**17.5**	**18**	**18.5**	**19**	**19.5**	**20**	**20.5**	**21**	**21.5**	**22**	**22.5**	**23**
Visit for TAC patients		Y						Y						Y				
Physical examination		S						S						S				
Pregnancy test Serum		S						S						S				
Pregnancy test Urine				S		S				S		S				S		S
Contact IRT[o]	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Administration of CFZ533 450mg S.C. study treatment [(6)]	x	X	x	x	x	x	x	X	x	x	x	x	x	X	x	x	x	x
TAC / MMF /EC-MPS /CS Dosage Record Administration		X						X						X				
Serum for donor specific antibodies								X										
ECG evaluation								X										
Safety laboratory tests		X						X						X				
Vital Signs:																		
-Weight		X						X						X				
-Temperature [(11)]		X						X						X				
-Blood pressure/pulse [(11)]		X						X						X				
EBV viral load																		
EBV, CMV & BK viral load [(12)]	Ongoing																	
MPA trough levels		X						X						X				
CFZ533 Pharmacokinetics[o] [(13)]		X						X						X				
Tacrolimus trough levels [(14)]		X						X						X				
[redacted]																		
CFZ533 Immunogenicity [(16)]		X						X						X				
[redacted]																		
Dose record for PFS for patients	x		x	x	x	x	x		x	x	x	x	x		x	x	x	x

[redacted]

Period	Treatment Cohort 2																	
Month	**14.5**	**15**	**15.5**	**16**	**16.5**	**17**	**17.5**	**18**	**18.5**	**19**	**19.5**	**20**	**20.5**	**21**	**21.5**	**22**	**22.5**	**23**
Kidney Allograft Biopsy [17]	As per local practice																	
AE, SAE [18]	Ongoing																	
Concomitant medications	Ongoing																	
Surgical & medical procedures	As required																	
Malignancies	As required																	
Infections	As required																	
Withdrawal of Informed Consent	As required																	
Kidney allograft rejection	As required																	
Dialysis	As required																	
Graft loss	As required																	
Hospitalizations	As required																	

Assessment schedule – Cohort 2: Month 23.5 to Month 33

Period	Treatment Cohort 2																	
Month	**23.5**	**24**	**24.5**	**25**	**25.5**	**26**	**26.5**	**27**	**27.5**	**28**	**28.5**	**29**	**29.5**	**30**	**30.5**	**31**	**31.5**	**32**
Visit for TAC patients		Y						Y						Y				
Physical examination		S						S						S				
Pregnancy test Serum		S						S						S				
Pregnancy test Urine				S		S				S		S				S		S
Contact IRT[o]	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Administration of CFZ533 450mg S.C. study treatment [6]	x	X	x	x	x	x	x	X	x	x	x	x	x	X	x	x	x	x
TAC / MMF /EC-MPS Dosage Record Administration		X						X						X				
Serum for donor specific antibodies		X												X				

[redacted]

Period	Treatment Cohort 2																	
Month	**23.5**	**24**	**24.5**	**25**	**25.5**	**26**	**26.5**	**27**	**27.5**	**28**	**28.5**	**29**	**29.5**	**30**	**30.5**	**31**	**31.5**	**32**
ECG evaluation		X												X				
Safety laboratory tests		X						X						X				
Vital Signs:																		
-Weight		X						X						X				
-Temperature (11)		X						X						X				
-Blood pressure/pulse (11)		X						X						X				
EBV viral load		X																
EBV, CMV & BK viral load (12)	Ongoing																	
MPA trough levels		X						X						X				
CFZ533 Pharmacokinetics[o] (13)		X												X				
Tacrolimus trough levels (14)		X						X						X				
[redacted]																		
CFZ533 Immunogenicity (16)		X												X				
[redacted]																		
Dose record for PFS for patients	x		x	x	x	x	x		x	x	x	x	x		x	x	x	x
Kidney Allograft Biopsy(17)	As per local practice																	
AE, SAE (18)	Ongoing																	
Concomitant medications	Ongoing																	
Surgical & medical procedures	As required																	
Malignancies	As required																	
Infections	As required																	
Withdrawal of Informed Consent	As required																	
Kidney allograft rejection	As required																	
Dialysis	As required																	
Graft loss	As required																	

[redacted]

Period	Treatment Cohort 2																	
Month	**23.5**	**24**	**24.5**	**25**	**25.5**	**26**	**26.5**	**27**	**27.5**	**28**	**28.5**	**29**	**29.5**	**30**	**30.5**	**31**	**31.5**	**32**
Hospitalizations	As required																	

Assessment schedule – Cohort 2: Month 32.5 to Month 41

Period	Treatment Cohort 2																	
Month	**32.5**	**33**	**33.5**	**34**	**34.5**	**35**	**35.5**	**36**	**36.5**	**37**	**37.5**	**38**	**38.5**	**39**	**39.5**	**40**	**40.5**	**41**
Visit for TAC patients		Y						Y						Y				
Physical examination		S						S						S				
Pregnancy test Serum		S						S						S				
Pregnancy test Urine				S		S				S		S				S		S
Contact IRT[o]	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Administration of CFZ533 450mg S.C. study treatment [(6)]	x	X	x	x	x	x	x	X	x	x	x	x	x	X	x	x	x	x
TAC / MMF /EC-MPS Dosage Record Administration		X						X						X				
Serum for donor specific antibodies								X										
ECG evaluation								X										
Safety laboratory tests		X						X						X				
Vital Signs:																		
-Weight		X						X						X				
-Temperature [(11)]		X						X						X				
-Blood pressure/pulse [(11)]		X						X						X				
EBV viral load								X										
EBV, CMV & BK viral load [(12)]	Ongoing																	
MPA trough levels		X						X						X				
CFZ533 Pharmacokinetics[o] [(13)]								X										

[redacted]

Period	Treatment Cohort 2																	
Month	**32.5**	**33**	**33.5**	**34**	**34.5**	**35**	**35.5**	**36**	**36.5**	**37**	**37.5**	**38**	**38.5**	**39**	**39.5**	**40**	**40.5**	**41**
Tacrolimus trough levels (14)		X						X						X				
CFZ533 Immunogenicity (16)								X										
[redacted]																		
Dose record for PFS for patients	x		x	x	x	x	x		x	x	x	x	x		x	x	x	x
Kidney Allograft Biopsy (17)	As per local practice																	
AE, SAE (18)	Ongoing																	
Concomitant medications	Ongoing																	
Surgical & medical procedures	As required																	
Malignancies	As required																	
Infections	As required																	
Withdrawal of Informed Consent	As required																	
Kidney allograft rejection	As required																	
Dialysis	As required																	
Graft loss	As required																	
Hospitalizations	As required																	

[redacted]

Assessment schedule – Cohort 2: Month 41.5 to 50

Period	Treatment Cohort 2																	
Month	**41.5**	**42**	**42.5**	**43**	**43.5**	**44**	**44.5**	**45**	**45.5**	**46**	**46.5**	**47**	**47.5**	**48**	**48.5**	**49**	**49.5**	**50**
Visit for TAC patients		Y						Y						Y				
Physical examination		S						S						S				
Pregnancy test Serum		S						S						S				
Pregnancy test Urine				S		S				S		S				S		S
Contact IRT[o]	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Administration of CFZ533 450mg S.C. study treatment [(6)]	x	X	x	x	x	x	x	X	x	x	x	x	x	X	x	x	x	x
TAC / MMF/EC-MPS Dosage Record Administration		X						X						X				
Serum for donor specific antibodies		X												X				
ECG evaluation		X												X				
Safety laboratory tests		X						X						X				
Vital Signs:																		
-Weight		X						X						X				
-Temperature [(11)]		X						X						X				
-Blood pressure/pulse [(11)]		X						X						X				
EBV viral load														X				
EBV, CMV & BK viral load [(12)]	Ongoing																	
MPA trough levels		X						X						X				
CFZ533 Pharmacokinetics[o] [(13)]		X												X				
Tacrolimus trough levels [(14)]		X						X						X				
CFZ533 Immunogenicity [(16)]		X												X				
[redacted]																		
Dose record for PFS for patients	x		x	x	x	x	x		x	x	x	x	x		x	x	x	x

[redacted]

Kidney Allograft Biopsy [17]	As per local practice
AE, SAE [18]	Ongoing
Concomitant medications	Ongoing
Surgical & medical procedures	As required
Malignancies	As required
Infections	As required
Withdrawal of Informed Consent	As required
Kidney allograft rejection	As required
Dialysis	As required
Graft loss	As required
Hospitalizations	As required

Assessment schedule – Cohort 2: Month 50.5 to end of study

Period	**Treatment Cohort 2**																			**Study Completion[19]**
																				EOS
Month	**50.5**	**51**	**51.5**	**52**	**52.5**	**53**	**53.5**	**54**	**54.5**	**55**	**55.5**	**56**	**56.5**	**57**	**57.5**	**58**	**58.5**	**59**	**59.5**	
Visit for TAC patients		Y						Y						Y						Y
Physical examination		S						S						S						S
Pregnancy test Serum		S						S						S						S
Pregnancy test Urine				S		S				S		S				S		S		
Contact IRT[o]	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	X
Administration of CFZ533 450mg S.C. study treatment [6]	x	X	x	x	x	x	x	X	x	x	x	x	x	X	x	x	x	x	x	
TAC / MMF/EC-MPS/ CS Dosage Record Administration		X						X						X						X

[redacted]

Serum for donor specific antibodies								X												X
ECG evaluation								X												X
Month	**50.5**	**51**	**51.5**	**52**	**52.5**	**53**	**53.5**	**54**	**54.5**	**55**	**55.5**	**56**	**56.5**	**57**	**57.5**	**58**	**58.5**	**59**	**59.5**	
Safety laboratory tests		X						X						X						X
Vital Signs:																				
-Weight		X						X						X						X
-Temperature (11)		X						X						X						X
-Blood pressure/pulse (11)		X						X						X						X
EBV viral load																				X
EBV, CMV & BK viral load (12)	Ongoing																			
MPA trough levels		X						X						X						X
CFZ533 Pharmacokinetics[o] (13)								X												
Tacrolimus trough levels (14)		X						X						X						X
CFZ533 Immunogenicity (16)								X												
[redacted]																				
Dose record for PFS for patients	x		x	x	x	x	x		x	x	x	x	x		x	x	x	x	x	
Kidney Allograft Biopsy (17)	As per local practice																			
AE, SAE (18)	Ongoing																			
Concomitant medications	Ongoing																			
Surgical & medical procedures	As required																			
Malignancies	As required																			
Infections	As required																			

[redacted]

Withdrawal of Informed Consent	As required
Kidney allograft rejection	As required
Dialysis	As required
Graft loss	As required
Hospitalizations	As required

S = assessment to be recorded in source documentation but not in CRF

X = Clinic visit. Assessment to be recorded in CRF

x = Optional in-home visit or starting from Month 12.5 self administration at home with PFS. Dosing to be recorded in CRF

Y = Visit is applicable to patients randomized to TAC treatment arms.

° = as applicable based on randomization treatment

= only need to be performed once in a 24-hour period if Screening, Baseline and Day 1 occur in close proximity

D = Day

BL+ Baseline

EOI = end of infusion (IV administration)

EOT: end of treatment

EOS: end of study

(1) Informed consent should be obtained prior to performing any study related procedures.

(1a) Retrospective eGFR, creatinine and proteinuria up to 1 month prior to randomization.

(2) Pregnancy tests should be carried out according to local practice. Testing is performed locally and results must be available and negative prior to randomization. Patient will perform monthly urine test in the home if not attending for visit.

(3) Screening may extend up to Baseline and ends when the patient is either randomized or becomes a screening failure.

(4) Qualitative viral serology test results for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), and hepatitis C virus (anti-HCV) antibodies must be negative for both recipient and donor. Recipients with positive anti-HCV can be included after anti-HCV treatment, if SVR12 was confirmed with a negative HCV-RNA qualitative/ quantitative test (historical results are acceptable). At baseline, qualitative IgG and IgM cytomegalovirus (CMV), Epstein Barr virus (EBV), and BK virus (BKV) per local standard of care should be assessed. Recipient should test IgG positive for Epstein Barr virus (EBV) to be eligible (historical positive EBV-IgG tests are acceptable).

(5) First dose (30 mg/kg) of CFZ533 will be administered intravenously at baseline, concomitantly with MMF/EC-MPS and 50% of the current TAC dose. At Day 15, CFZ533 will be administered subcutaneously at 450 mg, concomitantly with MMF/EC-MPS and the current TAC dose reduced by a further 50% (i.e., 25% of the TAC dose at time of enrollment).

[redacted]

(6) CFZ533 450 mg subcutaneously bi-weekly (Q2W) by authorized investigator staff at each of the study visits (X) or optional in-home dosing by in home vendor or self-administration at home (starting Month 12.5) (x) until Month 59.5 visit.

(7) TAC tapering on CFZ533 arm: current dose (at time of enrollment) will be reduced to 50% on Day 1, to 25% on Day 15 and completely withdrawn by Day 29 (Month1)

(8) Patients shall remain on their current SoC regimen.

(9) HLA antibodies (Donor Specific Antibodies) will be assessed locally, preferably by Luminex® single antigen assay, at screening to rule out the presence of newly formed DSA, at the defined time points as well as when a renal biopsy is performed in the event of clinically suspected rejection.

(10) Central laboratory tests include: hematology, urinalysis, serum chemistries, renal function, quantitative EBV and coagulation parameters. For baseline evaluation (hematology, blood chemistry, urinalysis and special analyses), blood samples can be analyzed at the central laboratory only. For patients discontinued from treatment, samples will be taken at the next scheduled 6 month and 12 month visit for testing of proteinuria and creatinine.

(11) Obtained every 15 minutes for 2 hours after the start of the CFZ533 IV infusion. Otherwise taken at every on-site visit.

(12) EBV, CMV, BKV viral load will be assessed locally if active infection is suspected. It is highly recommended to quantify the BK, EBV and CMV viremia and record the results on the corresponding CRF pages (number of copies/mL) as well as method used.

(13) PK blood collection at Day 1: should be taken pre-dose and 1-hour after the end of infusion. For remaining visits: Pre-dose only. Samples will also be taken immediately prior to IV-Ig and should also be collected at the next scheduled visit after IV-Ig infusion (visit x+1) before the next administration of CFZ533 (see details in Section 5.5.5.1).

(14) Arm 2 only: TAC C0 blood levels will be measured locally for TAC dose adjustments. Levels should be obtained at the time of any suspected acute rejections.

[redacted]

(16) Immunogenicity (anti-CFZ533 antibodies): all blood samples are taken pre-dose. Blood samples are obtained only from all patients treated with CFZ533.

(17) A kidney allograft biopsy will be performed at baseline unless a biopsy was taken within 12 weeks prior to enrollment and data can be recorded, at Month 12 visit and in case of suspected rejection. Please refer to Table 6-3 for biopsies in case of premature treatment discontinuation. Biopsies taken per routine practice prior to the introduction of amendment 01 will be sent to the adjudication committee for blinded review.

(18) All serious adverse events, serious infections and pregnancies must be reported from informed consent until 12 weeks following the end of study visit (Month 60). For patients who prematurely discontinue study or study treatment, SAEs should be captured until completion of last follow up visit or 14 weeks following the last administration of CFZ533 treatment and until 12 weeks for TAC subjects (whichever is later).

(19) If patients prematurely discontinue study treatment, patients will complete the EOS visits. Patients should continue in the study on SoC per local practice and return for the two follow up visits. Any permanent discontinuation of the randomized study regimen should be recorded on the appropriate CRF pages. After discontinuation of study regimen, the immunosuppressive regimen prescribed should be recorded on the appropriate CRF under the Immunosuppressive category. Follow-up phone calls will be conducted every 6 months after follow-up visits until Month 60.

[redacted]

Table 6-3 Assessment schedule – treatment discontinuation

Visit	**EOS visit**	**Follow up visit 1 (FU-1)**	**Follow up visit 2 (FU-2)**	**Graft survival follow-up**
Timepoint	**At treatment discontinuation**	**At next 6 monthly scheduled visit** (e.g., M6, M12, M18 etc.) (+/- 1 month)	**6 months after FU-1** (e.g., M12, M18, M24, etc.) (+/- 1 month)	**every 6 Months until Month 60**
Physical examination	S			
Pregnancy test Serum (1)	S			
Contact IRT	S			
Serum for donor specific antibodies (2)	X	X(7)	X(7)	
ECG evaluation	X			
Safety laboratory tests (3)	X			
Proteinuria and creatinine		X	X	
Vital Signs:				
-Weight	X	X	X	
-Temperature	X	X	X	
-Blood pressure/pulse	X	X	X	
EBV viral load	X			
MPA trough levels	X			
Tacrolimus trough levels (o)	X			
AE, SAE (8)	X	X	X	SAEs related to study treatment[8]
[redacted]				
Kidney allograft biopsy (5)	(X)	(X)	(X)	
Concomitant medications (6)	X	X	X	X
Malignancies	X	X	X	
Infections	X	X	X	
Withdrawal of Informed Consent	X	X	X	

[redacted]

Visit	**EOS visit**	**Follow up visit 1 (FU-1)**	**Follow up visit 2 (FU-2)**	**Graft survival follow-up**
Timepoint	**At treatment discontinuation**	**At next 6 monthly scheduled visit** (e.g., M6, M12, M18 etc.) (+/- 1 month)	**6 months after FU-1** (e.g., M12, M18, M24, etc.) (+/- 1 month)	**every 6 Months until Month 60**
Kidney allograft rejection	X	X	X	
Dialysis	X	X	X	
Graft loss	X	X	X	X
Hospitalizations	X	X	X	
Death	X	X	X	X

S = assessment to be recorded in source documentation but not in CRF

X = Clinic visit. Assessment to be recorded in CRF

° = as applicable based on randomization treatment

(1) Pregnancy tests should be carried out according to local practice.

(2) HLA antibodies (Donor Specific Antibodies) will be assessed locally, preferably by Luminex® single antigen assay as well as when a renal biopsy is performed in the event of suspected rejection.

(3) Central laboratory tests include: hematology, urinalysis, serum chemistries, renal function, quantitative EBV, MPA trough levels and coagulation parameters

(5) If premature study drug discontinuation occurs between Day 1 and Month 11 a biopsy should be collected at Month 12 (FU-1 or FU-2). If discontinuation occurs between Month 11 and Month 15 visits, a biopsy should be collected at time of discontinuation. If biopsy was collected at Month 12, no additional biopsy collection is required.

(6) After discontinuation of study, patients should continue on SoC per local practice. The immunosuppressive regiment prescribed should be recorded on the appropriate CRF under the Immunosuppressive category. Other concomitant medication does not need to be recorded after FU-2.

(7) Sample (local) is only collected if the follow-up visit is at Month 12.

(8) After FU-2 only SAEs considered to be related to randomized study treatment need to be reported but no other SAEs/AEs.

[redacted]

6.1 Information to be collected on screening failures

Patients who discontinue from the study prior to randomization are considered screen failures. If a patient discontinues before entering the partially-blinded or the open-label treatment period at baseline, the IRT system must be notified within 2 days and the reason for not being randomized will be entered on the appropriate CRF. In addition, only the CRFs related to the following assessments should be completed: demography, informed consent, re-screening, inclusion/exclusion, cohort identification, visit date and disposition. The CRF for adverse events (AEs) should be completed for any Serious Adverse Events (SAEs) that occurred during the screening period. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

Cohort 1 - Re-screening (with a maximum of one attempt) is only allowed for patients who were screen failures on the initial Screening visit due, e.g., to lab values out of range, but not yet transplanted. No transplanted subject can be rescreened once they have failed to enter the randomized treatment period.

Cohort 2 – Re-screening (with a maximum of one attempt) is only allowed for patients who were screen failures on the initial Screening visit due, e.g., to lab values out of range.

Re-screened subjects should be assigned a new subject ID number. A new ICF will need to be signed if the investigator chooses to re-screen the subject after a subject has screen failed.

All patients who have signed informed consent and are randomized into the Treatment Period of the study will have all AEs **occurring after informed consent is signed** recorded on the corresponding CRF.

6.2 Patient demographics/other baseline characteristics

After informed consent has been signed and the patient's eligibility to participate in the study has been determined, baseline patient information will be obtained in accordance with local regulations. In addition, relevant medical history (including chronic kidney disease and end-stage renal disease history) and current medical conditions at screening, a full physical examination, vital signs and a pregnancy test (when applicable) will also be performed. Where possible, diagnoses and not symptoms will be recorded.

Subject's race and ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities.

Investigators will have the discretion to record abnormal test findings on the CRF capturing medical history whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

At Baseline/Transplantation, information on the renal transplant procedure, recipient and donor transplant background, recipient and donor viral serology and recipient/donor HLA testing results will be recorded.

For randomization, the IRT must be contacted and the IRT will assign the randomization number.

[redacted]

When IRT is contacted to randomize *de novo* patients in **Cohort 1**, donor category (deceased versus living donor kidneys) and induction therapy (basiliximab versus rATG)) information must be provided and the IRT will assign the treatment arm.

When IRT is contacted to randomize maintenance patients in **Cohort 2**, information regarding corticosteroids use (yes/no) and time since transplant (6 - ≤ 12M and > 12-24M) must be provided and the IRT will assign the treatment arm.

For all patients regardless of randomization/enrollment status, the IRT and appropriate CRF to capture patient disposition must be completed to document all consented patients as either randomized or as screen failures and the reason for screen failure recorded.

6.3 Treatment exposure and compliance

Free CFZ533 concentrations in plasma and PK parameters (measures of treatment exposure) will be determined in all patients treated with CFZ533, as detailed in Section 6.6.1.

[redacted]

All pre-transplant (for Cohort 1) or current (for Cohort 2) immunosuppression administered pre-randomization such as basiliximab, rATG, TAC, MMF/EC-MPS and corticosteroids, will be recorded on the appropriate CRF, under Concomitant medications/Immunosuppressive category.

All post-randomization doses of CFZ533, TAC, MMF EC-MPS, corticosteroids as well as induction therapy administered, will be recorded on their respective CRFs.

For all these immunosuppressive drugs and induction therapies, the start date, total dose, stop date and reason for dose administration or dose change are to be provided. If study drug is interrupted due to inability to tolerate oral medication and rescue therapy via a nasogastric tube is administered, the non-study drug immunosuppressive should be recorded on the appropriate CRF under Concomitant Medications/Immunosuppressive category.

TAC trough levels will be determined locally and recorded on the appropriate CRF. The local trough values will be used to adjust the TAC dosing as needed.

Other drugs administered prior to and continuing at start of study medication will be entered on the appropriate CRF.

Compliance will be assessed by the Investigator and/or study personnel at each visit and information provided by the patient. This information should be captured in the source document at each visit.

6.4 Efficacy

During a Public Health emergency that limits or prevents on-site study visits or kidney biopsy collections, it is acceptable for Month 12 visit assessments required for calculation of composite efficacy failure [redacted] to be collected up to the Month 15 visit. Every effort should be made to obtain required assessments at Month 12 and to collect blood samples for central laboratory analysis. All Month 12 visit assessments should be taken at the same timepoint and no later than the Month 15 visit.

[redacted]

6.4.1 Kidney allograft biopsy

For cohort 1, a back table biopsy at baseline will be taken. For cohort 2, a biopsy at baseline will be taken, unless biopsy readings data available from 0 to 12 weeks prior to enrollment are available, in that case, these data will be retrospectively recorded in the corresponding eCRF page. If available, this pre-baseline biopsy specimen will be sent to the adjudication committee (AC) for assessment.

Any back table biopsies taken according to routine practice prior to the introduction of amendment 01 will be sent to the AC for blinded review.

For both cohorts, a biopsy will be taken at the end of the primary study treatment period, i.e., at Month 12 or at the time of premature study drug discontinuation as defined in Table 6-3.

Rationale for per-protocol biopsies

The incidence of acute rejection and graft loss in the first year after renal transplantation has fallen markedly in the past 20 years since the introduction of more potent immunosuppressive protocols. However, chronic allograft dysfunction leading to rejection and loss of graft function remain major problems after renal transplantation.

Failure rates for living donor kidney transplants at 1, 5, and 10 years are approximately 3%, 15%, and 40%, respectively. Deceased donor kidney transplant failure rates are even higher, with 8%, 27%, and 53% failing at 1, 5, and 10 years, respectively (TTC: https://c-path.org/programs/ttc/overview/public-health-needs-in-transplantation).

Interstitial fibrosis and tubular atrophy (IFTA) is the most common cause of late graft rejection and is strongly correlated with the number of acute rejection episodes during the first year after renal transplantation.

Recent reports have suggested that acute rejection episodes and IFTA may be subclinical without causing a measurable decrease in graft function. Moreover, persistent, unrecognized inflammatory injury, secondary to a low-grade rejection process, may result in long-term graft fibrosis and chronic dysfunction in the absence of episodes of overt clinical rejection.

Traditionally, renal allograft biopsies are performed mainly in the setting of acute graft dysfunction. Consequently, the possibility of graft failure is suspected only when a continued and irreversible fall in renal function has become apparent, generally in the setting of hypertension and proteinuria. By the time the clinical diagnosis is confirmed histologically by biopsy, irreversible graft damage may have occurred.

This raises the possibility that surveillance or protocol biopsies, which are performed during the first post-transplantation year irrespective of graft function, may be clinically useful by allowing the identification of early acute rejection or IFTA at a point when they are amenable to treatment.

The implementation of protocol biopsies may improve long-term graft function. In particular, a number of reports suggest that detection of IFTA in early protocol biopsies is predictive of subsequent graft function and loss and that early treatment may have a dramatic effect on the outcome of the graft.

[redacted]

Furthermore, the procedure is relatively straightforward and safe. The low rate of complication reported in the literature is 0–2.2% (Reschen 2018).

In experimental models, CFZ533 has shown the preservation of good histological graft morphology, making it an attractive approach for preventing solid organ transplant rejection (Cordoba et al 2015).

[redacted] **Missing protocol biopsies should be avoided** to ensure a complete evaluation of the effects of CFZ533 compared to the TAC control group.

All per protocol biopsy specimen slides, as well as biopsy slides taken per local practice, will be sent to the AC for blinded review and will be read according to Banff criteria 2017.

[redacted]

6.4.2 Acute Rejection/Biopsy Proven Acute Rejection (BPAR) assessment

All episodes of acute rejections must be recorded on the appropriate CRF. Recording should be done within 24 h of occurrence, to ensure timely information to the Data Monitoring Committee (DMC). The precise reason for suspicion of an acute rejection and the final diagnosis (either to confirm or rule out the diagnosis of acute rejection) and all anti-rejection therapy administered must be recorded.

A graft core biopsy must be performed **preferably** within 24 hours, latest within 48h for all cases of suspected acute rejection as well as blood sampling to detect the presence of newly formed DSA (analyzed at the local laboratory), regardless of initiation of anti-rejection treatment.

Biopsies will be read by a local pathologist according to Banff criteria 2017 and will be used to guide patient management. The results of the biopsy read by the local pathologist must be recorded on the corresponding CRF.

In addition, biopsy specimen slides from these for cause biopsies (in case of suspected rejection), will be sent to the AC for blinded review. Any biopsies taken according to routine local practice will also be sent to the AC for blinded review. The efficacy analysis will rely on the evaluations of the AC and will be based on acute rejection confirmed by a biopsy (BPAR).

Acute rejections are expected events and should not be recorded as AEs. Rejections which are unusual in severity should be reported as SAEs on SAE forms and as such on the corresponding CRF. Suspected acute rejection episodes ultimately diagnosed to be other conditions should also be recorded with the final diagnosis on the corresponding CRF.

[redacted]

[redacted]

[redacted]

6.4.4 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. If the patient undergoes allograft nephrectomy prior to starting permanent dialysis, then the day of nephrectomy is the day of graft loss. The reason for graft loss will be recorded on the appropriate CRF. In addition, it will be reported on the Month 60 Study Completion with Graft Loss as the reason for study discontinuation and on the appropriate CRF for dosage administration record if graft loss occurs while on randomized treatment. Graft loss is considered a SAE and should be reported on the appropriate CRF (as serious) and the SAE reported to the local Novartis Drug Safety and Epidemiology Department within 24 hrs.

6.4.5 Death

In the event of patient death, the SAE leading to death should be reported to Novartis safety department within 24 hrs. The events leading to the death should be entered on the appropriate CRF for Adverse Events.

6.4.6 Appropriateness of efficacy assessments

Composite efficacy failure

The composite efficacy endpoint of BPAR is standard in the kidney transplantation indication. This approach is consistent with the most recent Health Authorities guidance (CHMP/EWP/263148/06, effective February 2009) and discussions (FDA Workshop, 2012: Endpoints in Clinical Trials of Kidney Transplantation) on including an assessment of the traditional efficacy endpoints e.g., BPAR with or without clinical outcomes (i.e., Death and Graft loss). The endpoint represents an attempt to assess the clinical balance between having sufficient immunosuppression to prevent rejection while minimizing toxicity.

The composite of BPAR, graft loss or death has been used as an endpoint in many previous studies in kidney transplantation and has been widely accepted by Health Authorities for registration purposes in this indication.

6.5 Safety

During a Public Health emergency that limits or prevents on-site study visits, regular phone calls (at a minimum every 3 months) will occur for safety monitoring and discussion of the patient´s health status until the patient can again visit the site. Patients will however have on-site visits at least every 6 months and ensure that the Month 12 visit is on-site.

[redacted]

6.5.1 Physical examination

A complete physical examination should include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological systems. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed.

Information for all physical examinations must be included in the source documentation at the study site and will not be recorded on the database. Significant findings that are present prior to informed consent are included in the Relevant Medical History on the appropriate CRF. Significant findings observed after informed consent signature which meet the definition of an AE must be appropriately recorded on the appropriate CRF.

6.5.2 Vital signs

If possible, vital sign assessments should be performed by the same study site staff member using the same validated device throughout the study. This will include blood pressure and pulse rate measurements after 5 minutes rest in a sitting position, and body temperature measured as per local practice (the same method to be used consistently for all patients at each site).

6.5.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. If patient is dialyzed or in case of fluid retention after surgery, dry body weight (weight assessed after dialysis) measured at screening or baseline, will be used for calculation of dose at Day 1 and Day 5. A variation of the total administered amount of CFZ533 on Day 1 or Day 5 of up to +/- 10% from the calculated dose (e.g., due to the fluctuation of body weight or due to rounding of the final required volume) is acceptable.

Body mass index (BMI) will be calculated using the following formula:

- BMI = Body weight (kg) / [Height (m)]^2

Results will be recorded in the appropriate CRF.

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected listed below. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual. Clinically notable laboratory findings are defined in Appendix 1. All patients with laboratory tests containing clinically significant abnormal values are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined.

The central laboratory will perform blood biochemistry, hematology, urine assessments and trough levels for MPA as specified in Table 6-1 and Table 6-2.

Results from local laboratory can be used to assess eligibility criteria, only for those patients who received a transplant from a deceased donor in Cohort 1, and exceptionally if central lab samples cannot be obtained due to a Public Health emergency. If local lab samples are used for eligibility, a second sample should also be sent to central lab at the same time. For the evaluation

[redacted]

of the primary endpoint it is essential to have central laboratory results available for eGFR and proteinuria, as well as for safety assessments. Therefore, every effort must be made to obtain central lab samples at the time of biopsy for the Month 12 visits. Please refer to Section 6.4 in case of delay.

Cohort 2 inclusion criterion number 8: direct GFR measurement if performed locally may be used to determine eligibility.

Cohort 2 exclusion criterion number 12: for the assessment of the eGFR decline, it is recommended to assess any change in eGFR using results from one laboratory and avoid comparing results from different laboratories.

In all cases, the Investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the patient to continue in the study.

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an AE and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

Clinically notable laboratory findings are defined in Appendix 1.

6.5.4.1 Hematology

Platelets, hemoglobin, red blood cell (RBC), white blood cell (WBC) and differential count (e.g., neutrophils, basophils, eosinophils, monocytes and lymphocytes) will be measured.

6.5.4.2 Clinical chemistry

Albumin, alkaline phosphatase, total bilirubin, bicarbonate/CO2, calcium, cholesterol, chloride, creatinine, CK, gamma-GT, glucose, HbA1c, LDH, inorganic phosphorus, lipase, amylase, magnesium, potassium, total Immunoglobulin G (IgG), total protein, AST, ALT, sodium, triglycerides, blood urea nitrogen (BUN) and uric acid will be measured.

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

6.5.4.3 Urinalysis

The following parameters will be measured: protein, creatinine, albumin, glucose; proteinuria and albuminuria per 24hr period will be estimated from spot protein/creatinine and albumin/creatinine ratios.

6.5.4.4 Special clinical laboratory evaluations

Renal Function:

Renal function will be assessed at each visit by measuring serum creatinine and utilized to estimate GFR using the MDRD-4 formula.

[redacted]

For Cohort 2: eGFR measured at baseline/randomization will be used for randomization into the treatment phase (local measurement will be accepted for randomization purposes).

For Cohort 2, eGFR, creatinine and proteinuria measurements performed from 0 to 1 month prior to enrollment will be retrospectively recorded in the corresponding eCRF page.

Coagulation studies:

Coagulation studies will be performed, including prothrombin time and activated partial thromboplastin time (aPTT).

Donor specific antibodies (DSA)

Blood samples for donor specific antibodies will be collected and evaluated locally, preferably by Luminex® single antigen assay. Blood samples will be collected for all patients at screening, Month 3, Month 6 and Month 12, and every 6 months thereafter, and at time of rejection episodes and shipped to the referent local laboratory for analysis.

Viral serology:

Viral serology for recipients evaluated for screening will be performed by local laboratories. It includes:

- Hepatitis serology: hepatitis B surface antigen (HBsAg), and antibodies to hepatitis C virus (anti-HCV). For patients that are tested anti-HCV antibody positive, a negative HCV-RNA test checked by PCR qualitative or quantitative will be required to prove SVR12 (historical HCV-RNA results are acceptable)
- Human immunodeficiency virus (HIV).
- Qualitative viral serology tests for cytomegalovirus (CMV), Epstein Barr virus (EBV) and BK polyomavirus (BKV) (IgG and IgM or PCR) based on local standard of care.

In addition, quantitative viral serology test for EBV, CMV and BKV will be assessed locally if active infection is suspected. It is highly recommended to quantify the BKV, EBV and CMV viremia and record the results on the corresponding CRF pages (number of copies/mL) as well as method used.

Epstein Bar Virus (EBV) viral load

Continuous quantitative viral serology test for Epstein Barr virus (EBV) will be performed over the duration of the study by the central laboratory.

In immunosuppressed organ transplantation patients, EBV is one of the major pathogens. In seropositive patients under immunosuppressive treatment the impaired immuno-surveillance can lead to post-transplant lymphoproliferative disease (PTLD) (Blazques-Navarro et al 2018; Gully and Tang 2010). EBV establishes lifelong persistence, and symptomatic or asymptomatic reactivations occur, especially in immunosuppressed patients. In addition to the standard laboratory assays based on serology, in this trial the detection and quantification of EBV viral load should support the interpretation of the individual risk of a transplant patient to develop PTLD (Engelmann et al 2018). The EBV viral plasma load in patients treated with CFZ533 and MMF/EC-MPS /CS will be compared with viral loads from the concurrent SoC cohort with

[redacted]

TAC and MMF/EC-MPS /CS in order to reveal potential difference and how they relate to long-term outcome with respect to PTLD.

Immunogenicity

The presence of anti-CFZ533 antibodies will be determined in CFZ533-treated patients only, using a validated bridging ELISA-based assay.

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. Details of sample processing, handling, storage and shipment will be described in a separate laboratory manual. All samples will be given a unique sample number (as listed in the blood log, Appendix 5a). The detailed methods and analysis will be described in the Bioanalytical Data Report.

[redacted]

New onset diabetes mellitus after transplantation

New onset diabetes mellitus (American Diabetes Association 2010) is defined as no history of diabetes mellitus, which was active at study start (including HbA1c < 6.5% pre-transplant), AND:

- Two consecutive fasting plasma glucose (FPG) ≥ 126 mg/dL (7.0 mmol/L) or a random plasma glucose (RPG) ≥ 200 mg/dL (11.1 mmol/L) at any time after Day 29 OR
- HbA1c ≥ 6.5% (only from Month 3 forward) OR
- Diabetes reported as an AE that is prevalent after Day 29 OR
- Any concomitant medication with ATC level 2 code “A10” (drugs used in diabetes mellitus) if prevalent after Day 29

6.5.5 Electrocardiogram (ECG)

In this study, local ECG will be used. ECGs must be recorded after 5 minutes rest in the supine position to ensure a stable baseline. A single 12 lead ECG is collected. The Fridericia QT correction formula (QTcF) should be used for clinical decisions. The original ECGs (on non-heat-sensitive paper or a certified copy on non-heat sensitive paper), appropriately signed, must be collected and archived at the study site.

The ECG tracing must be labeled with study number, subject number, date and time, and filed in the study site source documents.

Clinically relevant abnormalities for the baseline ECG should be recorded on the relevant section of the CRFs capturing medical history/current medical conditions.

[redacted]

6.5.6 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum β-hCG test (serum pregnancy test) performed at the screening/baseline visit, month 3, 6, 10, 12 and every following 3 months to end of study. Local urine pregnancy tests will be performed monthly outside of these time points as indicated in Table 6-1 and Table 6-2. Patient will perform urine test in the home if not attending for visit. A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative. Additional pregnancy testing might be performed if requested by local requirements.

Study medication should not be given to pregnant women; therefore highly effective method of birth control must be used for women of child-bearing potential (see exclusion criteria definitions, Section 4.2).

Recommendations for female subjects taking CFZ533

In consideration of the patient population and overall CFZ533 risk benefit profile, women of childbearing potential must utilize highly effective contraception methods to avoid becoming pregnant while receiving CFZ533 and for 14 weeks after the last dose or until data from the reproductive toxicity studies suggest otherwise. Women who are nursing may not participate in this trial. The washout period of 14 weeks after the last dose is justified based on predicted PK profiles for CFZ533 in this study (rationale in Section 3.3.1.2, Figure 3-2).

Recommendations for female and male subjects taking MMF or EC-MPS

Mycophenolate (mycophenolate mofetil or mycophenolic acid) is a confirmed teratogen associated with an increased rate of spontaneous abortion and congenital malformation compared with other immunosuppressants. Therefore, investigators should ensure that female and male patients taking mycophenolate understand the risk of harm to the baby, the need for effective contraception, and the need to immediately consult the responsible investigator if there is a possibility of pregnancy or a suspected gap of contraception. For further recommendations and detailed information, please refer to the local product label.

a) Recommendations for female patients:

- Female participants who could become pregnant must use an effective method of contraception with MMF/EC-MPS. This includes before start taking MMF/ EC-MPS during the entire treatment period with MMF/ EC-MPS and for 6 weeks after the last dose of MMF/ EC-MPS.

- Two forms of contraception are preferable, as this will reduce the risk of unintended pregnancy.

-Female patients should not donate blood during therapy with mycophenolate and at least 6 weeks following discontinuation of mycophenolate.

b) Recommendations for male patients:

- The available evidence does not indicate an increased risk of malformations or miscarriage if the father takes mycophenolate. However, risk cannot be completely excluded.

[redacted]

-Male patients sexually-active, or the female partner, are recommended to use reliable contraception for sex during therapy with mycophenolate and at least 90 days following discontinuation of mycophenolate.

- Male patients should not donate blood during therapy with mycophenolate and at least 6 weeks following discontinuation of mycophenolate.

- Male patients should not donate semen during therapy with mycophenolate and for 90 days following discontinuation of mycophenolate.

Assessments of fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of childbearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, Follicle-stimulating Hormone (FSH) testing is required of any female subject, regardless of reported reproductive/menopausal status at screening/baseline.

6.5.7 Tolerability of investigational treatment

Tolerability will be assessed by adverse events, laboratory values and immunogenicity.

6.5.8 Appropriateness of safety measurements

The safety laboratory assessments (renal function, chemistry, and hematology) selected are standard for the kidney transplant population. The assessment of (serious) adverse events, including infections, graft loss, death, dialysis and details of viral infections (CMV, EBV and BKV) allow proper assessment safety related outcomes and side effects in this population.

6.6 Other assessments

6.6.1 Pharmacokinetics

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. Details of sample processing, handling, storage and shipment will be described in a separate laboratory manual. All samples will be given a unique sample number and a collection number (as listed in the blood log, Appendix 5a and Appendix 5b). The actual sample collection date and time will be entered on the PK blood collection page of the appropriate CRF.

Free CFZ533 plasma concentrations will be determined using a validated target-based sandwich ELISA method. The lower limit of quantification (LLOQ) is 0.03 µg/mL in 100% human plasma. The data and details of the analytical methods will be provided in a standalone Bioanalytical Data Report. Concentrations below the LLOQ will be reported as “zero” and missing data will be labeled as such in the Bioanalytical Data Report.

[redacted]

For standard pharmacokinetic abbreviations and definitions see the list provided at the beginning of this protocol.

The following pharmacokinetic parameters will be determined for free CFZ533 in plasma (i) Ctrough at steady state and Cmax will be directly derived from the bioanalytical data and listings, and (ii) AUC (Day 1 - Day 15; if data permit) will be determined using the actual recorded sampling times and non-compartmental methods with Phoenix WinNonlin (Version 6.2 or higher). The linear trapezoidal rule will be used for AUC calculation.

No other parameters (e.g., clearance, volume of distribution, or half-life) will be derived using non-compartmental analysis (NCA). The pharmacokinetics of CFZ533 is non-linear and characterized by target-mediated disposition where CD40 binding by CFZ533 is leading to CFZ533 elimination (this includes receptor-mediated endocytosis by the membrane bound CD40, and subsequent metabolism of the CFZ533-CD40 complexes). As such, it is expected that:

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

The NCA approach is not appropriate due to violations of the assumptions that the disposition of the drug is linear, and that the elimination is from sites that are in rapid equilibrium with blood.

For each PK samples, the actual recorded sampling time will be captured, and the elapsed time since the first and since the last dose will be calculated.

[redacted]

[redacted]

[redacted]

6.6.3 Other biomarkers

Any residual blood samples remaining after the protocol defined laboratory assessments have been performed may be used for additional unbiased profiling including, but not limited to proteomics (not including any genetic testing). Given the exploratory nature of the work, the analytical method used for those assessments will not be validated and results will be reported separately.

Details of sample processing, handling, storage and shipment are described in a separate laboratory manual.

[redacted]

[redacted]

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

The occurrence of adverse events must be sought by non-directive questioning of the patient at each visit during the study including an in-home visit by healthcare provider. Adverse events

also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Adverse events must be recorded in the appropriate CRF capturing AEs under the signs, symptoms or diagnosis associated with them, 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 serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met.
- action taken regarding [investigational] treatment

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g., further observation only)
- study treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

[redacted]

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient.

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events (SAE)

7.2.1 Definition of SAE

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g., defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might

[redacted]

require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 12 weeks following the end of study visit (Month 60) must be reported to Novartis safety within 24 hours of learning of its occurrence. For patients who prematurely discontinue study or study treatment, SAEs should be captured until completion of last follow up visit or 14 weeks following the last administration of CFZ533 treatment and until 12 weeks for TAC subjects (whichever is later).

Any SAEs experienced after this period should only be reported to Novartis safety if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up information to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to each specific component of study treatment, (if study treatment consists of several components) complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

[redacted]

Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

7.3 Liver safety monitoring

There has been no safety signal for liver toxicity with CFZ533 to date in all patients and healthy subjects exposed, and from a mechanism of action standpoint there is no known effect on the liver (refer to the actual Investigator Brochure). Standard liver function tests will be obtained at regular intervals, but special measures for liver safety monitoring are not planned. For further information on standard liver function tests, see Appendix 1.

7.4 Renal safety monitoring

Kidney allograft function is an important component in the kidney transplantation indication and patient's population. The nephrotoxic effects of CNIs such as TAC are directly associated with irreversible renal function deterioration.

Early identification, monitoring and evaluation of renal events are part of the study purpose and objectives. Protocol assessments were selected to ensure patient safety, minimize potential TAC related nephrotoxicity side effects, and determine the potential of CFZ533 to minimize or eliminate these nephrotoxicity effects in the setting of a CNI-free regimen.

7.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration (including self-administration at home) or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the appropriate CRF, irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

[redacted]

7.6 Pregnancy reporting

All pre-menopausal women who are not surgically sterile will have a serum β-hCG test (serum pregnancy test) performed at the screening/baseline visit, month 3, 6, 10, 12 and every 3 months until end of study. Local urine pregnancy tests will be performed monthly outside of these mentioned time points as indicated in Table 6-1 and Table 6-2. Patient will perform urine test in the home if not attending for visit. A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative. Additional pregnancy testing might be performed if requested by local requirements.

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign the pregnancy consent form to allow the Study Doctor to ask about her pregnancy. To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

The follow-up for both pregnant participants and pregnant partners of a trial participant should be done 1 month, 3 months (for a live birth only) and 12 months (for a live birth only) after estimated date of delivery.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capturing tools with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to the study medication specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data &

[redacted]

identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original ICF signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients/subjects will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the CRFs using fully validated, secure web-enabled software that conforms to US CRF 21 Part 11 requirements. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The investigator must certify that the data entered into the electronic Case Report Forms (CRFs) are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

The investigator is responsible for assuring that the data entered by the site personnel into the CRFs are complete, accurate and that entry and updates are performed in a timely manner.

8.3 Database management and quality control

Novartis personnel will review the data entered by investigator site staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

[redacted]

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis.

Randomization codes and data about the study drug dispensed to the patient will be tracked using an Interactive Response Technology (IRT) system. The system will be supplied by Novartis, who will also manage the database. Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

8.4 Data Monitoring Committee

An independent data monitoring committee (DMC) will be established to monitor the safety of the different treatment regimens. The DMC will be an independent board comprised of a group of physicians with experience in kidney transplantation and an independent statistician. A physician is not allowed to participate in this clinical trial while serving on the DMC.

The timing of the data cutoffs for DMC reviews are approximately:

- 10% of patients reach their Month 3 visit,
- and approximately every 6 months up to the Month 12 database lock.

In addition, a yearly data analysis, once all patients reach Year 2, 3, 4, and 5, will also be performed with the purpose to provide regular efficacy and safety updates and assess the long term overall benefit-risk.

[redacted]

The DMC charter outlines the organization and function of the DMC, describes the selected efficacy and safety variables that will be reviewed at each meeting. The results of the analyses will be delivered to the DMC by an independent statistician. The members will be primarily responsible for the clinical interpretation of the results. The members will be also responsible for advising Novartis as to whether or not any changes need to be made to the conduct of the study. The Trial Statistician and Clinical Medical Experts will be available for consultation. The members will report to the DMC chair who will inform Novartis whether or not there is a safety concern after reviewing all the information received.

Decisions based on the recommendations of the DMC will take into account the potential risks and benefits associated with continuing the enrollment of patients in the study, continuing the patients on the study drug and/or the study. Such information and recommendations will be used in the best interest of the patients enrolled in the trial. The final decision with respect to any modification of the protocol will be made by Novartis. In case of termination of the study, all health authorities and investigators will be notified within one working day. Study termination would take place in accordance with Novartis SOPs.

8.5 Adjudication Committee

An independent, blinded adjudication committee (AC), composed of three experienced pathologists, has been established to score all biopsies taken for suspected rejections, Baseline and Month 12 biopsies and any other biopsies taken according to local practice.

A consensus score from three independent histology reads, all blinded to each other, will be available for each of the biopsy samples. The AC charter outlines the organization and function of the AC.

9 Data analysis

An interim analysis is planned from the data cut-off date of 12-Mar-2021. Evaluation of safety and efficacy 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.

Additional analyses will be performed when all patients complete Year 2, 3, 4, and 5 to monitor long term efficacy and safety as described in the SAP.

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

Any data analysis carried out independently by the investigator must be submitted to Novartis before publication or presentation.

9.1 Analysis sets

Screened set (SCR) – All patients who signed the informed consent. The screened set includes only unique screened patients, i.e., in the case of re-screened patients only the chronologically last screening data is counted.

[redacted]

Randomized set (RAN) – All patients who received a randomization number, regardless of receiving trial medication.

Full analysis set (FAS) – Patients in the randomized set who are transplanted and excluding mis-randomized patients. Mis-randomized patients are defined as cases where IRT contacts were made by the Investigator/qualified site staff either prematurely or inappropriately prior to 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 their randomized treatment assignment.

Safety set (SAF) – All patients who received at least one dose of study drug. Patients will be analyzed according to their actual treatment regimen taken. All safety analyses will be performed on the SAF.

9.2 Patient demographics and other baseline characteristics

Summary statistics for the following background and baseline characteristics based on subjects in the FAS will be provided by treatment arm for background and demographic variables:

- **Recipient demographics:** age, gender, race, ethnicity, height, weight, BMI, and region
- **Recipient baseline characteristics:** renal function measured by eGFR (MDRD-4), diabetic status prior to randomization, spot urine protein/creatinine ratio (UPCR), delayed DGF status at baseline (*de novo* cohort only), corticosteroid use (maintenance cohort only), and time since transplant
- **Donor background information:** age, gender, race, donor category
- **Recipient transplant background information:** end stage disease leading to transplantation, current dialysis (*de novo* cohort only), time since continuous dialysis, peak PRA, most recent PRA, HLA matching, induction therapy (*de novo* cohort only)
- **Recipient and donor viral serology:** CMV, EBV, BKV, HCV, HBsAg, Anti-Hep B Surface Ab, Anti-Hep B Core Ab, and HIV. CMV, EBV, and BKV donor/recipient constellation
- **Presence of preexisting-donor specific antibodies (DSA) at baseline**

Continuous variables will be presented with mean, median, 25th percentile, 75th percentile, standard deviation, minimum and maximum, and the number of non-missing observations.

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

9.3 Treatments

9.3.1 Study medication

The duration (days) of study medication administration will be summarized. This 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 (i.e., 14 days for treatment administered once every 2 weeks). In calculating the duration of treatment, days of temporary interruption of study medication for any reason will be included. Further, the frequency of dose changes (including temporary dose interruption) will be presented by reason for the change.

[redacted]

Average daily doses will be presented by treatment. "Zero" will be used for periods of temporary interruption of study medication for any reason.

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

9.3.2 Concomitant immunosuppressants

The average daily dose of administered MMF/EC-MPS, TAC and CS will be summarized by treatment arm for subjects on study medication. The dose of the induction agent will be summarized for each of days when it was administered.

9.3.3 Other concomitant medications

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

9.4 Analysis of the primary variable

9.4.1 Primary Variable(s)

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 efficacy response is a composite efficacy failure event defined as any of the following:

- BPAR
- graft loss
- death

up to Month 12 post-transplantation (Cohort 1) or post-conversion (Cohort 2).

Identification of BPAR is based on the central and adjudicated assessment.

The primary efficacy response is:

- experienced (= "Y") if a subject experiences any one of the following:
  - death or graft loss; OR,
  - a for-cause central and adjudicated assessment with BPAR, regardless of a per-protocol central and adjudicated assessment; OR,
  - a per-protocol central and adjudicated assessment confirms BPAR, if a for-cause central and adjudicated assessment confirms BPAR or was not performed (or is missing)
- not experienced (= "N") if a subject has experienced all of the following:
  - no death; AND,
  - no graft loss; AND

[redacted]

  - a per-protocol central and adjudicated assessment does not confirm BPAR, if a for-cause central and adjudicated assessment does not confirm BPAR or was not performed (or is missing)
- missing (= "NA") if a subject has experienced all of the following:
  - no death; AND,
  - no graft loss; AND
  - a per-protocol central and adjudicated assessment was not performed (or is missing), if a for-cause central and adjudicated assessment does not confirm BPAR or was not performed (or is missing)

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

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.

9.4.2 Statistical model, hypothesis, 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:

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

[redacted]

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 $\theta_{\mathrm{CFZ533}} - \theta_{\mathrm{SoC}}$ 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 mean composite rates for each treatment group and the difference in mean response rates between treatments will be presented together with 95% credible intervals.

Posterior probabilities of the composite rates for each group being above various thresholds such as 10%, 15%, 20%, 25% (Cohort 1) or 5%, 10%, 15% (Cohort 2) will also be presented.

9.4.3 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.

A subject may be missing the primary efficacy response due to a missing biopsy from study discontinuation, treatment discontinuation, or lost to follow-up. A missing primary efficacy response occurs if a subject has experienced all of the following:

- no death; AND,
- no graft loss; AND
- a per-protocol central and adjudicated assessment was not performed (or is missing), if a for-cause central and adjudicated assessment did not confirm BPAR or was not performed (or is missing) up to Month 12 post-transplantation (Cohort 1) or post-conversion (Cohort 2) (i.e., Day 463).

A jump-to-reference (J2R) imputation using for-cause and per-protocol biopsy data in each Cohort will be used to impute the primary efficacy response when the missing data is due to treatment/study discontinuation or loss to follow-up.

9.4.4 Supplementary analyses

Simple event rate estimates (proportion of events) will be presented for the primary composite efficacy endpoint. In addition, the composite failure rates will be estimated with Kaplan-Meier product-limit formula and a 95% z-test based confidence interval using Greenwood's formula constructed as follows:

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

[redacted]

where

- r_{CFZ533} is the Kaplan-Meier estimate of the failure rate for each of the CFZ533 300 mg + MMF + CS, CFZ533 600 mg + MMF + CS arms (Cohort 1) and CFZ533 450 mg + MMF ± CS arms (Cohort 2)
- r_{SoC} is the Kaplan-Meier estimate of the failure rate for the TAC + MMF + CS arm (Cohort 1) and TAC + MMF ± CS arm (Cohort 2)
- SE_{CFZ533} is the estimated standard error using Greenwood's formula of the failure rate for each of the CFZ533 300 mg + MMF + CS, CFZ533 600 mg + MMF + CS arms (Cohort 1) and CFZ533 450 mg + MMF ± CS arms (Cohort 2)
- SE_{SoC} is the estimated standard error using Greenwood's of the failure rate for the TAC + MMF + CS arm (Cohort 1) and TAC + MMF ± CS arm (Cohort 2)

The primary efficacy analysis specified in Section 9.4.2 may be repeated:

- excluding primary composite efficacy events that occur beyond 14 days after treatment discontinuation (the "on treatment" analysis)
- using only for-cause biopsies

A tipping point analysis will be conducted to assess the impact of the imputation described in Section 9.4.3.

Further details on supplementary analyses can be found in the SAP.

9.4.5 Supportive analyses

The subgroup evaluation of:

- Living vs. deceased donors (*de novo* cohort)
- Induction therapy (basiliximab, rATG) (*de novo* cohort)
- Time since Tx (6 - ≤ 12 months, > 12-24 months) (maintenance cohort)
- Corticosteroid use (yes/no) (maintenance cohort)
- Recipient age group (< 0, ≥60 years)
- Donor age group (<60, ≥60 years)
- Gender (M, F)
- Race (Asian, Caucasian, Black or African American, Other)
- Region (US, EU, LACAN)
- Time since continuous dialysis started (< median, ≥ median)

on CFZ533 will be performed for the primary estimand. Additional subgroups to be evaluated and further details on supportive analyses will be specified in the SAP.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

Not applicable.

[redacted]

9.5.2 Safety variables

9.5.2.1 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).

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):

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

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 mean responses at each individual dose will be obtained through covariate-adjusted treatment effects by modeling the efficacy variable using MMRM with unstructured covariance matrix. The model will contain treatment group, visit, treatment group by visit interaction, baseline eGFR (Cohort 2 only) and stratification factors of donor category and induction therapy (Cohort 1) or corticosteroid use and time since transplant (Cohort 2).

The hypothesis of interest will be tested at a two-sided significance level of 0.10 and is as follows:

[redacted]

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 test statistic will be the estimated difference in Month 12 post-transplantation eGFR (Cohort 1) or estimanted difference in change from baseline in Month 12 post-conversion in eGFR (Cohort 2) least squares means from a mixed effects model (MMRM) to allow adjustment for correlations between time points within patients.

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 all eGFR measurements on/after the time of graft loss (composite strategy)

A jump-to-reference (J2R) imputation using all eGFR measurements in each Cohort will be used to impute the primary efficacy response when the missing data is due to treatment/study discontinuation or loss to follow-up.

Supplementary analyses

A supportive eGFR analysis will be performed excluding assessments that occur beyond 14 days after treatment discontinuation (the “on treatment” analysis).

Homogeneity of treatment effect with respect to time since transplant (6- ≤ 12M and > 12-24M) in Cohort 2 will be explored using the MMRM model described in this section.

Further details on supplementary analyses will be specified in the SAP.

Supportive analysesThe subgroup evaluation of:

- Living vs. deceased donors (*de novo* cohort)
- Induction therapy (basiliximab, rATG) (*de novo* cohort)

on CFZ533 will be performed for the secondary eGFR estimand. Further details on supportive analyses will be specified in the SAP.

9.5.2.2 Adverse events

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:

- AEs by primary SOC and preferred term

[redacted]

- AEs rated to have relationship to study drug by SOC and preferred term
- AEs by primary SOC, preferred term, and maximum severity
- 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
- Infections by type of infection (viral, bacterial, fungal, and others) and microorganism of infection
- Serious infections by type of infection and micro-organism of infection
- AEs by standardized MedDRA query (SMQ) levels (broad and narrow search)
- AEs by standardized MedDRA query (SMQ) and preferred term (broad and narrow search)
- MACE by SOC and preferred term
- Thromboembolic events by SOC and preferred term

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 termand SOC given by the MedDRA dictionary, start and end date, severity, and relationship to study drug as assessed by the Investigator.

9.5.2.3 Other safety endpoints

Laboratory data

Summary statistics for all laboratory data (including urinalysis, hematology, and clinical chemistry) will be provided by Cohort, treatment, and visit.

Values outside of the clinically notable limits will be flagged as abnormalities for all laboratory data (including urinalysis, hematology, and clinical chemistry); shift tables describing changes from baseline based on the clinical notable abnormalities will be presented by Cohort and treatment.

[redacted]

[redacted]

[redacted]

The frequency and percent of patients with newly formed DSA as identified from local laboratory assessments will be provided by Cohort, treatment, and visit.

Vital signs

Summary statistics for vital signs will be provided by Cohort, treatment, and visit.

ECG evaluations

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

Coagulation studies

Change from baseline in prothrombin time and aPTT will be summarized by Cohort, treatment, and visit.

A line graph of prothrombin time and aPTT over time will be provided.

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

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 FAS population who do not have DM at randomization/enrollment.

[redacted]

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.

All immunogenicity results will be listed by Cohort, treatment, patient, and visit/time point. No summary statistics will be provided.

[redacted]

9.5.3 Pharmacokinetics

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.

CFZ533 plasma concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ, which will be reported as zero. Summary statistics will include 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. Any other PK analyses will be described in a separate report (e.g., a CSR addendum).

If data permit, PK parameters will be calculated as described in Section 6.6.1 and will be listed by treatment and subject. Concentrations below the limit of quantification will not be considered for the calculation of PK parameters. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum.

9.5.4 Resource utilization

Not applicable.

9.5.5 DNA

Not applicable.

9.5.6 Biomarkers

Analysis will be reported in a separate standalone report.

[redacted]

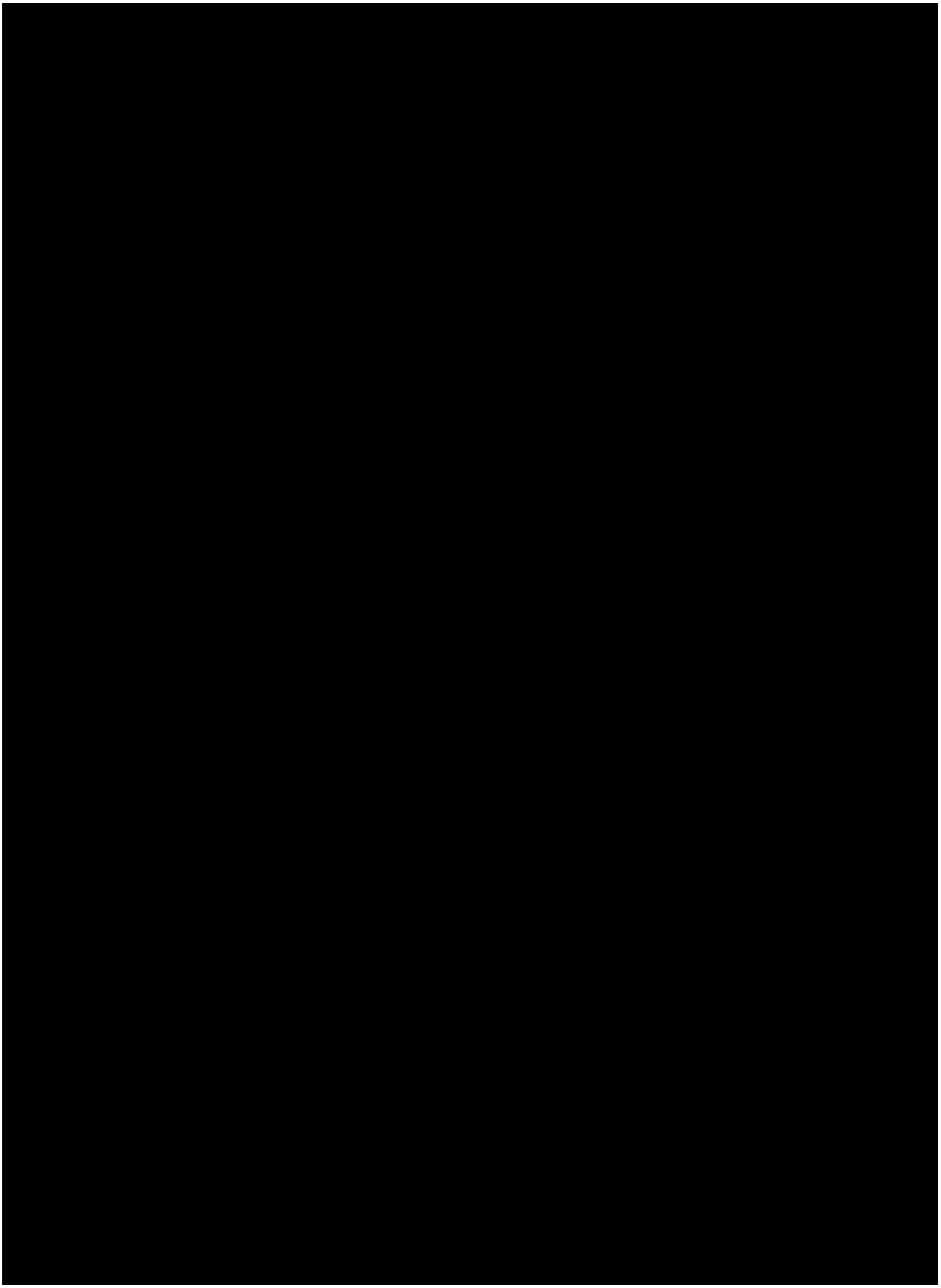
9.5.7 PK/PD

PK/PD modeling of the dose-response and exposure-response relationship for CFZ533 for selected endpoints (e.g., tBPAR, eGFR [redacted]) or biomarker parameters will be explored and reported in a separate modeling report, if appropriate.

The broad principles outlined in the "FDA Guidances for Industry: Population Pharmacokinetics and Exposure-Response Relationships" (CDER 2003) will be followed.

9.6 Analysis of exploratory variables

[redacted]



[redacted]

[redacted]

[redacted]

9.7 Interim analyses

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 patients who have completed Month 12 or discontinued prematurely will be used for the efficacy analyses including the primary analysis on composite efficacy failure and secondary analysis on eGFR. All data available on the interim analysis data cut-off will be used for PK and safety analyses. Further details will be provided in the SAP.

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.

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.

[redacted]

Table 9-1 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 SAP.

Table 9-1 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 9-2 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 SAP.

Table 9-2 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

9.8 Sample size calculation

9.8.1 Stopping rule

Cohort 1 – *de novo*

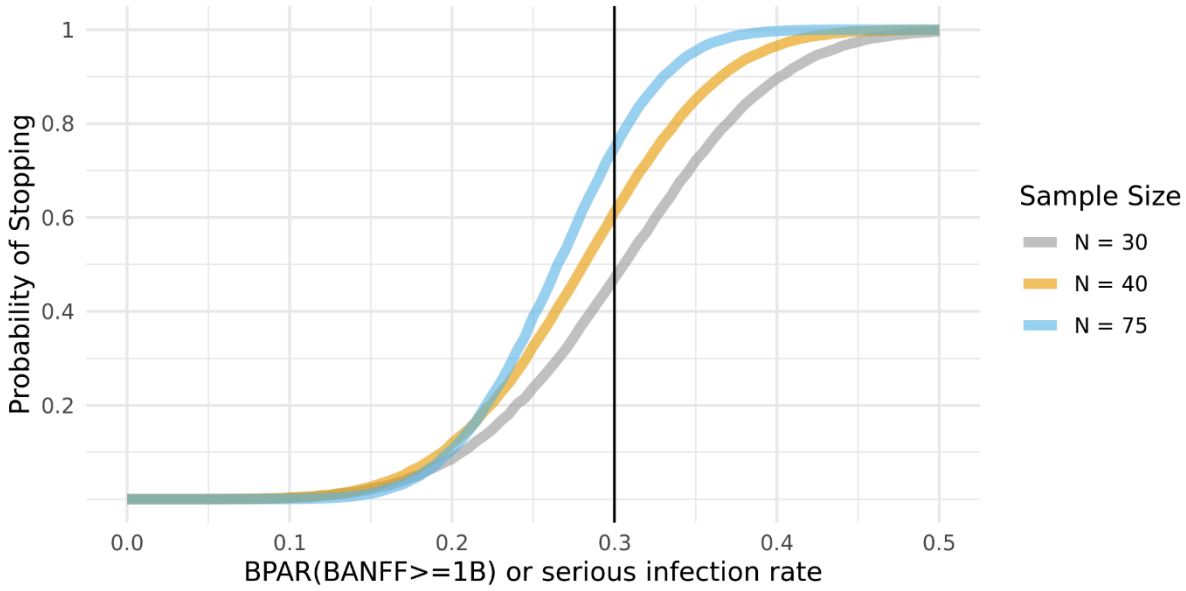
The stopping rules as defined in Section 5.6.2.2 are designed to ensure enrollment in a CFZ533 treatment arm will be stopped if there is a high probability (>90%) that the true BPAR (BANFF>=1B or ABMR) rate or true serious infection rate is greater than 30%. The stopping rules apply until enrollment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

[redacted]

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 9-1 indicates 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 9-1 Probability of stopping enrollment in the *de novo* cohort (Cohort 1) for various true BPAR or serious infection rates



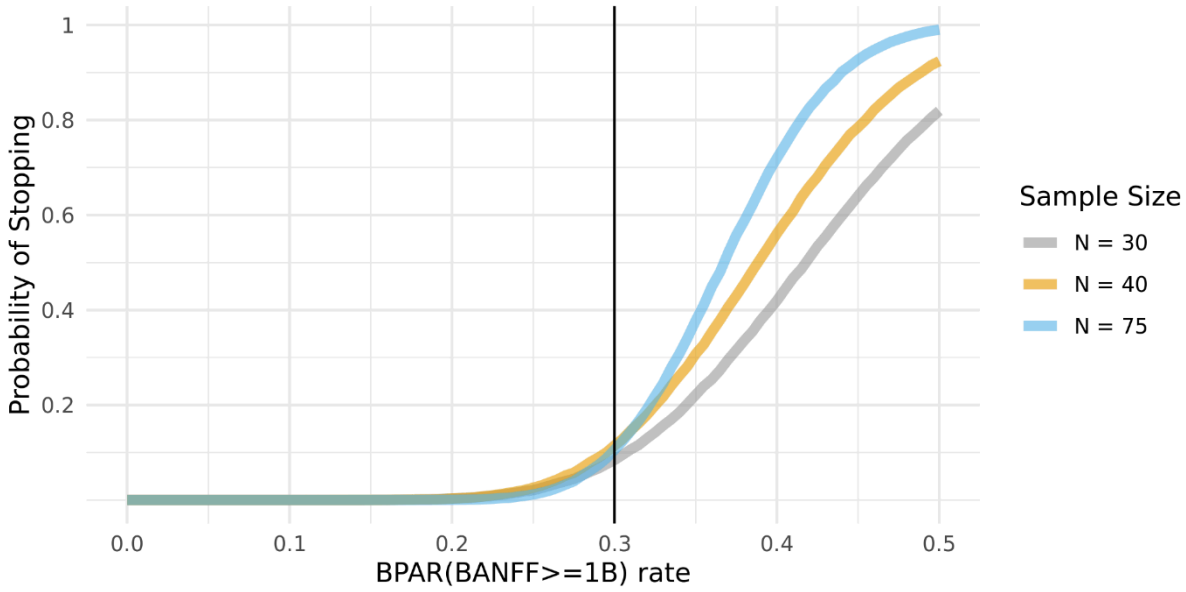
Cohort 2 - maintenance

The stopping rules as defined in Section 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 9-2 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.

[redacted]

Figure 9-2 Probability of stopping enrollment in the maintenance cohort (Cohort 2) for various true BPAR rates



9.8.2 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 9-3 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 9-3 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%

[redacted]

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 9-4 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 9-4 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%

9.8.3 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

[redacted]

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 9-5). 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 9-5 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 9-5 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).

[redacted]

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).

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients/subjects may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if applicable after such consent has been provided by a legally acceptable representative(s) of the patient. Informed consent must be obtained before conducting any study-specific procedures (e.g., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

As per Section 3.7, during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent or re-consent discussion remotely (e.g., telephone, videoconference) if allowable by a local Heath Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g., the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the patient.

The following informed consents are included in this study:

- Main study consent, which also included:

[redacted]

  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
- Consent for in home health care (as part of main consent or dedicated consent).
- As applicable, Pregnancy Outcomes Reporting Consent for female subjects or the female partners of any male subjects who took study treatment

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male patients must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, ICF, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients/subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance, a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

10.6 Patient Engagement

The following patient engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the timepoints indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis/Sponsor.

- Thank you letter - at randomization
- Understanding Clinical Trials - prior to enrollment
- Patient Study Overview - prior to enrollment
- The CIRRUS I Study Schedule - at enrollment
- Tote bags - at enrollment
- Four newsletters - at randomization and during study participation
- Two In My Shoes videos, kidney transplant patients talking about their experiences of transplantation and inclusion in a clinical trial - after randomization
- Microsite, a website that includes the engagement documents - after randomization
- Instructional video for use of pre-filled syringes - after randomization
- Plain language trial summary - after primary analysis
- Thank you letter - patients last study visit

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients/subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients/subjects may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is

[redacted]

expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

[redacted]

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13 Appendix 1: Clinically notable laboratory values and vital signs

The following criteria will be used to define expanded limits and notable abnormalities of key laboratory tests.

Laboratory variable	Standard units	SI units
Liver function and related variables		
SGOT (AST)	≥3 × ULN	≥3 × ULN
SGPT (ALT)	≥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 F ≥9 mg/dL	M ≥714 µmol/L F ≥535 µmol/L
Glucose	<45 mg/dL >250 mg/dL	<2.5 mmol/L >13.9 mmol/L
Cholesterol	≥350 mg/dL	≥9.1 mmol/L
Triglycerides	≥750 mg/dL	≥8.5 mmol/L
CK (MB)	None	None
Potassium	≤3.0 mEq/L ≥6.0 mEq/L	≤3 mmol/L ≥6 mmol/L
Calcium	≤6 mg/dL ≥13 mg/dL	≤1.5 mmol/L ≥3.2 mmol/L
Magnesium	< 1.0 mg/dL > 3.6 mg/dL	< 0.4 mmol/L > 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/mm^3 ≥700 k/mm^3	<50 × 10^9/L ≥700 × 10^9/L
Leukocytes (WBCs)	≤2.0 k/mm^3 ≥16 k/mm^3	≤ 2.0 × 10^9/L ≥16 × 10^9/L
Hematology variables: differential		
Granulocytes (poly, neutrophils)	≤1,000/mm^3	≤1 x 10^9/L
Eosinophils	≥12%	≥12%
Lymphocytes	≤1,000/mm^3	≤1× 10^9/L

[redacted]

Vital sign variables	**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)

[redacted]

14 Appendix 2: Updated 2017 Banff classification

Category 1: Normal biopsy or nonspecific changes

Category 2: Antibody-mediated changes

Active ABMR: all 3 categories must be met for diagnosis

1. Histologic evidence of acute tissue injury, including one or more of the following:
   - Microvascular inflammation (g > 0 and /or ptc > 0) in the absence of recurrent or *de novo* glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥1 alone is not sufficient and g must be ≥ 1
   - Intimal or transmural arteritis (v > 0)[1]
   - Acute thrombotic microangiopathy in the absence of any other cause
   - Acute tubular injury in the absence of any other apparent cause
2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following:
   - Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections or C4d > 0 by IHC on paraffin sections)
   - At least moderate microvascular inflammation ([g + ptc] ≥2) in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection; ptc ≥2 alone is not sufficient, and g must be ≥1
   - Increased expression of gene transcripts/classifiers in the biopsy tissue strongly associated with ABMR, if thoroughly validated
3. Serologic evidence of donor-specific antibodies (DSA to HLA or other antigens). C4d staining or expression of validated transcripts/classifiers as noted above in criterion 2 may substitute for DSA; however thorough DSA testing, including testing for not-HLA antibodies if HLA antibody testing is negative, is strongly advised whenever criteria 1 and 2 are met.

Chronic active ABMR: all 3 criteria must be met for diagnosis[2]

1. Morphologic evidence of chronic tissue injury, including one or more of the following:
   - Transplant glomerulopathy (TG) (cg > 0), if no evidence of chronic thrombotic microangiopathy or chronic recurrent/de novo glomerulonephritis; includes changes evident by EM alone (cg1a)
   - Severe peritubular capillary basement membrane multilayering (requires EM)[3]
   - Arterial intimal fibrosis of new onset, excluding other causes; leukocytes within the sclerotic intima favor chronic ABMR if there is no prior history of TCMR, but are not required
2. Identical to criterion 2 for active ABMR, above
3. Identical to criterion 3 for active ABMR, above, including strong recommendation for DSA testing whenever criteria 1 and 2 are met

[redacted]

C4d staining without evidence of rejection: All four features must be present for diagnosis[4]

1. Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d >0 by IHC on paraffin sections)
2. Criterion 1 for active or chronic, active ABMR not met
3. No molecular evidence for ABMR as in criterion 2 for active and chronic, active ABMR
4. No acute or chronic active TCMR, or borderline changes

Category 3: Borderline changes

Suspicious (Borderline) for acute TCMR

- Foci of tubulitis (t > 0) with minor interstitial inflammation (i0 or i1), or moderated-severe interstitial inflammation (i2, i3) with mild (t1) tubulitis; retaining the i1 threshold for borderline with t > 0 is permitted although this must be made transparent in reports and publications

No intimal or transmural arteritis (v = 0)

Category 4: TCMR

Acute TCMR

Grade IA.	Interstitial inflammation involving >25% of nonsclerotic cortical parenchyma (i2 or i3) with moderate tubulitis (t2) involving 1 or more tubules, not including tubules that are severely atrophic[5]
Grade IB.	Interstitial inflammation >25% of nonsclerotic cortical parenchyma (i2 or i3) with severe tubulitis (t3) involving 1 or more tubules, not including tubules that are severely atrophic[5]
Grade IIA[1].	Mild to moderate intimal arteritis (v1) with or without interstitial inflammation and/or tubulitis
Grade IIB[1].	Severe intimal arteritis (v2) with or without interstitial inflammation and/or tubulitis
Grade III[1].	Transmural arteritis and/or arterial fibrinoid necrosis of medial smooth muscle with accompanying mononuclear cell intimal arteritis (v3), with or with interstitial inflammation and /or tubulitis

Chronic active TCMR

Grade 1A.	Interstitial inflammation involving >25% of the total cortex (ti score 2 or 3) with moderate tubulitis (t2) involving 1 or more tubules, not including severely atrophic tubules[5]; other known causes of i-IFTA should be ruled out

[redacted]

Grade 1B.	Interstitial inflammation involving >25% of the total cortex (ti score 2 or 3) and >25% of the sclerotic cortical parenchyma (i-IFTA score 2 or 3) with severe tubulitis (t3) involving 1 or more tubules, not including severely atrophic tubules5; other known causes of i-IFTA should be ruled out
Grade 11[1].	Chronic allograft arteriopathy (arterial intimal fibrosis with mononuclear cent inflammation in fibrosis and formation of neointima)

Legend:
Updates from Banff 2015[1] are indicated in boldface type.
[1]It should be noted that these arterial lesions may be indicative of ABMR, TCMR, or mixed ABMR/TCMR. "v" lesions and chronic allograft arteriopathy are only scored in arteries having continuous media with ≥2 smooth muscle layers.
[2]Lesions of chronic active ABMR can range from primarily active lesions with early transplant glomerulopathy (TG) evident only by EM (cg1a) to those with advanced TG and other chronic changes in addition to active microvascular inflammation. For biopsy specimens showing TG and/or peritubular capillary basement membrane multilayering in the absence of evidence of current/recent antibody interaction with the endothelium (criterion 2) but with a prior documented diagnosis of active or chronic active ABMR or documented prior evidence of DSA, the term "chronic ABMR" should be applied.
[3]Indicates ≥7 layers in 1 cortical peritubular capillary and ≥5 in 2 additional capillaries, avoiding portions cut tangentially.
[4]The clinical significance of these findings may be quite different in grafts exposed to anti-blood group antibodies (ABO-incompatible allografts), where they do not appear to be injurious to the graft and may represent accommodation. However, with anti-HLA antibodies, such lesions may progress to chronic ABMR, and more outcome data are needed.
[5]A severely atrophic tubule is defined as one with each of the following 3 features: a diameter <25% of that of unaffected or minimally affected tubules on the biopsy, an undifferentiated-appearing, cuboidal or flattened epithelium, and pronounced wrinkling and/or thickening of the tubular basement membrane. (Source: Loupy et al 2017).

Abbreviations: ABMR, antibody-mediated rejection; cg, Banff chronic glomerulopathy score; DSA, donor-specific antibody; EMA, European Medicines Agency; EM, electron microscopy; FDA, US Food and Drug Administration; g, Banff glomerulitis score; IF, immunofluorescence; IFTA, interstitial fibrosis and tubular atrophy; i-IFTA, inflammation in areas of interstitial fibrosis and tubular atrophy; ptc, Banff peritubular capillaritis score; TCMR, T cell-mediated rejection; TG transplant glomerulopathy

[redacted]

15 Appendix 3: Stopping Rules for CFZ533

Cohort 1:

Treatment arm (N)	Number of patients with BPAR (BANFF>=1B) that would lead to stopping the treatment arm (n_1)	Observed BPAR (BANFF>=1B) rate (n_1/N)	Number of patients with serious infections that would lead to stopping the treatment arm (n_2)	Observed serious infection rate (n_2/N)
10	5	50%	5	50%
11	6	55%	6	55%
12	6	50%	6	50%
13	6	46%	6	46%
14	7	50%	7	50%
15	7	47%	7	47%
16	8	50%	8	50%
17	8	47%	8	47%
18	8	44%	8	44%
19	9	47%	9	47%
20	9	45%	9	45%
21	9	43%	9	43%
22	10	45%	10	45%
23	10	43%	10	43%
24	10	42%	10	42%
25	11	44%	11	44%
26	11	42%	11	42%
27	12	44%	12	44%
28	12	43%	12	43%
29	12	41%	12	41%
30	13	43%	13	43%
31	13	42%	13	42%
32	13	41%	13	41%
33	14	42%	14	42%
34	14	41%	14	41%
35	14	40%	14	40%
36	15	42%	15	42%
37	15	41%	15	41%
38	15	39%	15	39%
39	16	41%	16	41%
40	16	40%	16	40%
41	16	39%	16	39%
42	17	40%	17	40%
43	17	40%	17	40%
44	17	39%	17	39%
45	18	40%	18	40%

[redacted]

Treatment arm (N)	Number of patients with BPAR (BANFF>=1B) that would lead to stopping the treatment arm (n_1)	Observed BPAR (BANFF>=1B) rate (n_1/N)	Number of patients with serious infections that would lead to stopping the treatment arm (n_2)	Observed serious infection rate (n_2/N)
46	18	39%	18	39%
47	19	40%	19	40%
48	19	40%	19	40%
49	19	39%	19	39%
50	20	40%	20	40%
51	20	39%	20	39%
52	20	38%	20	38%
53	21	40%	21	40%
54	21	39%	21	39%
55	21	38%	21	38%
56	22	39%	22	39%
57	22	39%	22	39%
58	22	38%	22	38%
59	23	39%	23	39%
60	23	38%	23	38%
61	23	38%	23	38%
62	24	39%	24	39%
63	24	38%	24	38%
64	24	38%	24	38%
65	25	38%	25	38%
66	25	38%	25	38%
67	25	37%	25	37%
68	26	38%	26	38%
69	26	38%	26	38%
70	26	37%	26	37%
71	27	38%	27	38%
72	27	38%	27	38%
73	27	37%	27	37%
74	28	38%	28	38%
75	28	37%	28	37%

Cohort 2:

Treatment arm (N)	Number of patients with BPAR (BANFF>=1B) that would lead to stopping the treatment arm (n_1)	Observed BPAR (BANFF>=1B) rate (n_1/N)
10	5	50%

[redacted]

Treatment arm (N)	Number of patients with BPAR (BANFF>=1B) that would lead to stopping the treatment arm (n_1)	Observed BPAR (BANFF>=1B) rate (n_1/N)
11	6	55%
12	6	50%
13	6	46%
14	7	50%
15	7	47%
16	8	50%
17	8	47%
18	8	44%
19	9	47%
20	9	45%
21	9	43%
22	10	45%
23	10	43%
24	10	42%
25	11	44%
26	11	42%
27	12	44%
28	12	43%
29	12	41%
30	13	43%
31	13	42%
32	13	41%
33	14	42%
34	14	41%
35	14	40%
36	15	42%
37	15	41%
38	15	39%
39	16	41%
40	16	40%
41	16	39%
42	17	40%
43	17	40%
44	17	39%
45	18	40%
46	18	39%
47	19	40%
48	19	40%

[redacted]

Treatment arm (N)	Number of patients with BPAR (BANFF>=1B) that would lead to stopping the treatment arm (n_1)	Observed BPAR (BANFF>=1B) rate (n_1/N)
49	19	39%
50	20	40%
51	20	39%
52	20	38%
53	21	40%
54	21	39%
55	21	38%
56	22	39%
57	22	39%
58	22	38%
59	23	39%
60	23	38%
61	23	38%
62	24	39%
63	24	38%
64	24	38%
65	25	38%
66	25	38%
67	25	37%
68	26	38%
69	26	38%
70	26	37%
71	27	38%
72	27	38%
73	27	37%
74	28	38%
75	28	37%

[redacted]

16 Appendix 4: Blinding and unblinding

Randomization data are kept strictly confidential. Prior to final clinical database lock, unblinding is allowed only for authorized personnel as described in the table below.

Blinding levels	**Time or Event**								
Role	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Drug Supply	UI	UI	UI	UI	UI	UI	UI	UI	UI
Randomization Office	UI	UI	UI	UI	UI	UI	UI	UI	UI
Unblinded Physician	B	B	UT	UT	UT	UI	UI	UI	UI
PK Bioanalytics	B	UI	UI	UI	UI	UI	UI	UI	UI
Data Manager	B	B	UI	UI	UI	UI	UI	UI	UI
Clinical Scientific Expert	B	UI	UI	UI	UI	UI	UI	UI	UI
Global Trial Director	B	B	UT	UT	UT	UI	UI	UI	UI
Study Monitor	B	B	UT	UT	UT	UI	UI	UI	UI
Subject	B	B	UT	UT	UT	UI	UI	UI	UT
Treating Physician	B	B	UT	UT	UT	UI	UI	UI	UT
Primary Investigator	B	B	UT	UT	UT	UI	UI	UI	UT
Data Monitoring Committee; Independent statistician; Independent modeler; Independent programmer	B	B	B	UI	UI	UI	UI	UI	UI
Select Novartis management associates not involved in site monitoring activities	B	B	UT	UT	UT	UT	UI	UI	UI
Clinical Development Director, Blinded physician	B	B	B	B	B	B	UI	UI	UI
PK Expert	B	B	UT	UT	UT	UT	UI	UI	UI
Statistician, Modeler, Programmer	B	B	B	B	B	B	UI	UI	UI
Adjudication committee (independent central pathologists) for biopsy review	B	B	B	B	B	B	B	B	B

UI Allowed to be unblinded on individual patient level

[redacted]

UT Allowed to be unblinded on individual patient level with regards to investigational vs. control treatment, but NOT the dose level of investigational treatment in Cohort 1 (high vs. low CFZ533 doses)

B Remains blinded

All efforts will be made to minimize unblinding.

1 Generation of randomization list, QC and lock randomization list
2 Patient allocation to treatment
3 Treatment administration
4 Safety emergency event (unblinding of a single subject)
5 (First) DMC report
6 After End of Treatment or early treatment discontinuation (unblinding of a single subject)
7 After 12 month database lock of Cohort 1 and Cohort 2
8 Until final database lock, Month 60
9 After IA database lock of both cohorts

The laboratory bioanalyst will receive a copy of the randomization schedule to facilitate analysis of the PK samples and avoid unnecessary PK testing on placebo patients. The laboratory bioanalyst may provide concentration data to the PK expert under blinded conditions and will keep unblinding information confidential until the clinical database lock for IA for Cohort 1 and Cohort 2. Unblinding of site and patient will only occur in the case of patient emergencies (see Section 5.6) and at completion of the primary analyses at Month 12.

[redacted]

17 Appendix 5a: Blood log for scheduled PK, PD, Immunogenicity, [redacted] and DSA sampling

Cohort 1 - Blood collection log for pharmacokinetics, pharmacodynamics, immunogenicity, [redacted] and DSA

Day / Month	Time point	Dose reference ID#2 [a#]	PK sample number [*#+]	[redacted]	Immunogenicity sample number+	[redacted]	DSA
Day 1	Pre-dose	1	100	200	300	400	
Day 1	EOI+1h	1	101				
Day 5	Pre-dose	2	102	202			
Day 5	EOI+1h	2	103				
Day 15	Pre-dose	3	104	204			
Month 1 (day 29)	Pre-dose	4	105	205	305		
Month 1.5 (day 43)	Pre-dose	5	106				
Month 2 (day 57)	Pre-dose	6	107	207	307		
Month 2.5 (day 71)	Pre-dose	7	108				
Month 3 (day 85)	Pre-dose	8	109	209	309	409	
Month 4 (day 113)	Pre-dose	10	110				
Month 6 (day 169)	Pre-dose	14	111	211	311	411	
Month 8 (day 225)	Pre-dose	18	112	212	312		
Month 10 (day 281)	Pre-dose	22	113	213	313		
Month 12 (Day 337)	Pre-dose	26	114	214	314	414	514
Month 15 (Day 421)	Pre-dose	32	115	215	315		
Month 18 (Day 505)	Pre-dose	38	116	216	316		
Month 21 (Day 589)	Pre-dose	44	117	217	317		
Month 24 (Day 673)	Pre-dose	50	118	218	318		
Month 30 (Day 841)	Pre-dose	62	119		319		
Month 36 (Day 1009)	Pre-dose	74	120		320		
Month 42 (Day 1177)	Pre-dose	86	121		321		
Month 48 (Day 1345)	Pre-dose	98	122		322		
Month 54 (Day 1513)	Pre-dose	110	123		323		

[a] Dose reference ID#2 is used to calculate elapsed time EACLTM_2, e.g., a Dose Reference ID of 14 for pre-dose PK Sample 111 on Month 6 (14th planned dose of CFZ533 in Cohort 1) means the elapsed time is calculated with reference to planned 14th CFZ533 dose timing (and is negative). **Note**: Dose Reference ID#2 is 1 for all PK samples to calculate elapsed time since first dose (EACLTM_1)

* If a PK sample is collected at an unscheduled visit, the sample numbers will follow the pattern 1001, 1002, 1003 etc.

If an extra subcutaneous dose(s) of CFZ533 due to IV-Ig administration is administered at an unscheduled visit, the Dose Reference ID#2 will be derived from the closest previously scheduled administered dose (Dose reference ID#2 = x) and the unscheduled Dose Reference ID#2 will be x001. (e.g., Dose reference ID#2 39001 will be assigned to unscheduled dose of CFZ533 administered following the scheduled administration with the Dose Reference ID#2 of 39) This dose reference ID#2 is used to calculate elapsed time EACLTM_2 for the unscheduled pre-dose PK sample collected prior IV-Ig administration at an unscheduled visit.

+ Taken only in CFZ533 patients

[redacted]

° Taken in CFZ533 & SoC patients

Cohort 2 - Blood collection log for pharmacokinetics, pharmacodynamics, immunogenicity, [redacted] and DSA

Day / Month	Time point	Dose reference ID#2 [a#]	PK sample number[*#+]	[redacted]	Immunogenicity sample number+	[redacted]	DSA
Day 1	Pre-dose	1	150	250	350	450	
Day 1	EOI+1h	1	151				
Day 15	Pre-dose	2	152	252			
Month 1 (Day 29)	Pre-dose	3	153	253	353		
Month 1.5 (Day 43)	Pre-dose	4	154				
Month 2 (Day 57)	Pre-dose	5	155	255	355		
Month 2.5 (Day 71)	Pre-dose	6	156				
Month 3 (Day 85)	Pre-dose	7	157	257	357	457	
Month 4 (Day 113)	Pre-dose	9	158				
Month 6 (Day 169)	Pre-dose	13	159	259	359	459	
Month 8 (Day 225)	Pre-dose	17	160	260	360		
Month 10 (Day 281)	Pre-dose	21	161	261	361		
Month 12 (Day 337)	Pre-dose	25	162	262	362	462	562
Month 15 (Day 421)	Pre-dose	31	163	263	363		
Month 18 (Day 505)	Pre-dose	37	164	264	364		
Month 21 (Day 589)	Pre-dose	43	165	265	365		
Month 24 (Day 673)	Pre-dose	49	166	266	366		
Month 30 (Day 841)	Pre-dose	61	167		367		
Month 36 (Day 1009)	Pre-dose	73	168		368		
Month 42 (Day 1177)	Pre-dose	85	169		369		
Month 48 (Day 1345)	Pre-dose	97	170		370		
Month 54 (Day 1513)	Pre-dose	109	171		371		

[a] Dose reference ID#2 is used to calculate elapsed time EACLTM_2, e.g., a Dose Reference ID of 79 for pre-dose PK Sample 171 on Month 39 (79th planned dose of CFZ533 in Cohort 2) means the elapsed time is calculated with reference to planned 79th CFZ533 dose timing (and is negative). **Note:** Dose Reference ID#2 is 1 for all PK samples to calculate elapsed time since first dose (EACLTM_1).

* If a PK sample is collected at an unscheduled visit, the sample numbers will follow the pattern 1501, 1502, 1503 etc.

[#] If an extra subcutaneous dose(s) of CFZ533 due to IV-Ig administration is administered at an unscheduled visit, the Dose Reference ID#2 will be derived from the closest previously scheduled administered dose (Dose reference ID#2 = x) and the unscheduled Dose Reference ID#2 will be x001. (e.g., Dose reference ID#2 39001 will be assigned to unscheduled dose of CFZ533 administered following the scheduled administration with the Dose Reference ID#2 of 39). This dose reference ID#2 is used to calculate elapsed time EACLTM_2 for the unscheduled pre-dose PK sample collected prior IV-Ig administration at an unscheduled visit.

+ Taken only in CFZ533 patients

° Taken in CFZ533 & SoC patients

[redacted]

17 Appendix 5b: Blood log for unscheduled PK, PD and immunogenicity samples

Before intravenous immunoglobulin (IV-Ig; see protocol for additional details), a blood sample will be taken to assess the CFZ533 concentration in plasma (PK sample).

For a PK, PD or immunogenicity sample collected at an unscheduled visit/event, for each subject, a *unique sample number* will be given and the *timing* of blood sample will be recorded.

The unique sample number will follow the pattern

PK

- Cohort 1 (*de novo* patients): 1001, 1002, 1003, 1004, 1005 ... etc ...
- Cohort 2 (conversion patients): 1501, 1502, 1503, 1504, 1505 ... etc ...

PD

- Cohort 1 (*de novo* patients): 2001, 2002, 2003, 2004, 2005 ... etc ...
- Cohort 2 (conversion patients): 2501, 2502, 2503, 2504, 2505 ... etc ...

Immunogenicity

- Cohort 1 (*de novo* patients): 3001, 3002, 3003, 3004, 3005 ... etc ...
- Cohort 2 (conversion patients): 3501, 3502, 3503, 3504, 3505 ... etc ...

[redacted]

18 Appendix 6: Injecting the study drug

The recommended areas for injection are the skin on the lower abdomen and the skin at the front of the middle abdomen, upper thigh and upper arm. In case of injection on the upper arm or thigh, one injection is applied to each arm or each thigh (do not apply both syringes to one arm or thigh only). Patients should not self-inject into their arms when using the PFS. For regular subcutaneous injections, the injection site must be rotated each time to keep the skin healthy.

- Use an alcohol wipe to clean the skin at the injection site chosen, allowing the skin to dry.
- Pinch a fold of skin (approximately 2.5 to 5 cm in size) at the cleaned injection site and hold it firmly. With a quick, short motion, inject the needle at an angle between 45° and 90°, depending on the amount of subcutaneous fat.
- When the needle is completely inserted into the skin, let go of the skin and hold the syringe near its base to stabilize it. Push the plunger to inject all the study medication at a slow and steady rate, i.e., count approximately 10 seconds total injection time. Make sure that the full dose is injected.
- When the syringe is empty, remove the needle out of the skin, being careful to keep it at the same angle as inserted. Press a cotton ball or gauze over the injection site for 10 seconds and thereafter apply a plaster. Do not rub the injection site.

Subcutaneous dosing of CFZ533 – Cohort 1

Guidance for 600 mg dose: 2 injections of 2 mL CFZ533

Guidance for 300 mg dose: 1 x 2 mL CFZ533 plus 1 x 2 mL Placebo (Placebo will be removed after unblinding).

Subcutaneous dosing of CFZ533 – Cohort 2

Guidance for 450 mg dose: 1 x 2 mL CFZ533 plus 1 x 1 mL CFZ533

More details are provided in the pharmacy manual.

[redacted]