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CFZ533 (Iscalimab)

Clinical Trial Protocol CCFZ533A2202 / NCT03781414

A 12-month, open-label, multicenter, randomized, safety, efficacy, pharmacokinetic (PK) and pharmacodynamic (PD) study of two regimens of anti-CD40 monoclonal antibody, CFZ533 vs. standard of care control, in adult *de novo* liver transplant recipients with a 12-month additional follow-up and a long-term extension (CONTRAIL I)

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List of abbreviations

AE	Adverse Event
ADA	Anti-Drug Antibodies
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AR	Acute Rejection
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
b.i.d.	bis in die/twice a day
BMI	Body Mass Index
BPAR	Biopsy Proven Acute Rejection
BUN	Blood Urea Nitrogen
CMV	Cytomegalovirus
CO	Country Organization
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CS	corticosteroids
CSR	Clinical study report
CTC	Common Terminology Criteria
DMC	Data Monitoring Committee
EBV	Epstein Barr Virus
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
ELISA	Enzyme-linked immunosorbent assay
EOI	End of Infusion
EOS	End Of Study
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GL	Graft Loss
h	Hour
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
HCP	Health Care Provider
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus

i.v.	intravenous
IA	Interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IG	Immunoglobulin
IMP	Investigational Medicine Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDH	lactate dehydrogenase
LFT	Liver function test
LLOQ	lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MMF	Mycophenolate mofetil
MPA	Mycophenolate Acid
NCDS	Novartis Clinical Data Standards
NODM	New Onset of Diabetes Mellitus
p.o.	oral(ly)
PCP	Pneumocystis carinii pneumonia
PD	Pharmacodynamic(s)
PFS	Pre-filled syringes
PK	Pharmacokinetic(s)
PT	prothrombin time
pTNM	Modified Tumor Node Metastases
QD	Once a day
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
RAP	The Report and Analysis Plan
RBC	red blood cell(s)
RNA	Ribonucleic acid
RoW	Rest of World
s.c.	subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome associated coronavirus - 2

SBP	Systolic Blood Pressure
sCR	serum creatinine
SD	standard deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SVR12	Sustained virologic response defined as HCV-RNA undetectable 12 weeks after completing HCV treatment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAC	tacrolimus
tAR	treated Acute Rejection
tBPAR	treated Biopsy Proven Acute Rejection
ULN	upper limit of normal
ULQ	upper limit of quantification
UTI	Urinary Tract Infection
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g., any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Control drug	A study drug (active or placebo) 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 participant 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
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and 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
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest
Investigational drug/ treatment	The drug whose properties are being tested in the study
Long-term extension period	Period after Month 24 visit until end of study
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e., concomitant or rescue therapy)
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
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	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized participant
Run-in Failure	A participant who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to participant's intervention or other treatment)
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
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
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

Amendment 04

Amendment Rationale

The key purpose of this amendment is to increase the study duration by adding an extension period to collect long-term data in a controlled, clinical trial setting. Patients will stay in the long-term extension for at least 3 years.

Further, this amendment clarifies that in exclusion No. 12, "any history of coagulopathy", will exclude only recipients that have a history of non-liver related coagulopathy or medical condition requiring long-term anticoagulation. Moreover, a new exclusion criterion No. 31 is added to exclude donors with confirmed history of SARS-CoV-2 infection given the unknown long term sequelae of SARS-CoV-2 infection in the liver.

Finally, several sections were updated with instructions for conducting the study during a public health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits.

This clinical study is ongoing since September 2019 and 59 subjects have been randomized as of 28-Feb-2021. The changes proposed by this amendment will not restrict the patient population or have a major impact on study results.

Changes to 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.

List of abbreviations: new abbreviations added and non-applicable ones deleted

Glossary of terms: new terms added

Protocol summary: updated with Amendment 4 changes

Section 1.1 – Background: updates on number of patients treated with CFZ533 according to IB edition 10 released in December 2020.

Table 2-1 – Objectives and related endpoints: secondary objective updated to remove redundancy with key secondary objective; [redacted]

Section 3 – Study design: Study design figure updated; addition of the extension period; update of the treatment period for every arm up to the end of extension; clarification that from Month 12, self-administration at home will be possible using the PFS; CFZ533 compensation procedure deleted to avoid redundancy with Section 6.1.4; clarification that minimum cortisone dose is 5mg/day prednisone or equivalent dose of another oral corticosteroid.

Figure 3-1-Study design: Figure updated with amendment 4 changes.

Section 4.2 – Rationale for dose/regimen and duration of treatment: end of study updated to consider the extension. Updated study CCFZ533X2203 as completed.

Section 4.3 – Rationale for CFZ533 dosing to compensate for drug loss due to ascites drainage: CFZ533 compensation procedure deleted to avoid redundancy with section 6.1.4.

Section 4.5 – Purpose and timing of interim analyses/design adaptations: Clarification that participants will receive study treatment for a variable duration depending on when they join the study and complete the extension; addition of a study analysis at the end of the extension; clarification that additional IAs may be conducted to support decision making concerning the current clinical study or project, the sponsor's clinical development projects in general or in case of any safety concerns; clarification that the stopping rules only apply up to Month 24 and not during the extension.

Section 4.6 – Risks and benefit: Removal of a duplicated paragraph; Information that new mitigation procedures in case of Public Health emergency have been added to the protocol.

Section 5 – Study population: Latin America added to the study

Section 5.1 – Inclusion criteria: criterion 8 updated to revise ULN for total bilirubin.

Section 5.2 – Exclusion criteria: criterion 9 updated to change < symbol to ≤ for Milan criteria; Exclusion criteria 12 and 17 updated to provide more clarity, exclusion criterion 31 added. Criteria 20 updated to clarify that bilateral tubal ligation surgery is required to consider women as not of child bearing potential.

Section 6.1.3 – Treatment arms/groups: end of treatment period updated

Section 6.1.5 – Post-trial access: Deletion of "The planned duration of treatment is the 24-month study period. Participants may be discontinued from treatment earlier due to unacceptable toxicity, graft rejection, graft loss, pregnancy, and/or treatment discontinuation at the discretion of the investigator or the participant. For participants who are in the opinion of the investigator are still deriving clinical benefit from CFZ533A2202 study, every effort will be made to continue provision of study treatment" as not required.

Section 6.2.2- Prohibited medication: Clarification that non-protocol immunosuppressants are only allowed for participants in follow-up, up to Month 24.

Section 6.5.2 – Permitted dose adjustments and interruptions of other study treatment: Clarification that corticosteroids considered for the minimal dose of 5 mg is prednisone or equivalent dose of another oral corticosteroid.

Section 6.6.1 – Treatment compliance: Period for local TAC trough level assessment updated until end of study.

Section 6.6.2 – Recommended treatment of adverse events: Clarification that central biopsy readings in case of suspicion of acute rejection are mandatory until Month 24; Clarification that patient discontinued due to prohibited concomitant medications will be followed-up up to Month 24 and not until EOS; Clarification that anti-T cell antibody therapy for rejection is prohibited until Month 24; clarification that participants requiring anti-T cell antibody therapy for rejection during the long-term extension will be discontinued from the study.

Section 6.7.1.2 – Handling of Tacrolimus, MPA and corticosteroids: Addition of a new paragraph describing mitigation procedures allowed during a Public Health emergency.

Section 6.7.2.1 – CFZ533 administration: reference to assessment tables updated to add Table 8-3; schedule of on-site visits if patient self-administers CFZ533 using PFS clarified; investigator responsibility to evaluate patient's storage capacity of study treatment; treatment

duration updated to consider extension period; paragraph deleted as redundant with previous information.

Section 6.7.2.2 – Tacrolimus administration: Treatment duration updated to consider extension period

Section 8 - Visit and assessments: Reference to Table 8-3 related to extension period added; Update of a paragraph regarding the mitigation procedures allowed during a Public Health emergency; Study participation in case of treatment discontinuation prior to or during extension period described.

Table 8-1: 1 footnote added for EOS visit if extension period continues beyond Month 72; 1 footnote updated to remove information to take an ascites aliquot from the collection bag.

Table 8-2- Assessment schedule (Treatment period 2): EOT and end of period/EOS at M24 visit removed;.

Table 8-3 – Assessment schedule (extension period): Addition of table describing assessment schedule during extension period.

Section 8.3.1 – Suspected Acute Rejection/Biopsy Proven Acute Rejection (BPAR): Clarification that central biopsy reading of for-cause biopsies only applies up to Month 24.

Section 8.3.3 – Graft loss: Clarification on CRF pages to be used to report graft loss according to time of occurrence

Section 8.4 – Safety: Table 8-3 renumbered as Table 8-4 and references to Table 8-3 added; addition of a new paragraph describing mitigation procedures allowed during a Public Health emergency.

Section 8.4.1 – Laboratory evaluations: Addition of a new section describing mitigation procedures allowed during a Public Health emergency.

Section 8.4.3 – Pregnancy and assessment of fertility: Reference to Table 8-3 added. Visits at which B-hCG serum pregnancy test is to be performed has been updated. In case treatment is discontinued prior to Month 24 visit, then urine pregnancy tests will be performed at the applicable follow-up visit. A new paragraph has been added describing the mitigation procedures allowed during a Public Health emergency.

Table 8-5: renumbered from Table 8-4 to Table 8-5

Section 8.5 – Additional assessments: Language of this section is updated to describe the mitigation procedures allowed during a Public Health emergency.

Section 8.5.3 - Pharmacodynamics: Reference to Appendix 6b removed as not applicable.

[redacted]

Section 8.5.6 - CFZ533 concentration in drained ascites fluid: Clarification that it only applies up to Month 24; collection of ascites aliquot from the bag with highest volume deleted, as not aligned with local practices.

[redacted]

Section 9.1.1 – Study treatment discontinuation and study discontinuation: typos corrections; clarification of visit to be performed in case of treatment discontinuation; deletion of term "special interest" for AEs; description of visit to be completed in case of discontinuation during extension period.

Section 9.1.5 – Stopping rules: Clarification that stopping rules apply up to Month 24, and not to the extension period.

Section 9.2 – Study completion and post-study treatment: Update of the end of study definition; clarification when the study will end; update on time to start TAC after study completion.

Section 10.1.1 - Adverse events: Period for SAE reporting updated according to last CFZ533 dose.

Section 10.1.3 – SAE reporting: clarified that SAE reporting will be required until 14 weeks after EOS visit.

Section 10.1.4 – Pregnancy reporting: Reference to Table 8-3 added.

Section 12 – Data analysis and statistical method: Addition of a study analysis at the end of the extension; sentence "PK/PD and immunogenicity analysis is up to Month 24 (Day 673)" has been removed.

Section 12.1 – Analysis sets: update of the full analysis set (FAS) definition and addition of misrandomized definition.

Section 12.4.4 – Supportive analyses: clarification that Kaplan-Meier graph for BPAR will consider BPAR censored at Month 12.

Section 12.5.1 – Efficacy endpoint(s): Text formatting updates for more clarity.

Section 12.5.2.1 – Renal function: Deletion of evaluation of eGFR at Month 24 as key secondary objective is applicable at Month 12 time point only. Deletion of the MDRD as formula is already described in section 16.4; clarification that the Renal function at Month 24 measured by eGFR will follow the same analysis strategy as the Month 12 analysis.

Section 12.5.2.3 – Other safety evaluation: Table 8-3 added as reference.

[redacted]

Section 12.6 – Clarification that stopping rules are applied up to Month 24.

Section 12.7 – Sample size calculation: Update of erroneous Figure 12-2.

Section 15 – Reference: Article from Levey (2003) deleted and article from Levey (2006) added.

Section 16.1 - Appendix 1: update of bilirubin range.

Section 16.4 – Appendix 4: eGFR formula updated according to Levey et al (2006) article.

Section 16.6 - Appendix 6a: Samples numbering updated to consider extension period.

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.

Summary of previous amendments

Amendment 3 (August 2020)

Amendment 2 (March 2020)

Amendment 1 (July 2019)

Amendment 03

Amendment Rationale

The key purpose of this amendment is to introduce pre-filled syringes (PFS) to allow for self-administration after Month 12 visit, to offer more flexibility and improve adherence. This will reduce the frequency of visits for patients at the sites during the second year of the study to only those visits that require clinical assessments. Pre-filled syringe is a new presentation of CFZ533 and the formulation is identical in vials and PFS. The PFS is intended to be used by healthcare professionals, lay caregivers assisting with the treatment administration, or adult patients self-administering at home. The lay caregivers and adult patients will be allowed to use the PFS once they are trained by the study team.

Further, this amendment is aimed to add three inclusion/exclusion criteria:

- To clarify when a patients must be screen failed, we included an inclusion criterion to mandate transplantation to occur within a defined screening period following informed consent signature. Re-screening up to 3 times is allowed if the wait time for transplantation is extended.
- Due to the variability in the hepatocellular carcinoma (HCC) diagnosis among countries and sites, the explant liver graft pathology reading is added prior to randomization to standardize the evaluation of patients with HCC.
- To ensure appropriate dosing of CFZ533, we added a body weight range to exclude patients who are underweight or obese (<30 kg or >180 kg).

Moreover, one of the secondary objectives “To assess the safety and tolerability of CFZ533 regimens compared to TAC control at Month 12 and Month 24” was revised to remove the endpoint of “AEs of special interest”. We are evaluating the whole safety profile and no particular AEs of special interest have been identified as of this time in the program.

The risk and benefit assessment in relation to COVID-19 was performed, and conclusion was that it remains unchanged in the target population and this is added to this protocol amendment Section 4.6.

Finally, there are few other key reasons for this amendment:

- codify a number of actions recommended to ameliorate the effects of the COVID-19 pandemic as it interferes with the normal course of this trial in the past or future
- clarify the stopping rule for serious infections where for the purpose of this rule, serious infections will be considered as those, which are fatal or life-threatening
- [redacted]
- allow more flexibility regarding CFZ533 interruption during the study
- add information about Cytomegalovirus (CMV) treatment guidance to standardize CMV treatment
- add severe acute respiratory syndrome associated coronavirus - 2 (SARS-CoV-2) treatment recommendation to follow local guidelines

- add reason for collection of race and ethnicity which is required by Health Authorities to identify variations in safety or efficacy due to these factors and to assess the diversity of the study population
- revise criteria for the diagnosis of new onset diabetes to remove "reason for transplantation was not diabetes" since this will be true for all patients in the study; for assessments after randomization change from Day 30 to Day 29 to better match the visit schedule; and for HbA1c, change from Day 30 to Day 85 to assess it 3 months after transplantation

This clinical study is ongoing since September 2019 and 20 subjects have been randomized as of 30-Jul-2020. The changes proposed by this amendment will not restrict the patient population since the added body weight range is very broad. The HCC diagnostic interpretation criteria will standardize the evaluation of patients with HCC. The changes proposed in this amendment will not have a major impact on study results.

Changes to 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.

Throughout the document, changes were implemented based on a new clinical trial protocol template released by Novartis earlier this year:

- Replacement of "subject" term with "participant"
- Update of the pregnancy section to clarify safety information reporting during pregnancy and once baby is born
- Describe post-trial access considered after the study
- Describe the different informed consents in use for the study
- Update in the adverse event section. Update in the list of information to collect, and clarification about abnormal laboratory values or test results to consider reporting an AE

List of amended sections includes:

List of abbreviations – updated with new and missing ones

Glossary of terms – updated with new terms

Protocol Summary Section – updated to align with changes made in this amendment.

Table 2-1: objectives and related endpoints – removed AEs of special interest from the secondary endpoints pertaining to the safety and tolerability of CFZ533 objective' for more clarity.

Figure 3-1: figure was replaced to correct inversion of arrow descriptions and footnotes. Blue arrow referred to 15 mg/kg instead of 30 mg/kg, and white arrow the contrary. Footnote ** referred to one injection instead of 2 and the footnote *** to 2 injections instead of 1.

Section 2 – heading updated from 'objectives and related endpoints' to 'objectives and endpoints'.

Section 4.2.1 – removed in the description of safety follow up words "subject and graft survival" since these are SAEs already covered by statement "to monitor any related serious adverse events".

Section 4.6 – Risks and Benefits: updated to include assessment due to COVID-19 pandemic

Section 5.1 – Inclusion criteria: added an inclusion criterion (criteria #11) to define period between ICF signature and transplantation to align with the definition of the screening period.

Section 5.2 – Exclusion criteria: added 2 new criteria to:

- Add explant liver graft pathology reading for participants with HCC prior to randomization (exclusion # 29)
- Provide a range for patients' body weight (exclusion # 30)

Section 6.1.1 – Investigational and control drugs: Implementation of PFS

Section 6.1.3 – Mention added that "PFS will be used upon availability once patient has completed M12 visit".

Section 6.1.4: Cross-reference added to section 4.3.

Section 6.1.5 – Post Trial Access: new section added based on new Novartis clinical trial protocol template to discuss post-trial access.

Section 6.2.1 – Concomitant therapy: Added recommendation to use the guideline of the American Society of Transplantation Infectious Diseases Community of Practice to treat cytomegalovirus infection in solid organ transplant recipients. Added information regarding treatment of SARS-CoV-2 patients.

Section 6.2.4 – Rescue medication: For participants with history of Hepatitis C virus (HCV) infection, added clarification that only patients with sustained virologic response (SVR) of at least 12 weeks will be eligible for the study.

Section 6.4 – Treatment blinding: wording update based on the new Novartis clinical trial protocol template.

Section 6.5.1 – Permitted dose adjustments and interruptions of CFZ533 study treatment: Added more flexibility regarding treatment interruptions allowed in the study.

Section 6.6.2 – Recommended treatment of adverse events: added that increases in tacrolimus dose to manage rejection will be captured in the CRF.

Section 6.6 – Additional treatment guidance: sub-section number and title (6.6.3 – Emergency breaking of assigned treatment code) removed since it is not applicable to this study.

Section 6.7 – Preparation and dispensation: added new information based on the new Novartis clinical trial protocol template.

Sections 6.7.1 – Handling of study treatment and additional treatment: added this new section based on new Novartis clinical trial protocol template.

Section 6.7.2 - Instruction for prescribing and taking study treatment: update in section number and title.

Section 6.7.2.1 – CFZ533 administration: this was Section 6.7.1.1 in prior protocol, it was updated to include instructions on PFS use and a mitigation plan to continue study drug at in-home administration either by site staff or HCP in case of a new pandemic.

Section 6.7.2.2 – Tacrolimus administration: this was Section 6.7.1.2 in prior protocol, it was updated to clarify that all participants need to be on a treatment regimen comprising tacrolimus (TAC), corticosteroids (CS) and mycophenolate mofetil (MMF) at the time of randomization.

Section 6.7.2.3 – MMF administration: this was section 6.7.1.3 in prior protocol, it was updated to align with changes in Section 6.7.2.2.

Section 6.7.2.4 – Corticosteroids administration: this was section 6.7.1.4 in prior protocol, no new changes introduced in this amendment.

Section 7 – Informed consent procedures: description of the different ICF available for the study.

Section 8 – Visit schedule and assessments: clarified that the injection schedule should be determined based on the randomization date; added actions to consider in case of new pandemic.

Table 8-1 Assessment schedule:

- Footnote 9 revised to indicate that participants who discontinue the randomized study treatment prior to Month 12 should continue in the study until Month 24 on standard of care and come for follow up visits

Footnote 10 added to clarify that TAC trough levels are not applicable to participants in Arms 2 & 3 from D29; TAC trough levels will continue to be applicable only for Arm 1 patients from D29 onwards

- Footnote 11 added to explain types of biomarkers to be assessed
- Footnote 12 added to ensure that after switching to PFS, CFZ533 dosing will be done after collection of PK labs which are required at pre-dose
- [redacted]
- correction of some typographical errors

Section 8.1 – Screening: clarification that participants awaiting organ transplantation can be re-screened 3 times.

Section 8.1.1-Information to be collected on screening failures: new section added, text implemented from the new Novartis clinical trial protocol template.

Section 8.2 – Participant demographic/other baseline characteristics: added reason for race and ethnicity collection.

Section 8.3.3 – Graft loss: clarification that graft loss will lead to study discontinuation.

Table 8-4 – Laboratory assessments: list of surface biomarkers in the viral serology section updated

Section 8.4.4 – Other safety evaluations: criteria to define new onset of diabetes mellitus updated to remove “reason for transplantation was not diabetes”, change D30 to D29 to match visit schedule, delay HbA1C to D85 to capture only information after transplantation; added

central pathologist review of explant biopsy for participants with HCC recurrence; This section is also updated with the definitions for diabetic related diagnoses are according to the American Diabetes Association (2013) and WHO-ADA criteria.

Section 8.5 – Additional assessments: added flexibility to continue study assessment in case of a new pandemic.

Section 8.5.3 – Pharmacodynamics: clarification that CD40 is not mandatory for Arm1 patients (on TAC treatment) at M4.5 visit.

[redacted].

[redacted]

Section 9.1.1 – Study treatment discontinuation and study discontinuation: updated reasons for study treatment discontinuation to align with the new Novartis clinical trial protocol template; clarified that in case of pregnancy or graft loss, the participant will be discontinued from the study and complete Month 24 EOS visit as soon as possible.

Section 9.1.2 – Withdrawal of informed consent: based on the new Novartis protocol template updated the definition of withdrawal of consent and added information regarding use of personal data.

Section 9.1.5 – Study stopping rules: clarification about infection events considered for the stopping rule.

Section 9.2 – Study completion and post-study treatment: clarification about SAEs reporting procedure during safety follow-up period.

Section 10.1.1 – Adverse events: updated to align with the new Novartis clinical trial protocol template, clarified that AEs will be collected until EOS visit, after which only SAEs will be reported in the Novartis safety database for additional period of 12 weeks; Paragraph on clinically significant laboratory values identification added.

Section 10.1.4 – pregnancy reporting: Updated to align with the new Novartis clinical trial protocol template, added that pregnancy follow up information will be collected at 3 time points after delivery for a period of 12 months.

Section 10.2.3 – Data Monitoring Committee: updated to align with the new Novartis clinical trial protocol template.

Section 11.2 – Database management and quality control: clarification of data recorded by IRT.

Section 12.2 – Participant demographic and other baseline characteristics: addition of data to consider.

Section 12.3 – Treatment: section number and title (12.3.1 - Concomitant immunosuppressant) deleted as there is no other sub-section

Section 12.4.3 – Handling of missing values not related to intercurrent event: clarification of lost to follow-up definition.

Section 12.4.4 – Supportive analyses: title changed from "Sensitivity analyses", clarification on the composite failure efficacy failure and analysis results presentation, and addition of analysis to assess impact of COVID-19 pandemic.

Section 12.5.1 – Efficacy endpoints: additional parameters included to further subdivide types of treated rejections and composite of graft loss and death.

Section 12.5.2.1 – Renal function: sentence moved up to Section 12.4.3.

Section 12.5.2.2 – General safety: updated to align with the new Novartis clinical trial protocol template: clarification that all listings and tables will be presented by treatment group; addition of a summary of death on treatment and post treatment death report; clarification of on-treatment period considered for CFZ533 and TAC arms; updates on the adverse events analysis; deletion of the new onset of diabetes mellitus as it is redundant with Section 8.4.4.

Section 12.5.3 – Pharmacokinetics: added a comparison of PK before and after introduction of PFS in the study.

Section 12.7 – Sample size calculation: Figure 12-2 was updated with correct representation of probability of success.

Section 15 – References: added one reference.

Section 16.1 – Appendix 1: updated vital signs notable criteria.

Section 16.6 – Appendix 6a: added sample number for other assessments.

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.

Summary of previous amendments

Amendment 2 (March 2020)

Amendment 1 (July 2019)

Amendment 02

Amendment Rationale

The key purpose of this amendment is:

To clarify that the stopping rule for biopsy proven acute rejection (BPAR) is based on moderate and severe events (Rejection Activity Index (RAI) ≥6) evaluated by a blinded central pathologist. Borderline and mild rejections generally do not present with clinically apparent graft malfunction and do not require additional treatment (Demetris et al 1997 and 2002). As stopping rules are established as a safety measure, only moderate or severe events will be considered.

To change the screening period from 6 months to 2 months to adapt to sites practice and reduce period of eligibility assessments results.

To increase the visit window for the randomization visit at Day 8 from ±1 to ±2 days to allow for more flexibility at the hospital.

To allow combining screening and baseline visit if these visits happen within a 48 h period.

To clarify Inclusion criteria:

- # 6: Included are patients with Model for End stage Liver Disease (MELD) score ≤ 30 (based on laboratory values, using the United Network for Organ Sharing (UNOS) MELD calculator:[https://unos.org/resources/allocation-calculators/]).
- #7: Included are recipients with HCV antibody positive with no detectable HCV-RNA. Recipients with Hepatitis B infection should have no detectable HBV-DNA. Cases of spontaneous HCV clearance should be discussed with sponsor.

To clarify Exclusion criteria:

- #9: Excluded are patients with Hepatocellular carcinoma that does not fulfill Milan criteria (1 nodule ≤5 cm, 2-3 nodules all <3 cm, without evidence of metastatic disease or vascular invasion.
- #17: Excluded are recipients with positive HCV antibody without proof of sustained viral response (SVR) 12 weeks after anti HCV treatment.
- # 18: Excluded are donor organs showing macro-vesicular steatosis > 30%.

The drug target trough level for tacrolimus (TAC) was changed from 8 to 12 ng/mL to 5 to 15 ng/mL to better reflect local practice and allow more flexibility at clinical sites to adjust TAC drug levels in subjects. This dose range is consistent with the TAC product label information.

Changes to the protocol

Throughout the document the following changes have been made:

- Replacing remaining “patients” term with “subjects” according to the glossary term definition.
- Replacing randomization visit window “+/-1 day” to “+/-2 days”

The following sections have been changed as follow:

Section 1.1- Background: update on subjects treated under CFZ533 according to IB #9 release.

Section 3- Study design: update on screening period (2 months instead of 6); clarification that corticosteroids can be stopped once Month 4 visit has been completed and Figure 3-1 updated.

Section 4.1- Rationale for study design: TAC blood target trough levels change from 8-12ng/mL to 5-15ng/mL; randomization visit window (+/-2 days) added.

Section 4.2.1 and Section 4.2.2-Arm 2 (600mg regimen)/Arm 3 (300mg): randomization visit window (+/-2 days) added.

Figure 4-2- Predicted CFZ533 exposure: randomization visit window deleted and correction of Arm receiving CFZ533 at Day 15 (Arm 2 not Arm 3).

Section 4.6- Benefits and risks: wording change.

Section 4.8- Rationale for liver histopathology: wording change.

Section 5- Population: deletion of the percentage of expected screening failure and number of expected subjects to complete recruitment.

Section 5.1- Inclusion criteria:

- #6 updated to: “Model for End stage Liver Disease (MELD) score ≤ 30 (based on laboratory values, using the United Network for Organ Sharing (UNOS) MELD calculator: [https://unos.org/resources/allocation-calculators/])”
- #7 updated to: “Recipients with no active HCV and HBV replication. Recipients with HCV antibody positive should have no detectable HCV-RNA. Recipients with Hepatitis B infection should have no detectable HBV-DNA”

Section 5.2- Exclusion criteria:

- #9 update to: “Hepatocellular carcinoma that does not fulfill Milan criteria (1 nodule ≤5 cm, 2-3 nodules all <3 cm, without evidence of metastatic disease or vascular invasion, see Appendix 2, Mazzaferro et al 1996) at the time of transplantation.”
- #17 updated to: “Recipients with positive HCV antibody without proof of sustained viral response (SVR) 12 weeks after anti HCV treatment. Recipients with donors HCV positive”
- #18 updated to: “Recipients with donors with macro-vesicular steatosis > 30%.”

Section 6.1.2- Additional study treatments: addition of “mycophenolate” with MMF and wording update.

Section 6.1.3- Treatment arms: addition of the randomization visit window “+/-2 days” and deletion of the expected on-site visits list to perform PK/PD assessment.

Section 6.2.1- Concomitant therapy: wording update.

Table 6-1- Prohibited medication: typo corrected.

Section 6.3.2- Treatment assignment, randomization: deletion of randomization visit window “+/-1 day”.

Section 6.5.1- Permitted dose adjustment and interruption of CFZ533 study treatment: typo corrected

Section 6.5.2- Permitted dose adjustment and interruption of other study treatment: clarification that corticosteroids can be stopped once Month 4 visit has been completed.

Section 6.6.1- Study treatment: wording update.

Section 6.6.2- Other treatments: wording updates.

Section 6.7- Preparation and dispensation: wording updates.

Section 6.7.2.1- CFZ533 administration: deletion of "which correspond to one of the three 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)" as was not accurate and redundant with other sentence in the same section; change "at time of" randomization to "on day of" randomization for accuracy. Addition that "HCP (if applicable) can prepare the medication for administration".

Section 6.7.2.2- Tacrolimus administration: change of TAC trough level "8-12 ng/mL" to "5-15 ng/mL"; wording updates.

Section 7- Informed consent procedures: sentence moved within the same section.

Section 8- Visit schedule and assessments:

- Wording updates.
- [redacted]
- Clarification that randomization visit (Day 8) has visit window of +/-2 days and other visits are expected to occur according to the study schedule based on randomization date.
- Clarification that even if a visit date is changed, next visit should occur according to initial schedule.
- Clarification that screening and baseline visits can occur on same day, and if these visits occur within 48 hours assessments don't need to be repeated.

Table 8-1 and Table 8-2- Assessment schedule:

- Baseline visit = pre-LTx; similar footnote to clarify that all baseline assessments are expected to occur prior to LTx.
- Screening period update = -1 to -60 days.
- Weight measurements added to visits with temperature control.
- Uncheck of Day 22 visit for TAC dose administration in Arm 2 and 3.
- Footnote deletions.
- New footnote to identify assessments that can be performed at home.
- New footnote to clarify expected local lab assessments.
- Footnote update to clarify that central lab chemistry test expected at time of suspected BPAR.
- Footnote update to clarify that ascites aliquots expected from Day 8 visit onward.

- New footnote to clarify that CD40 at Month 4.5 visit is not mandatory for patients in Arm 1.
- In Table 8-2 lines for not applicable assessments have been deleted.
- "Day schedule" corrected.

Section 8.1 - Information to be collected on screening failure: clarification of patients eligible for re-screening and clarification that AEs will be captured from baseline onward. Deletion of the sentence requesting all AEs to be recorded in CRF from ICF consent signature as AEs will be recorded from baseline only.

Section 8.2- Subject demographics/other baseline characteristics: wording updated to viral serology "will be obtained".

Section 8.3.1- Suspected Acute rejection/BPAR: wording update and addition of a central lab chemistry test assessment to be performed at the time of suspected BPAR. LDH test result, if available locally, to be captured in the eCRF.

Section 8.4.1- Laboratory evaluations: Clarification that patient's eligibility will be assessed based on local lab results, not central ones. Only tests needed to assess patient's eligibility are mandatory to be performed locally.

Table 8-4- Laboratory assessments: clarification that qualitative viral serology apply to donors and recipients; 24 hour collection period for proteinuria removed; qualitative and/or quantitative HCV-RNA and HBV-DNA (using PCR) tests will be performed locally for those patients who are tested anti-HCV positive and HBsAg positive, respectively.

Section 8.4.3- Pregnancy and assessment of fertility: clarification of visits for urine and serum tests and addition of urine pregnancy test allowed to be done at home for subjects in Arm 1 and subjects receiving treatment at home, after Month 6 visit.

Section 8.4.4- Other safety evaluation: previous footnotes "For recurrent and de novo cases, α-fetoprotein will be evaluated as needed" and "Quantitative EBV and CMV viral load will be assessed locally if active infection is suspected" integrated in the section.

Section 8.5.2- Pharmacokinetics: wording updates and deletion of Day 8 visit window.

Section 8.5.3- Pharmacodynamics: deletion of Day 8 visit window.

[redacted].

Section 8.5.6- CFZ533 concentrations in drained ascites fluids: clarification that ascites fluid sample collection is expected from the date of first CFZ533 administration and onward.

Section 9.1.5- Study stopping rules: clarification that a true BPAR is considered as RAI ≥6, evaluated by central reader.

Section 10.1.1- Adverse events: screening period reduced from 6 months to 2 months.

Section 12.4.4- Sensitivity analysis: deletion of visit window at Day 8.

[redacted]

Section 12.6- Study stopping rules: wording updates and clarification that the stopping rule will be based on central biopsy review when BPARs are rated moderate to severe.

Table 12-2- Probability of success under different event rates for 48 subjects of CFZ533 arm and 32 subjects of control arm: table updated as was previously not correct, columns were inverted.

Section 15- References updated.

Section 16.6- Blood log for PK, PD and immunogenicity: update of the Arm 1 CD 40 samples numbers as were previously incorrect.

Section 16.7: deletion of the maximum volume of ascites aliquot to be collected.

Amendment 01

Amendment rationale

The key purpose for this amendment is:

[redacted]

Iscalimab has shown preservation of graft quality with normal renal morphology in a sub-set of subjects from the kidney transplant study CCFZ533X2201 (NCT02217410) (Nashan et al. 2018). Thus, iscalimab has the potential of offering better graft quality and thereby improve long-term outcomes for transplanted patients.

In patients after orthotopic liver transplantation, liver biopsy is used to detect acute or chronic rejection, potential recurrence of the underlying disease, and to evaluate the degree of fibrosis and stage of liver disease (Jiang and Farber 2017, Sebagh and Samuel 2004). Morphology plays an important role in differential diagnosis and subsequent treatment of post-transplant complications (Demetris et al 2000, Demetris et al 2016, Ormonde et al 1999).

Routine surveillance biopsies can support clinical decision-making and allow for the identification of recipients who might benefit from immunosuppression treatment adjustments and inform the potential for immunosuppression minimization protocols (Demetris et al 2016, Feng and Bucuvalas 2017, Feng et al 2018, Sebagh and Samuel 2004). It also can assess the impact of chronic low grade injury, and help better understand low-grade chronic inflammation or allograft hepatitis and progressive fibrosis (Arias et al 2017, Feng and Bucuvalas 2017, Feng et al 2018, Londono et al 2018). Taken altogether, routine surveillance liver biopsies provide essential and clinically relevant information after liver transplantation with an acceptable benefit-risk profile (Banff Working Group on Liver Allograft 2012, Pereira et al 2016).

[redacted]

Changes to the protocol

The following sections have been changed in the amended protocol:

Title page - Introduction of International Nonproprietary Name (INN) name, Iscalimab.

Section 1.1 - Background: Update on patients treated with CFZ533.

[redacted]

Section 3 - Study design: Adaptations to treatment with MMF and CS.

Section 4.4 - Rationale for choice of control drugs (comparator): Deletion of MPA, azathioprine and sirolimus.

Section 4.7 - Previous clinical experience with CFZ533: New section defined and additional information added from CFZ533X2201 study.

[redacted]

Section 5.2 - Exclusion criteria: Exclusion #4 deleted since already covered by Inclusion #5; Exclusion #5, clarification added to allow EBV results up to 28 days prior to baseline visits; Exclusion #15, re-wording.

Section 6.1.1 - Deletion of the note mentioning that only MMF is allowed.

Section 6.2.2 - Clarification that non-protocol immunosuppressants are only allowed for patients in follow-up and who discontinued from randomized study treatment.

Table 6-1 - Removal of mycophenolic acid and anti-viral treatment for Hepatitis C from the list of prohibited concomitant treatments.

Section 6.5.1 - Permitted dose adjustments and interruptions of CFZ533 study treatment: clarification on missed doses permission.

Section 6.5.2 - Permitted dose adjustments and interruptions of other study treatment: In case of persistent intolerance MMF can be discontinued and patients switched to other mycophenolates. Guidance for CS treatment and over-immunosuppression management was added.

Section 6.7.2.4 - Corticosteroids administration up to Month 24 was removed and wording aligned with Section 6.5.2.

Section 7 - Inform consent procedures: Addition of contraceptive recommendations.

Section 8 - Update of the expected follow-up visit list to match assessment schedule.

Table 8-1 - Update of the assessment schedule:

- [redacted]
- A-fetoprotein reported on a separate line (previously contained in the safety laboratory test line).
- Clarification of footnotes.

Table 8-4 - Implementation of quantitative assessments for EBV and CMV if active infection is suspected.

Section 8.4.3 – Pregnancy and assessments of fertility: Recommendations for female and male subjects taking MMF was updated

Section 8.4.4 - Other safety evaluations: deletion of CMV and EBV assessment by donor/ recipient constellation.

Section 8.5.6 - CFZ533 concentrations in drained ascites fluid: specified volume of the ascites aliquot was removed. Instruction to refer to lab manual procedure.

[redacted]

Section 9.1.1 - Update of the expected follow-up visit list to match assessment schedule.

Section 9.2 - Study completion and post-study treatment: Move TAC initiation time for Arms 2 and 3, from EOS to EOS plus 2 weeks. Change in information to be reported in safety database at end of safety follow-up period.

Section 10.1.1 - Adverse Event: Clarification that AEs will not be recorded from ICF signature date. AEs will be recorded from date of transplantation, as screening period can last up to 6 months prior to transplantation.

Section 12.5.2.1 - Renal function: Null and alternative hypothesis based on eGFR value at randomization, not baseline.

[redacted]

Section 15 - References: addition of new references.

Section 16.6, Appendix 6a - Blood log for PK, PD [redacted] sampling: Blood collection log for Arm 1 (TAC regimen) added.

In addition minor corrections of typos were performed and are highlighted in track change.

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) and Health Authorities.

Protocol summary

Protocol number	CCFZ533A2202
Full Title	A 12-month, open-label, multicenter, randomized, safety, efficacy, pharmacokinetic (PK) and pharmacodynamic (PD) study of two regimens of anti-CD40 monoclonal antibody, CFZ533 vs. standard of care control, in adult *de novo* liver transplant recipients with a 12-month additional follow up and a long-term extension (CONTRAIL I).
Brief title	CONTRAIL I - Study of efficacy, safety, tolerability, PK/PD of anti-CD40 monoclonal antibody, CFZ533, in de novo liver transplant recipients.
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Biological
Study type	Interventional
Purpose and rationale	The purpose of the study is to investigate the safety, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) of two calcineurin inhibitor (CNI)-free regimens of CFZ533, compared to standard of care control, in adult *de novo* liver transplant recipients. This study will allow the assessment of the ability of CFZ533 to replace calcineurin inhibitors (CNIs) in terms of anti-rejection efficacy, while providing potentially better renal function with an expected similar safety and tolerability profile. The study results will be used to inform the CFZ533 dose and regimen selection for a pivotal Phase III trial in de novo liver transplant population.
Primary Objective(s)	To evaluate the rate of composite efficacy failure (Biopsy Proven Acute Rejection (BPAR), graft loss (GL) or death) with CFZ533 600 mg and 300 mg regimens compared to tacrolimus (TAC) Control at Month 12 post-transplantation.
Secondary Objectives	**Key secondary:** • To evaluate the renal function (estimated Glomerular Filtration Rate (eGFR) by MDRD-4 formula) with CFZ533 600 mg and 300 mg regimens compared to TAC Control at Month 12 post-transplantation. **Secondary:** • To evaluate the composite of BPAR, Death, Graft Loss and Loss to Follow-up with CFZ533 600 mg and 300 mg regimens compared to TAC Control at Month 12 and Month 24 post-transplantation. • To evaluate whether CFZ533 600 mg or 300 mg regimens have lower incidence rates over 12 months and 24 months post-transplantation compared to the control arm for the following events: - BPAR - Treated Biopsy Proven Acute Rejection (tBPAR) - Acute Rejection (AR) - Treated Acute rejection (tAR) - Antibody mediated (humoral) rejection - Graft Loss (GL) - Death. • To evaluate eGFR and change in eGFR up to Month 24 post-transplantation. • To assess the safety and tolerability of CFZ533 regimens compared to control at Month 12 and Month 24. • To assess the pharmacokinetics of multiple doses of CFZ533 over the 12-month and 24-month treatment and explore the dose-exposure relationship. • To assess the levels of peripheral soluble CD40 (sCD40) at baseline, over the 12-month and 24-month treatment period (to inform target biology, target engagement). • To evaluate the immunogenicity of CFZ533 by analysis of anti-CFZ533 antibodies (over the 12-month and 24-month treatment period).
Study design	Study CFZ533A2202 is a randomized, 12-month, active-controlled, open-label, multi-center, dose range finding study to evaluate the efficacy, safety, tolerability, PK and PD

	of two CFZ533 regimens with a 12-month additional follow-up and a long-term extension in adult *de novo* liver transplant recipients.
Study population	The study population is adult male and female *de novo* liver transplant recipients of a primary graft from a deceased donor. It is planned to randomize at least 128 participants.
Key Inclusion criteria	**Screening period up to liver transplantation:** • Written informed consent obtained before any assessment. • Male or female subjects between 18 to 70 years of age. • Recipients of a primary liver transplant from a deceased donor. • Up to date vaccination as per local immunization schedules. • Recipients tested negative for HIV. • MELD score ≤ 30 *(*based on laboratory values, using the United Network for Organ Sharing (UNOS) MELD calculator: *MELD calculator: [https://unos.org/resources/allocation-calculators/]).* • Transplantation to occur within defined screening period following informed consent signature. **At randomization (Day 8±2):** • Recipients with no active HCV and HBV replication. Recipients with HCV antibody positive should have no detectable HCV-RNA. Recipients with Hepatitis B infection should have no detectable HBV DNA. Cases of spontaneous HCV clearance should be discussed with sponsor. • Allograft is functioning at an acceptable level by the time of randomization as defined by AST, ALT and Alkaline Phosphatase levels ≤ 5 times ULN and Total Bilirubin ≤ 2 times ULN. • Renal function (eGFR, MDRD-4 formula) ≥ 30 mL/min/1.73 m^2 based on most recent post-transplant value prior to randomization. • Recipients who have been initiated on an immunosuppressive regimen that contains TAC, mycophenolate mofetil (MMF) and corticosteroids (CS) as per protocol.
Key Exclusion criteria	**Screening period up to liver transplantation:** • Use of other investigational drugs at screening within 30 days or 5 half-lives of screening. • Recipients of multiple solid organ or islet cell transplants, or recipients that have previously received a tissue transplant, or a combined liver-kidney transplant. • Recipients of a liver from a donor after cardiac death (DCD), from a living donor, or of a split liver. • Recipient who tests negative for Epstein Barr virus (EBV). • Recipients receiving an ABO incompatible allograft. • History of malignancy of any organ system (except hepatocellular carcinoma (HCC) or localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases. • Hepatocellular carcinoma that does not fulfill Milan criteria (1 nodule ≤ 5 cm, 2-3 nodules all ≤ 3 cm, without evidence of metastatic disease or vascular invasion) at the time of transplantation. • Recipients transplanted for acute liver failure (does not apply to acute on chronic liver failure). • Any use of antibody induction therapy, or use of any immunosuppressive medications (or other medications prohibited by the protocol) • Participants who have received a live vaccine within four weeks prior to transplantation. • Recipients with donors HIV positive. • Recipients with donors HBsAg positive.

	• Recipients who are HCV antibody-positive without documented sustained viral response (SVR) at 12 weeks after finishing anti HCV treatment (e.g., direct-acting antivirals). • Recipients with HCV RNA-positive donors • Recipients with donors with macrovesicular steatosis > 30%. • Pregnant or nursing (lactating) women. **At randomization (Day 8±2):** • Any post-transplant history of thrombosis, occlusion or stent placement in any hepatic arteries, hepatic veins, portal vein or inferior vena cava at any time during the run-in period prior to randomization. Absence of any graft vascular thrombosis or occlusion (by diagnostic method used at the site to assess vascular patency) must be confirmed by imaging prior to randomization. • Recipients with platelet count < 50,000/mm^3. • Recipients with an absolute neutrophil count of < 1,000/mm^3 or white blood cell count of < 2,000/mm^3. • Recipients with clinically significant systemic infection requiring use of intravenous (IV) antibiotics. • Evidence of active tuberculosis (TB) infection (after anti-TB treatment, patients with history of latent TB may become eligible according to national guidelines). • Recipients who are in a critical care setting at the time of randomization requiring life support measures such as mechanical ventilation, dialysis, requirement of vasopressor agents. • Recipients who are on renal replacement therapy at randomization. • Any episode of acute rejection or suspected rejection prior to randomization. • HCC participants whose explanted liver graft pathology report shows i) pTNM stage beyond T2N0M0, ii) presence of mixed carcinoma, iii) microvascular invasion despite pTNM stage. • Participants with body weight < 30 kg or > 180 kg
Study treatment	• Arm 1 - TAC Control:Tacrolimus + MMF + CS (n=32). • Arm 2 - CFZ533 600 mg regimen:30 mg/kg IV (Day 8), 15 mg/kg IV (Day 15), then CFZ533 SC 600 mg every 2 weeks from Day 29 to End of Study (EOS) + MMF + CS (n=48). • Arm 3 - CFZ533 300 mg regimen - 30 mg/kg IV (Day 8), and then CFZ533 300 mg every 2 weeks SC from Day 29 to EOS + MMF + CS (n=48). • For Arm 2 and 3, use of vials from Day 29 to Month 12, and then switch to pre-filed syringes once available.
Efficacy assessments	• BPAR (Banff classification) • tBPAR • Graft Loss (GL) • Death
Pharmacodynamic Assessments	• Soluble CD40 plasma concentrations (up to End of Study (EOS)).
Pharmacokinetic assessments	• CFZ533 plasma concentrations (up to EOS). • CFZ533 concentrations in drained ascites fluid (as appropriate up to Month24).
Key safety assessments	• Renal Function (eGFR). • Proportion of participants with AEs, SAEs, AEs related to study drug.
[redacted]	

[redacted]	
Data analysis	**Primary** The efficacy analysis for the first 12 months evaluates whether at least one of the two CFZ533 treatment arms meets the pre-defined success criterion. The number of participants with composite efficacy failure is assumed to follow a binomial distribution, i.e.,r_i ~ binomial (n_i, θ_i), where r_i is the number of participants with composite efficacy failure in treatment arm i, n_i is the number of participants in treatment arm i and θ_i is the probability of composite efficacy failure. A CFZ533 arm is considered successful if the composite efficacy failure rate difference between this CFZ533 arm and the control arm is < 15% with probability ≥ 80%: Pr ($\theta_{CFZ533} - \theta_{control}$ <0.15 | data) > 80% based on the FAS. The required posterior probabilities will be estimated from simulations of the posterior distributions of $\theta_{CFZ533} - \theta_{control}$ and compared to the threshold for level of proof. The prior distributions will be assumed to be non-informative. The posterior mean composite efficacy failure rates for each treatment arm and for the difference in mean response rates between CFZ533 treatment arms and control will be presented together with 95% credible intervals. **Key Secondary** The mean change in eGFR (MDRD-4) from randomization to Month 12 between a CFZ533 arm and control will be evaluated as follows: The mean change for each arm will be obtained through covariate-adjusted treatment effects using MMRM. The model will contain treatment arm, visit, treatment arm*visit, and randomization GFR with unstructured covariance matrix. The estimand will be evaluated in the FAS population by comparing the difference in mean change between each CFZ533 arm and control.
Key words	Liver transplantation, *de novo* liver transplant recipient, deceased donor, CFZ533, CNI-free immunosuppression.

1 Introduction

1.1 Background

Liver transplantation is now recognized as the treatment of choice for end-stage liver failure. Its success can be attributed largely to the generation of selective immunosuppressive agents, which have resulted in a dramatic reduction in the incidence of acute rejection and improvements in the short- and long-term outcomes of patients (Selzner et al 2010). The current gold standard of care is based on the triple combination regimen with tacrolimus, mycophenolate and corticosteroids (CS).

Despite the ability of current immunosuppressive agents to reduce the incidence of acute rejection, the long-term toxicity associated with current regimens now has become a major challenge for liver transplant recipients and is increasingly perceived as an unmet clinical need. The most common side effects of these agents include: increases in the incidence of bacterial and viral infections, nephrotoxicity with chronic renal impairment (Zhang et al 2017) *de novo* diabetes mellitus, hyperlipidemia, arterial hypertension, cardiovascular disease, osteoporosis, neurotoxicity/neurocognitive impairment (Pflugrad et al 2018), hematological toxicity [including an increased rate of post-transplant lymphoproliferative disorder (PTLD)], the development of *de novo* or recurrent solid organ cancers and disease recurrence after liver transplantation. The recognition of these life-threatening side effects has now driven interest in the use of calcineurin inhibitors (CNI)-sparing strategies to limit CNI exposure (e.g., tacrolimus, cyclosporine), including CNI minimization, avoidance, and withdrawal (Flechner et al 2008). However, to date, the majority of these minimization strategies have failed to reduce the incidence and severity of long-term renal and cardiovascular disease after transplantation.

To fulfill this important unmet medical need, an exploratory Phase II study was conducted to evaluate the efficacy and safety of the co-stimulation blocker belatacept in adult recipients of first liver transplant from a deceased donor in the context of CNI-free regimen (NCT 00555321). At the conclusion of this study, two of three belatacept groups had higher rates of death and graft loss relative to the standard-of-care control group tacrolimus + MMF. All three belatacept groups also had higher rates of AR, and there was an increase in viral and fungal infections, the majority of which were not serious. Two cases of PTLD and one case of Progressive Multifocal Leukoencephalopathy (PML) were reported in belatacept-treated subjects. The two belatacept high dose groups had substantially better mGFR than the remaining three groups, while all three belatacept groups had better eGFR. There was also evidence of fewer neurotoxicity events in the belatacept groups.

In belatacept-treated subjects, the tendency toward more viral and fungal infections observed raises the possibility of over-immunosuppression in some subjects, as observed with regimens that include MMF. Paradoxically, the higher rates of AR would suggest under immunosuppression or immunomodulatory effects, not yet understood in the context of liver transplantation. It is also possible that the management of AR placed subjects at risk for subsequent infectious complications. The standard treatment for rejection may have been more intense than was needed in belatacept-treated subjects, suggesting that over-immunosuppression may explain the infectious complications (Klintmalm et al 2014).

Findings from this phase II study did not allow the identification of a safe and effective dose or regimen for further development of belatacept in the liver transplant indication.

The authors of the study mention that the liver may be subject to CD28- independent T cell activity as is surely to be expected, and they cite the potential negative effect of CD28 blockade on regulatory T cell activity. Recent understanding of the pathways of cell activation has resulted in the development of a new immunosuppressive agent that may address the challenges facing transplantation today and allow the substitution of existing agents by offering similar efficacy in terms of prevention of graft rejection but offering better renal function and good safety profile.

CD40 signaling is implicated in the pathology of transplant rejection as well as a range of autoimmune diseases. CFZ533, 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 (CFZ533 Investigator's Brochure (IB); Cordoba et al 2015).

Up to 15-Nov-2020 approximately 837 subjects (comprising healthy volunteers, subjects with various autoimmune diseases and transplant subjects, for details please refer to the Investigator Brochure), receiving either CFZ533 (n=approximately 608) or control drug (n=254, 125 on placebo and 129 on standard of care (SoC) treatment), have been enrolled in the CFZ533 clinical development program.

In the First-in-human Phase 1 clinical study, single doses of IV or SC CFZ533 up to 30 mg/kg (inclusive) were evaluated and showed a favorable safety and tolerability profile in healthy volunteers and in rheumatoid arthritis (RA) subjects. Similarly, in a Phase 1 study of Japanese healthy volunteers, single IV (0.3, 1, 3 mg/kg), and SC (3 mg/kg) doses of CFZ533 were well tolerated. Furthermore, interim Phase 2a results in primary Sjöegren's syndrome (pSS) with multiple doses (8 doses over 21 weeks) of 3 mg/kg SC or 10 mg/kg IV CFZ533 or placebo suggest a favorable safety and tolerability profile in both dose cohorts. Preliminary efficacy data from this study also suggest that multiple doses of 10 mg/kg IV CFZ533 may have therapeutic benefit in pSS subjects. In kidney transplantation, a Proof of Concept (PoC) trial (CCFZ533X2201) was conducted in *de novo* renal transplant recipients, to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of multiple doses of CFZ533 in combination with MMF and corticosteroid (CS), compared to a TAC-based regimen. The CFZ533 treated participants received a loading regimen of 10 mg/kg IV on Days 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 12-month data, following review by an independent adjudication committee, showed that in comparison to TAC-based regimen, CFZ533 regimen had i) a comparable efficacy on the composite endpoint of treated BPAR, graft loss, or death, ii) a superior renal function and iii) a favorable safety profile for up to 12 months of treatment. In conclusion, the data supports the potential of CFZ533 to become an effective CNI-free treatment, improving transplant outcomes by preventing graft rejection without nephrotoxic and other CNI adverse effects. For the most up-to-date information, please refer to the latest CFZ533 Investigator's Brochure.

Based on these data, a dose range finding study (CCFZ533A2201) is ongoing to evaluate the efficacy, safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of CFZ533, in *de novo* and maintenance kidney transplant recipients (study name: CIRRUS I; NCT03663335).

Study CCFZ533A2202 represents the first clinical investigation of CFZ533 in *de novo* adult liver transplant recipients. The purpose of this study is to investigate the safety, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) of two CNI free regimens of CFZ533 in *de novo* liver transplant recipients, compared to a standard of care control (SoC) arm of tacrolimus, MMF and corticosteroids (CS). This study will allow the assessment of the ability of CFZ533 to replace CNIs in terms of anti-rejection efficacy, while providing potentially better renal function with an expected similar safety and tolerability profile.

CNI regimens can lead to renal failure and the need for kidney transplant in many non-kidney transplant recipients (Ojo 2003). Stage 4 or 5 chronic kidney disease (CKD) has been reported in ~18% of liver transplant recipients by 5 years post-transplant and is associated with increased morbidity and mortality. Data from 1997 to 2008 in the Organ Procurement Transplant Network/United Network for Organ Sharing (OPTN/UNOS) database showed a threefold increased rate of kidney transplantation in subjects who previously received a liver transplant.

It is expected that CFZ533 will provide a benefit in renal function while maintaining a comparable anti-rejection efficacy to CNIs. In addition, other benefits of the CNI-free regimen may be in the areas of new-onset diabetes, neurological/neurocognitive impairment symptoms and other CNI-related toxicities.

The two CFZ533 regimens proposed for Study CCFZ533A2202 are anticipated to be favorable and tolerable in liver transplant subjects based on clinical results in kidney transplant participants exposed up to 12 months to the 10 mg/kg IV dosing regimen in the CCFZ533X2201 trial.

1.2 Purpose

To investigate the safety, efficacy, pharmacokinetics (PK) and pharmacodynamics (PD) of two CNI-free regimens of CFZ533, compared to standard of care control, in adult *de novo* liver transplant recipients.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s) • To evaluate the rate of composite efficacy failure (Biopsy Proven Acute Rejection (BPAR), graft loss or death) with CFZ533 600 mg and 300 mg regimens compared to TAC Control at Month 12 post-transplantation.	**Endpoint(s) for primary objective(s)** Incidence of composite efficacy failure at Month 12, where BPAR is from biopsy data indicating a rejection activity index (RAI) ≥3 (Appendix 3).
Key Secondary Objective • To evaluate the renal function (estimated Glomerular Filtration Rate (eGFR) by MDRD-4	**Endpoint(s) for Secondary Objective(s)** • Mean change in eGFR from randomization to Month 12.

Objective(s)	Endpoint(s)
formula) with CFZ533 600 mg and 300 mg regimens compared to TAC Control at Month 12 post-transplantation.	
Secondary Objective(s)	
• To evaluate the composite of BPAR, Death, Graft Loss and Loss to Follow-up with CFZ533 600 mg and 300 mg regimens compared to TAC Control at Month 12 and Month 24 post-transplantation.	• BPAR as above, Death, Graft Loss and Study completion/disposition datasets.
• To evaluate whether CFZ533 600 mg or 300 mg regimens have lower incidence rates over 12 and 24 months post-transplantation compared to TAC control arm for the following events: - BPAR - tBPAR - AR - Treated Acute rejection (tAR) - Antibody mediated (humoral) rejection - Graft Loss - Death	• Event rates over 12 months and 24 months post-transplantation.
• To evaluate eGFR and change in eGFR up to Month 24 post-transplantation.	• To evaluate eGFR values and change from randomization to Month 24.
• To assess the safety and tolerability of CFZ533 regimens compared to TAC control at Month 12 and Month 24.	• Proportion of participants with: - Adverse events - Serious adverse events - AEs related to study drug • Means and mean change over time of: - Vital sign parameters - Lab parameters (Section 8.4.1) • Proportion of participants with: - Premature discontinuation from study - Premature discontinuation of study drug - Dose interruption - Dose adjustment
• To assess the pharmacokinetics of multiple doses of CFZ533 over the 12-month and 24-month treatment and explore the dose-exposure relationship.	• Free CFZ533 plasma concentrations over time (CFZ533-treated participants only).
• To assess the levels of peripheral soluble CD40 at baseline and over the 12-month and 24-month treatment period (to inform target biology, target engagement).	• Total sCD40 in plasma (all participants).
• To evaluate the immunogenicity of CFZ533 by analysis of anti-CFZ533 antibodies (over the 12-month and 24-month treatment period).	• Semi-quantitative analysis of anti-CFZ533 antibodies in plasma (CFZ533-treated participants only).
[redacted]	

3 Study design

This study is a 12-month, multicenter, open-label, randomized study with a 12-month additional follow-up and a long-term extension that will consist of:

- A screening period (up to 2 months) starting from informed consent, screening visit, and including successful liver transplantation (LTx).
- Run-in treatment period following the successful transplantation that ends on the day of randomization or randomization failure, at Day 8 (with visit window of ±2 days) post-LTx.
- The primary treatment period (Treatment period 1) starting at randomization Day 8±2 post-LTx up to Month 12 followed by a 12-month follow-up treatment period (Treatment period 2) until Month 24 (Figure 3-1).
- The long-term extension period (Treatment Period 3) starting post Month 24 until the end of the study (EOS).

Participants will be consented and screened for eligibility prior to liver transplantation. Consented participants who have met the screening inclusion criteria, undergone a successful liver transplantation and been initiated on a tacrolimus-based regimen that includes mycophenolate mofetil (MMF) and CS according to local practice, will enter the run-in period. Transplanted participants who meet the additional inclusion criteria will be randomized at Day 8±2 days post-LTx.

At least 128 participants will be randomized at a ratio of 2:3:3 to TAC Control (**Arm 1**) or one of two regimens of CFZ533: 600 mg CFZ533 subcutaneous (SC) injections every 2 weeks (**Arm 2**) or 300 mg CFZ533 SC injections every 2 weeks (**Arm 3**) combined with MMF and CS (Figure 3-1).

Each CFZ533 arm will have a loading period where CFZ533 will be administered IV in order to rapidly achieve concentrations providing complete CD40-CD40L pathway blockade in target tissues in conditions where CD40 expression levels may be enhanced (Section 4.2 for dose rationale). Participants who do not meet the randomization criteria will be designated randomization failures. The randomized failure participants will not be further followed-up in the study.

The study treatments will be as follows:

- **Arm 1** (TAC Control) - TAC, MMF and CS will be started in the peri-transplant period and at randomization these will continue up to the EOS. Initial tacrolimus target trough levels will be between 5-15 ng/mL, based on b.i.d dosing and will be maintained throughout the run-in period. From randomization onwards, the TAC levels will be adjusted as per local label.
- **Arm 2** (CFZ533 600 mg regimen) - Loading doses will be 30 mg/kg IV on Day 8 post-transplantation, with a second dose of 15 mg/kg IV on Day 15 and SC administration of 600 mg every 2 weeks will begin on Day 29, with MMF and CS until the EOS.
- **Arm 3** (CFZ533 300 mg regimen) - A single loading dose of 30 mg/kg IV will be administered on Day 8 and SC administration of 300 mg every 2 weeks will begin on Day 29, with MMF and CS until the EOS.

In CFZ533 Arms 2 and 3, during the immediate peri- and post-transplant period, TAC will be given to provide immunological coverage but must be completely weaned off by Day 22. For details, please refer to Section 6.7.2.2.

CFZ533 sub-cutaneous injections will be administered by authorized Investigator/staff at each study visit. After the Month 6 visit (at site), in-home administration may be allowed by a health care provider (HCP). After Month 12 visit, the pre-filled syringes (PFS) use will allow self-administration at home.

The participants in the Control arm will receive their last dose of TAC on the day of the EOS. From EOS onwards, participants will be treated according to local standard of care practice.

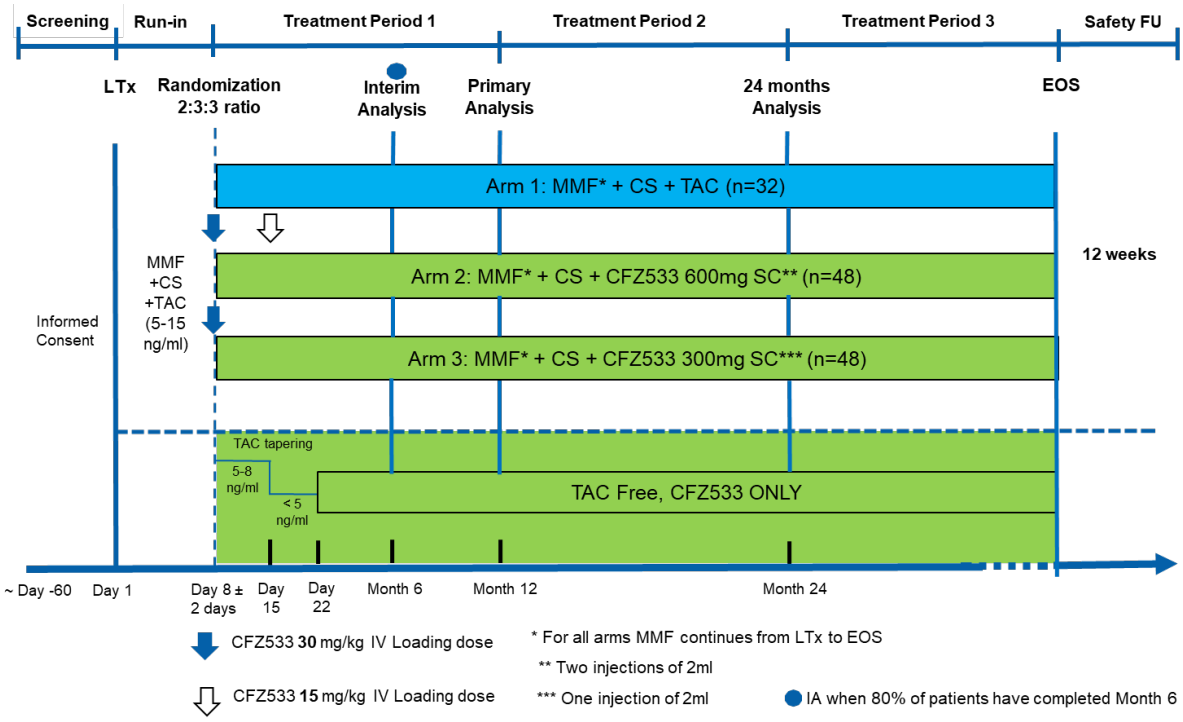
For all participants, MMF will be initiated at the time of liver transplantation, mycophenolates should be maintained throughout the study with CFZ533 or TAC; however adaptations are possible in case of signs of over-immunosuppression (see Section 6.5.2).

For all participants after the last study visit (EOS), there will be a 12-week safety follow-up period.

MMF and Corticosteroid doses will be administered according to local practice. Corticosteroid use is mandatory until Month 4 visit has been completed but the initiation and dose is according to local practice, with a minimum prednisone dose of 5 mg/day or equivalent dose of another oral corticosteroid.

All dose changes must be recorded in the appropriate CRF.

Figure 3-1 Study design



4 Rationale

4.1 Rationale for study design

- The design was chosen using a relatively conservative approach (delayed randomization, 12 months treatment duration and 12 months additional follow-up on treatment) given that this is the first study investigating CFZ533 in the liver transplant population.
- Due to the potential risk of serious infections and higher incidence of post-transplant surgical complications in the liver transplant population versus other type of transplants, possibly leading to death/graft loss in the immediate post-transplant period, delayed introduction of CFZ533 has been preferred.
- At the time of LTx (Day 1) the TAC blood target trough levels will be 5-15 ng/mL and will be maintained throughout the run-in period for all participants (Arms 1, 2, 3).

- For the Arm 1 participants, they will continue on TAC, MMF and CS. TAC levels will be adjusted as per local label.
- For the CFZ533 (Arms 2 and 3) participants; TAC dose will be progressively decreased until Day 21 as described thereafter. On Day 8, at the time of the first CFZ533 loading dose (30 mg/kg IV), the TAC dose will be reduced to achieve a TAC blood trough level of 5-8 ng/mL. The TAC dose will be further decreased by Day 15, to target a TAC blood trough level below 5 ng/mL. By Day 22, TAC must be completely weaned-off.
- The delayed randomization at Day 8±2 post-LTx was chosen to mitigate the risk of post-surgical complications, over-immunosuppression, infections and drug-loss through abdominal fluid and to take advantage of the vasoconstrictive and pro-fibrotic effect of tacrolimus.
- The long-term extension was added to collect long-term safety and efficacy data in a controlled clinical trial setting. Patients will stay in the long-term extension for at least 3 years.

4.1.1 Rationale for choice of background therapy

CFZ533 will be utilized as part of the typical triple therapy regimen in association with the anti-proliferative agent MMF and CS in the context of a CNI-free regimen. Corticosteroids have been the mainstay for induction of immunosuppression since the first successful cases of solid organ transplantation but the doses are reduced normally during the maintenance phase to minimize its side effects. If medical conditions allow, some centers may tend to eliminate corticosteroids from the regimen, resulting in a final dual therapy regimen composed by a backbone immunosuppressant (TAC or CFZ533) and MMF.

4.2 Rationale for dose/regimen and duration of treatment

4.2.1 Arm 2 (600 mg regimen)

CFZ533 treatment starts with two loading doses where CFZ533 is administered at 30 mg/kg IV on Day 8±2, and at 15 mg/kg IV on Day 15, followed by a subcutaneous maintenance regimen starting on Day 29 and up to the EOS, where CFZ533 is administered at 600 mg every 2 weeks.

The predicted median CFZ533 plasma concentration-time profile is presented on Figure 4-1.

Rationale for the loading dose(s)

CFZ533 is subject to target-mediated elimination, and the level of expression of CD40 receptors in target tissues has the potential to affect exposure to CFZ533, and ultimately target engagement. High CD40 expression may be associated with high elimination rate of CFZ533 and loss of CD40 pathway blockade, if CD40 receptors are not fully saturated. The loading dose(s) are aiming to achieve, at start of treatment, full CD40 receptor saturation and minimal CD40-mediated elimination, in conditions where, after transplantation, CD40 expression may be enhanced (as after kidney transplantation - illustrated below with ASKP1240 data).

ASKP1240 (bleselumab) in kidney transplantation

The risk associated with under dosing in conditions where CD40 expression is enhanced is illustrated through the ASKP1240 (bleselumab) program. This IgG4 anti-CD40 blocking antibody with similar PK and pharmacology properties as CFZ533 was investigated in kidney transplant participants (Phase 2). We refer to 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 participant) was administered on Days 0, 7, 15, then every 2 weeks (Q2W) and every 4 weeks (Q4W). The cumulative dose for ASKP1240 up to Days 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, suboptimal 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).

Previous experience with CFZ533 in kidney transplant and RA participants

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

Similarly, in Study CCFZ533A2202 (liver transplant), assuming an absolute bioavailability of about 75% for CFZ533 doses administered subcutaneously (preliminary data from the first-in-human Study CCFZ533X2101), the cumulative dose for CFZ533 in liver transplant participants are expected to be 3600 and 4500 mg up to Day 29 and 57, respectively.

The proposed IV loading - SC maintenance regimen (further details in the section below) is expected to provide similar plasma exposure levels, during the first 3 months, to those observed in Study CCFZ533X2201-Part 2 (kidney transplant).

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

Rationale for the maintenance regimen

In **Arm 2**, the 600 mg regimen is expected to provide steady state median trough CFZ533 plasma concentration of about 200 µg/mL, which is in the upper range (Figure 4-1) of the CFZ533 trough concentrations measured in Study CCFZ533X2201-Part 2. In that study, preliminary efficacy data suggest comparable biopsy proven acute rejection (BPAR) rates 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. In addition, the every 2 weeks regimen in this study is expected to provide less between-participant variability as compared to the Q4W IV regimen in Study CCF533X2201-Part 2 in kidney transplant.

Rationale for the duration of the safety follow-up period (target engagement after the last dose)

Based on the predicted median CFZ533 plasma concentration-time profile in liver transplant participants (Figure 4-1), at about 14 weeks after the last dose (Day 659, Month 23.5), CFZ533 plasma concentrations are expected to drop below 20 µg/mL with no expected pharmacodynamic activity in target tissues (e.g., germinal centers; data from non-human primates in Investigator's Brochure).

A 14 weeks follow-up period after the last CFZ533 dose has been selected, and it is justified to monitor any related serious adverse events.

4.2.2 Arm 3 (300 mg regimen)

The CFZ533 treatment starts with a loading dose where CFZ533 is administered at 30 mg/kg IV on Day 8±2, followed by a subcutaneous maintenance regimen starting on Day 29 and up to EOS, where CFZ533 is administered at 300 mg every 2 weeks.

Rationale for testing a lower CFZ533 regimen in liver transplant participants

The decision and rationale for testing a lower regimen for CFZ533 in liver transplant is motivated and guided by the following considerations:

- **High tissue penetration in liver**

As compared to kidney, a tissue with tight and size-selective capillaries where CFZ533 is mainly restricted to the vascular space and poorly distributed in the interstitial space, higher interstitial antibody concentrations are expected in liver.
In liver, due to discontinuous capillaries, the vessel wall does not provide a clear separation of the vascular and interstitial space for IgGs. This would translate into a rapid equilibrium

between the two spaces, and interstitial concentrations that are reflected by plasma concentrations.

- **Immune tolerance in liver transplantation**

It is now well recognized that the liver exhibits immune tolerogenic properties that contribute to a unique propensity toward spontaneous acceptance in the context of transplantation and to a far lower risk of graft loss secondary to rejection episodes, as compared with other transplanted organs (Calne 2000, Clavien et al 2017, Mastoridis et al 2017, Vionnet and Sanchez-Fueyoc 2018).

In addition, successful liver transplantation can be obtained with lower immunosuppressive requirements than other organs, and liver allografts can recover from advanced acute and chronic rejection episodes (Doyle et al 1996, Olausson 2007, Sugawara 2009).

- **Infection risks**

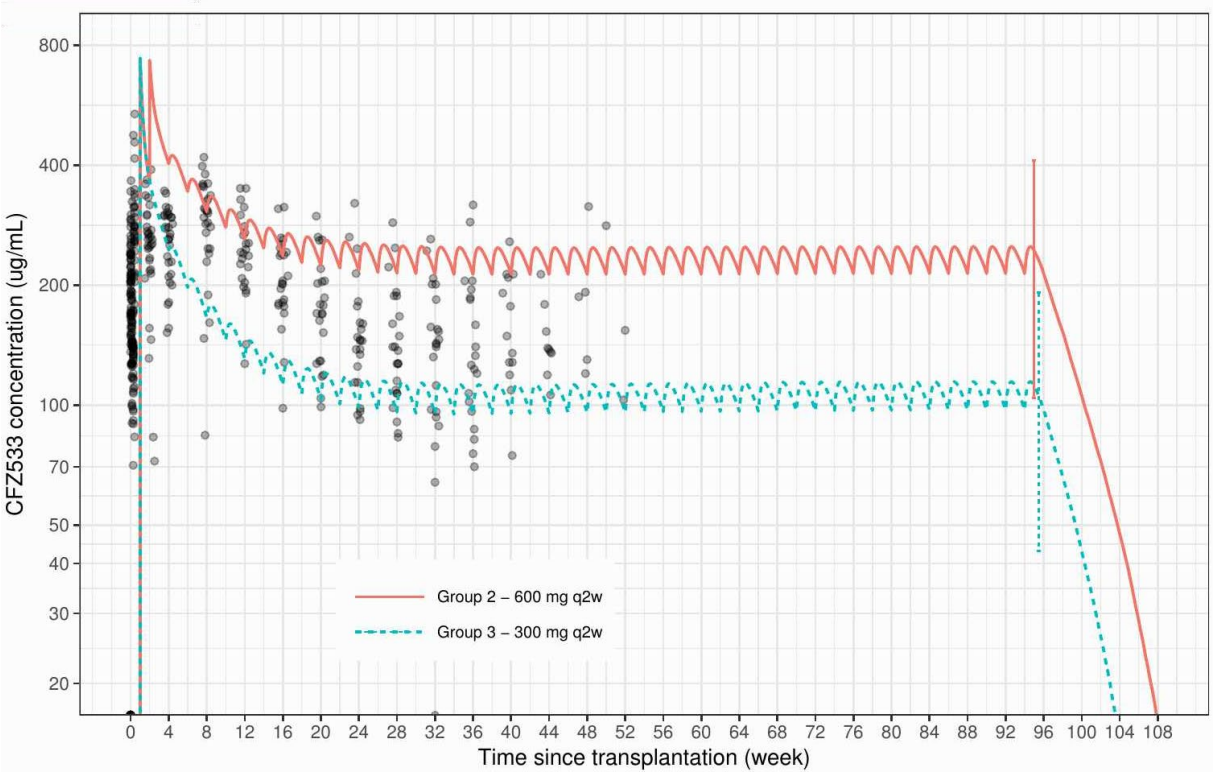
While remarkable improvements in short-term allograft and transplant recipient survival have been achieved in the last three decades, complications (*de novo* malignancies, infections, chronic renal failure, cardiovascular and metabolic diseases) remain associated with the chronic use of immunosuppressive therapies. This warrants the evaluation of lower immunosuppressive regimens and exposures.

In **Arm 3**, the loading regimen is limited to a single intravenous dose of 30 mg/kg CFZ533 on Day 8, and the 300 mg 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 4-1).

In pSS participants (Study CCFZ533X2203, completed) CFZ533 trough levels of approximately 100 µg/mL were associated with clinical efficacy (clear improvement in European League Against Rheumatism (EULAR) Sjöegren's Syndrome Disease Activity Index), and suppression of a biologically relevant biomarker CXCL13 (chemokine CXC ligand 13 protein, a marker of germinal center activity).

In addition, for 95% of participants, this maintenance regimen is expected to provide plasma concentrations that are above 40 µg/mL, a threshold that was associated with a complete suppression of germinal center development in cortical B cell areas of lymph nodes (26-week toxicity study in cynomolgus monkeys; 1 mg/kg weekly), and of T cell dependent antibody response (recall antibody responses to immunization challenge) in non –human primate (NHP).

Figure 4-1 Predicted median CFZ533 plasma concentration time-profile in liver transplant participants overlaid with measured plasma concentrations in kidney transplant participants (Study CCFZ533X2201-Part 2; interim data)



The lines represent the predicted time-course of the CFZ533 plasma concentration for the typical transplant participant in **Arm 2** (after 2 loading doses IV, 600 mg regimen - continuous red line), or **Arm 3** (after 1 loading dose IV, 300 mg regimen – dotted light blue 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 participants with body weight ranging from 50 to 120 kg (random distribution). The CFZ533 plasma concentrations measured in Study CCFZ533X2201-Part 2 in *de novo* transplant participants are displayed as gray dots (after a loading IV regimen, the maintenance regimen for CFZ533 was 10 mg/kg IV Q4W; 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).

4.3 Rationale for CFZ533 dosing to compensate for drug loss due to ascites drainage

Ascites is an accumulation of fluid in the peritoneal cavity.
It is associated with end-stage liver disease and portal hypertension. It is expected to resolve with a liver transplantation, but ascites can also be removed by large volume paracentesis or surgical drainage.

Ascites occurs with moderate volume (< 0.25 L/day) in the majority of liver transplant recipients, but a non-negligible proportion of participants (7%) present with a median volume of 1 L/day for a median duration of 77 days post transplantation (Cirera et al, 2000).

Ascites has the potential to affect CFZ533 exposure in particular if ascites are removed after paracentesis or surgery. The drug loss depends on the amount of ascites removed, and on the drug concentration in the ascites.

In the context of this study, drained ascites will be considered relevant when the cumulative volume of ascites or fluid loss through paracentesis/surgical drainage collected from a participant reaches a cumulative volume of **4 L** (similar to belatacept liver transplant study; Klintmalm 2014). CFZ533 compensation will be administered as described in Section 6.1.4.

Figure 4-2 displays the predicted CFZ533 plasma exposure during 2 weeks post first dose of CFZ533 on Day 8:

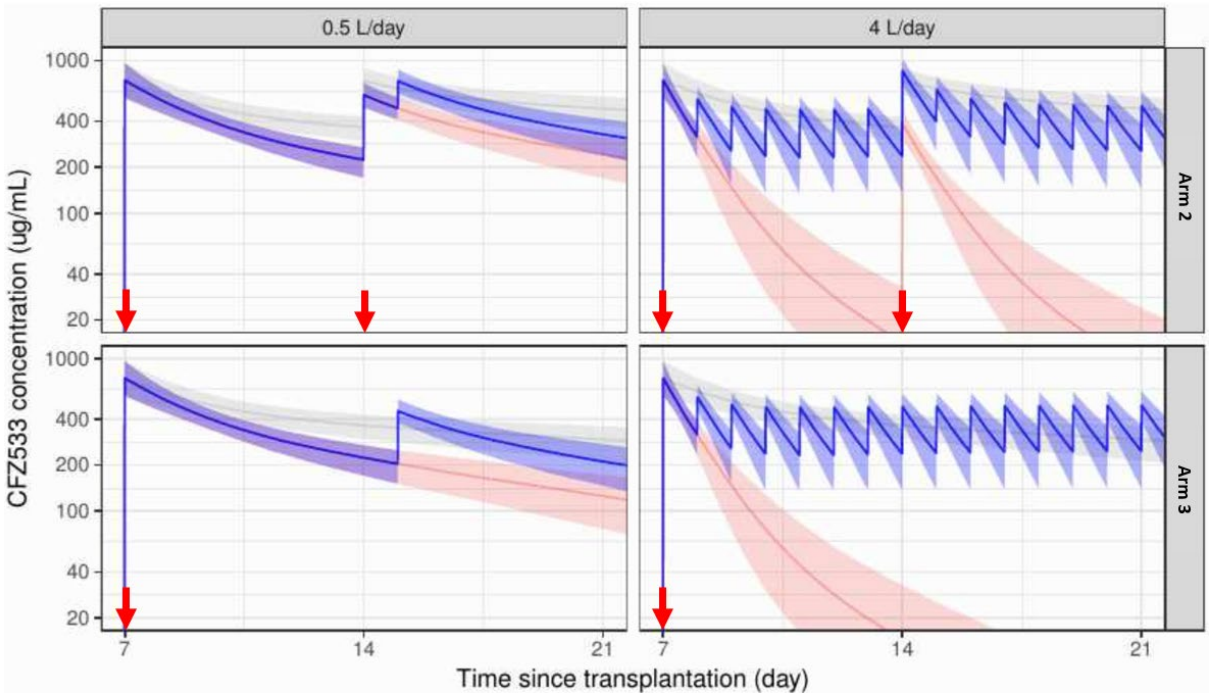
- in case of no ascites (light gray),
- in case of ascites and no additional/compensating CFZ533 dose (pink),
- in case of ascites **with an additional**/compensating CFZ533 dose **each time** the cumulative ascites volume reaches **4 L** (blue).

As shown in Figure 4-2 where two scenarios of ascites drainage are presented (0.5 and 4 L/day), the additional/compensating intravenous dose is expected to adjust the participants' exposure adequately during the first days of treatment.

After Day 29, when CFZ533 concentrations are approaching steady state, a compensating dose specific to the treatment arm (10 mg/kg IV and 5 mg/kg IV in Arm 2 and Arm 3, respectively) should bring the concentration in the range of their respective steady state exposure (not shown).

Note: Until Month 24, each time an additional/compensating intravenous CFZ533 dose (10 or 5 mg/kg) will be administered; a pre-dose blood sample will be taken to assess the CFZ533 concentration in plasma.

Figure 4-2 Predicted CFZ533 exposure in case of (i) no ascites drainage (light grey), (ii) ascites drainage but no compensating dose (pink), and (iii) ascites drainage with compensating dose (blue)



The lines represent the typical CFZ533 concentration-time profiles during 2 weeks post first administration of CFZ533 on Study Day 8 in Arm 2 and Arm 3 in case of (i) no ascites drainage (light grey), (ii) ascites drainage but no compensating dose (pink), and (iii) ascites drainage with **additional** compensating dose(s) of 10 mg/kg IV CFZ533, every time the cumulative ascites volume reaches at least 4 L (blue). The areas of corresponding color represent the 90% percentile of the individual profiles. The vertical red arrows indicate the **scheduled** CFZ533 doses (30 mg/kg IV on Study Day 8 (Arm 2 and Arm 3), and 15 mg/kg IV on Study Day 15 (Arm 2 only)). The figure illustrates two scenarios of ascites: in the left panels, participants are losing 0.5 L of ascites per day, resulting in the administration of an (**additional)** compensating dose on Study Day 16 (8 days post first dose on Study Day 8); in the right panels, participants are losing 4 L of ascites per day, resulting in daily administration of a compensating dose (10 mg/kg IV). Note that 2 weeks post 1st dose (Day 15), Arm 2 participants loosing 4 L/day of ascites (top right panel) will get**, on the same day, the scheduled dose (15 mg/kg IV) and the compensating dose (10 mg/kg IV)**.

4.4 Rationale for choice of control drugs (comparator)

Initial therapy following liver transplantation includes a calcineurin inhibitor, used as the base immunosuppressive agent in combination with CS and MMF. Maintenance therapy is often with (i) reduced dosage and/or (ii) reduced number of immunosuppressive drug (e.g.: corticosteroid elimination), the calcineurin inhibitor remains as the base immunosuppressive in renal or liver transplantation [EMA guideline Doc. Ref. CHMP/EWP/263148/06].

4.5 Purpose and timing of interim analyses/design adaptations

Participants participating in this study will receive study treatment for a variable duration depending on the date of study entry and completion of the extension. The main analysis will be performed at 12 months to assess efficacy and safety variables. A 24-month analysis will be

performed as a safety and efficacy follow-up assessment. Then, at the EOS, a final analysis will be performed to analyze data from the long-term extension.

An interim analysis (IA) is planned after 80% participants have reached the Month 6 visit (or have prematurely discontinued the study before Month 6). All efficacy data up to the cutoff date, including data beyond Month 6 and participants not yet reaching Month 6 will be included. The Poisson model (see Section 12.4.4) will be used to evaluate the composite efficacy failure rate to adjust for the differential follow-up time of participants at the IA. The primary objective of the IA is to enable the overall benefit-risk assessment. There are no plans to stop the study early for good efficacy, since it is desired to collect long-term efficacy and safety data. Following 24-month analysis until final analysis, additional IAs may be conducted to support decision making concerning the current clinical study or project, the sponsor's clinical development projects in general or in case of any safety concerns.

Until Month 24, the stopping rules will be evaluated by the Clinical Team as outlined in Section 12.6. Stopping rule analysis and the Data Monitoring Committee (DMC) review will not be conducted during the extension period. The DMC will review data at regular intervals as described in Section 10.2 and the DMC charter.

The analyses will be outlined in the Statistical Analysis Plan (SAP).

4.6 Risks and benefits

Stage 4 or 5 chronic kidney disease (CKD) has been reported in ~18% of liver transplant recipients by 5 years post-transplant and is associated with increased morbidity and mortality. Data from 1997 to 2008 in the Organ Procurement Transplant Network/United Network for Organ Sharing (OPTN/UNOS) database showed a threefold increased rate of kidney transplantation in participants who previously received a liver transplant. While the causes of CKD in liver transplant participants are multifactorial, including pre-transplant and peri-transplant factors like hepatitis C virus (HCV), diabetes and hepatorenal syndrome, calcineurin inhibitors (CNIs) appear to be significant contributing factors. In the OPTN/UNOS analysis, ~50% of liver transplant participants who received a kidney transplant had a diagnosis consistent with CNI toxicity. Thus, there is a need for immunosuppressive regimens that provide similar anti-rejection efficacy while avoiding the nephrotoxic, cardiovascular and metabolic risks of CNIs in liver transplant recipients.

To fulfill this important unmet medical need, an exploratory Phase II study was conducted to evaluate the efficacy and safety of the co-stimulation blocker belatacept in adult recipients of first liver transplant from a deceased donor (NCT 00555321).

Belatacept is a selective T-cell co-stimulation blocker, which binds to CD 80/86 ligands of antigen-stimulating cells and thereby inhibits the CD-28-mediated T-cell co-stimulation.

Findings from this phase II study did not allow the identification of a safe and effective dose or regimen for further development of belatacept in liver transplant indication.

The authors of the study mention that the liver may be participant to CD28- independent T cell activity as is surely to be expected, and they cite the potential negative effect of CD28 blockade on regulatory T cell activity.

Novartis has performed a study-specific medical and safety risk assessment and concluded that, based on the current data, 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 and managed in study participants.CFZ533

Differently from belatacept, CFZ533 targets the CD40 receptor that is a transmembrane glycoprotein constitutively expressed on B cells and other antigen presenting cells (APCs) including monocytes, macrophages, and dendritic cells (DCs), as well as by platelets, and inflamed parenchyma. The binding of CD40 to its ligand CD154 results in cell-type specific activation outcomes, including DC maturation, monocyte survival and cytokine secretion by many cell types including renal epithelial cells.

In addition, co-stimulatory CD40 pathway is required for many aspects of humoral immunity including germinal center (GC) formation, memory B cell development, immunoglobulin (Ig) isotype switching, and affinity maturation. Pharmacological inhibition of CD40-CD154 pathway using anti-CD4- or anti-CD154 antibodies reduced autoimmune disease pathology in numerous pre-clinical and clinical studies and prolonged allograft survival in NHPs (refer to the current [Investigator's Brochure, Section 4]).

The proof of concept trial CFZ533X2201 conducted in kidney transplant recipients has shown the ability of CFZ533, in the context of CNI-free regimen, to provide similar efficacy, better renal function and comparable safety profile compared to CNI-based regimen (TAC+MMF+CS), including absence of PTLD, PML, absence of donor specific antibodies, reduced frequency of new onset diabetes.

The promising data have opened the possibility for CFZ533 to represent a viable alternative to CNIs in liver transplant recipients fulfilling the important unmet medical need in this participant population.

Benefits: Based on the mechanism of action of CFZ533 and its use in a CNI-free setup in de-novo transplant participants it is anticipated that the CFZ533 regimen will provide long term graft survival without compromising short term efficacy, with potentially better renal function, less development of *de novo* Donor-Specific Antibodies (DSA) and an improved cardiovascular and metabolic profile with less hyperlipidemia, hypertension and New Onset of Diabetes Mellitus (NODM), and less neurotoxicity compared to standard of care.

Based on the anticipated overall risk-benefit, and because there is a large unmet need for new immunosuppressive treatment with less severe side effects and improved long-term graft and participant survival, the current study evaluating CFZ533 in *de novo* liver transplant participants is justified.

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

Beyond the potential risks described in the Investigator Brochure (IB), there may be risks that may be serious and unforeseen in relation to the use of CFZ533.

The risk to subjects 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 12.6).

The list of potential risks related to CFZ533 administration, in the current Investigator 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, therapeutic failure of vaccination during CFZ533 treatment, loss of efficacy or allergic/immune-mediated inflammatory reactions due to development of anti-CFZ533 antibodies, thrombophilia and lymphoproliferative disorders (refer to the actual IB for more details). 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 (lower risk compared to humanized or chimeric antibodies) with immunosuppressive properties and that will be co-administered with MMF, further limiting the risk for the generation anti-CFZ533 antibodies.

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.

4.7 Previous clinical experience with CFZ533

In Study CCFZ533X2101 (First In Human (FIH)), one participant 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 (ADAs) in this participant did not compromise exposure, and was not associated with an immune related safety signal. This corresponds to a ADAs 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 participants enrolled in Study CCFZ533X2205 (myasthenia gravis) during the 12-week treatment and 24-week follow up period after the last dose of CFZ533.

The presence of anti-CFZ533 antibodies is assessed in all CFZ533-treated participants in all clinical studies with CFZ533.

A Proof of Concept trial (CCFZ533X2201) has evaluated the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of multiple doses of CFZ533 in combination with MMF and corticosteroids, compared to a tacrolimus-based regimen, in *de novo* renal transplant recipients. CFZ533 participants 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.

Results at Month 12 have shown that the regimen was well tolerated and specifically not associated with an increased risk of over-immunosuppression such as neutropenia and the rate of infections was comparable (85.3% in CFZ533 vs. 88.9% in TAC). There were no

thromboembolic events on CFZ533 (but 1 episode with TAC). There were no deaths, no PTLD, no PML and no graft loss in the CFZ533 arm. A trend was observed towards fewer participants in the CFZ533 group with New Onset Diabetes (12.5% in CFZ533 vs. 30.0% in TAC) and BK polyomavirus (BKV) positive PCR >10000 copies in serum (18.2% in CFZ533 vs 22.2% in TAC). Renal function (eGFR) difference of about 10 mL/min favored CFZ533 over Tacrolimus, while the combined endpoint (Graft Loss + tBPAR) was similar (21.2% in CFZ533, 22.2% in TAC). No antibodies against CFZ533 were detected in any participant enrolled into study CFZ533X2201 (refer to current CFZ533 IB for more details).

The risk of insufficient efficacy in the present study 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 12.6).

4.8 Rationale for liver Histopathology - optional surveillance biopsies

Iscalimab has shown preservation of graft quality with normal renal morphology in a sub-set of participants from the kidney transplant study CCFZ533X2201 (NCT02217410) (Nashan et al. 2018). 3 of 5 subjects treated with iscalimab had normal histology at Month 12 or 24 (Farkash et al. 2019) while none of 7 control tacrolimus-treated subjects had normal histology. Similar observations were made in nonhuman primates treated with iscalimab (Cordoba et al. 2015). Thus, iscalimab has the potential of offering better graft quality and thereby improve long-term outcomes for transplanted participants. This is further being studied in the ongoing kidney transplant trial CCFZ533A2201 (NCT03663335).

Compared to other transplanted solid organs, the transplanted liver has some unique features. It has a higher regenerative capacity than most organs (Muller et al. 2004, Wadstrom et al. 2017), Wadstrom et al. 2017), higher tolerogenic capacity (Benitez et al. 2013, Feng and Bucuvalas 2017, Feng et al. 2012) and liver allograft rejection does not contribute to late graft failure to the same extent as other solid organ allografts (Kim et al. 2018). The induced tolerance can even make it possible to withdraw immunosuppression in a selection of participants (Benitez et al. 2013, Feng et al. 2012). Despite these qualities of the transplanted liver, there is a need for improved liver graft histology.

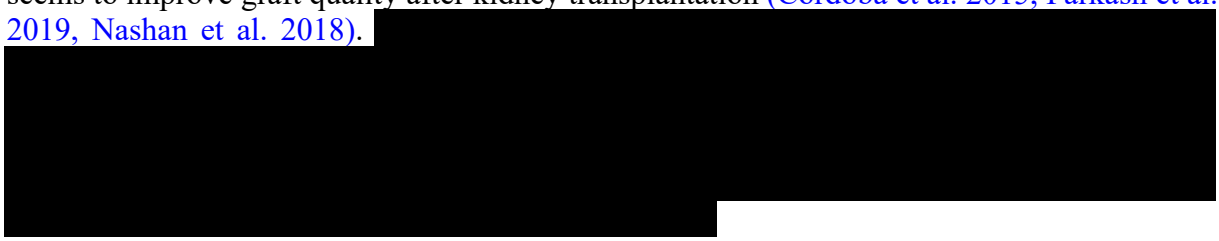
Approximately 90% of biopsy samples from adult recipients surviving more than 1 year show significant abnormalities (Banff Working Group on Liver Allograft 2012). These changes occur in patients with abnormal liver function tests (LFTs), but histological signs of chronic inflammation and fibrosis seem to be present in up to 85% of recipients with normal LFTs (Feng and Bucuvalas 2017). Even with state-of-the-art immunosuppressive therapy, only one third of pediatric liver transplants were free from signs of inflammation (Feng et al. 2018). Commonly present changes that might be clinically significant include recurrent disease, fatty liver disease, and biliary tract strictures, while changes attributable to classic acute or chronic rejection are usually seen in less than 25% of biopsy samples (Banff Working Group on Liver Allograft 2012).

In participants after orthotopic liver transplantation, liver biopsy is used to detect acute or chronic rejection, potential recurrence of the underlying disease, and to evaluate the degree of

fibrosis and stage of liver disease (Jiang and Farber 2017, Sebagh and Samuel 2004). Biochemistry tests are insensitive and unspecific for liver allograft monitoring. Therefore, histopathological biopsy analysis remains the most sensitive modality for evaluating graft parenchymal injury (Banff Working Group on Liver Allograft 2012, Ekong et al. 2008, Gonzalez and Washington 2016, Mells and Neuberger 2008, Sebagh and Samuel 2004). Morphology plays an important role in differential diagnosis and subsequent treatment of post-transplant complications (Demetris et al. 2000, Demetris et al. 2016, Ormonde et al. 1999).

Routine surveillance biopsy monitoring of asymptomatic long-term participants with normal or nearly normal liver tests is more controversial (Mells and Neuberger 2008, Pereira et al. 2016). Arguments against the use of routine surveillance biopsy include potential morbidity and mortality, costs, inconvenience, resource utilization, and the uncertain clinical significance of unexplained histopathological findings. However, an advantage of routine surveillance biopsies is that it allows early detection of clinically relevant disease (Sebagh and Samuel 2004). Furthermore, routine surveillance biopsies can support clinical decision-making and allow for the identification of recipients who might benefit from treatment adjustments of immuno-suppressant drugs. It also can assess the impact of chronic low grade injury or alcohol use, categorize HCV+ recipients more accurately, and inform the potential for immune suppression minimization protocols (Demetris et al. 2016, Feng and Bucuvalas 2017, Feng et al. 2018, Sebagh and Samuel 2004). Routine biopsies can help understanding low-grade chronic inflammation or allograft hepatitis and progressive fibrosis (Arias et al. 2017, Feng and Bucuvalas 2017, Feng et al. 2018, Londono et al. 2018). New techniques based on molecular profiling suggest that subclinical inflammation, indicative of low-grade rejection, is more common than is evident from histology alone (Arias et al. 2017, Feng et al. 2018, Garcia-Carro et al. 2018, Loupy et al. 2017, Menon et al. 2017). Minor infiltrates could represent rejection, autoimmunity, viral infection, or regulatory immunological reactions (Banff Working Group on Liver Allograft 2012). Taken altogether, routine surveillance liver biopsies provide essential and clinically relevant information after liver transplantation with an acceptable benefit-risk profile (Banff Working Group on Liver Allograft 2012, Pereira et al. 2016).

The relationship between histology and long-term outcomes is not as well understood for the liver compared to the kidney. However, there is evidence suggesting an association between liver histology and long-term outcome after liver transplantation (Pappo et al. 1995, Sebagh et al. 2003, Slapak et al. 1997). However, there is no specific study so far for the commonly used IS therapies and their effects on liver histopathology. Currently, there is also no information about potential effects of iscalimab on liver graft histology. As described above, iscalimab seems to improve graft quality after kidney transplantation (Cordoba et al. 2015, Farkash et al. 2019, Nashan et al. 2018).



5 Study Population

The study population will consist of *de novo* liver transplant recipients, aged 18-70 years, receiving a primary allograft from a deceased donor. It is planned to randomize at least 128 participants from multiple centers located in Europe, North America and Latin America.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

Screening period up to liver transplantation

1. Written informed consent must be obtained before any assessment is performed.
2. Male or female subject between 18-70 years of age.
3. Recipient of a primary liver transplant from a deceased donor.
4. Up to date vaccination as per local immunization schedules.
5. Recipient tested negative for Human Immunodeficiency Virus (HIV).
6. Model for End stage Liver Disease (MELD) score ≤ 30 (based on laboratory values, using the United Network for Organ Sharing (UNOS) MELD calculator: https://unos.org/resources/allocation-calculators/).
11. Transplantation to occur within defined screening period following informed consent signature.

At Randomization (Day 8±2)

7. Recipients with no active Hepatitis C Virus (HCV) and Hepatitis B (HBV) replication. Recipients with HCV antibody positive should have no detectable HCV-RNA. Recipients with Hepatitis B infection should have no detectable HBV DNA. Cases of spontaneous HCV clearance should be discussed with sponsor.
8. Allograft is functioning at an acceptable level by the time of randomization as defined by AST, ALT, Alkaline Phosphatase levels ≤ 5 times ULN and Total Bilirubin ≤ 2 times ULN.
9. Renal function (eGFR, MDRD-4 formula) ≥ 30 mL/min/1.73m^2 based on most recent post-transplant value prior to randomization.
10. Recipients who have been initiated on an immunosuppressive regimen that contains TAC, MMF and corticosteroids as per protocol.

5.2 Exclusion criteria

Participants fulfilling any of the following criteria are not eligible for inclusion in this study.

Screening period up to liver transplantation

1. Use of other investigational drugs at screening, within 30 days or 5 half-lives of screening (until the expected pharmacodynamics effect has returned to baseline), whichever is longer.
2. Recipients of multiple solid organ or islet cell transplants have previously received a tissue transplant, or recipients who have a combined liver-kidney transplant.
3. Recipients of a liver from a donor after cardiac death (DCD), from a living donor, or of a split liver.

4. Not-applicable
5. Recipient who tests negative for Epstein Barr virus (EBV) within 28 days prior to baseline visit.
6. Patients who have received a live vaccine within four weeks prior to transplantation.
7. Recipients receiving an ABO incompatible allograft.
8. History of malignancy of any organ system (except hepatocellular carcinoma or localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
9. Hepatocellular carcinoma that does not fulfill Milan criteria (1 nodule ≤5 cm, 2-3 nodules all ≤3 cm, without evidence of metastatic disease or vascular invasion, see Appendix 2, Mazzaferro et al 1996) at the time of transplantation.
10. Participants transplanted for acute liver failure (does not apply to acute on chronic liver failure).
11. Any use of antibody induction therapy or use of any immunosuppressive or other medications prohibited by the protocol (see Section 6.2.2).
12. Recipients with history of non-liver related coagulopathy or medical condition requiring long-term anticoagulation. Participants treated with low dose aspirin and patients with asymptomatic liver-related coagulopathy not on treatment, may be enrolled into the study.
13. Recipients who have any serious condition, which might significantly affect the outcome of the study or their ability to participate in the study.
14. History of hypersensitivity to any constituent of the product (any of the study drugs) or its excipients or to drugs of similar chemical classes.
15. Recipients with HIV positive donor.
16. Recipients with donors HBsAg positive.
17. Recipients who are HCV antibody-positive without documented sustained viral response (SVR) at 12 weeks after finishing anti HCV treatment (e.g., direct-acting antivirals).
    - Recipients with HCV RNA-positive donors
18. Recipients with donors with macrovesicular steatosis > 30%.
19. Pregnant or nursing (lactating) women.
20. Women of childbearing 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 stopping of study treatment. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Note 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 the study treatment. In the case of oophorectomy alone, this is 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 participants on the study, the vasectomized male partner should be the sole partner for that participant otherwise other highly effective contraceptive methods should be used.
- 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 the 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), total hysterectomy or bilateral 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 she is considered not of childbearing potential.

Sexually active male participants, or the female partner, are recommended to use highly effective contraception during therapy with MMF and at least 90 days following discontinuation of mycophenolate (see additional information in Section 8.4.3).

In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the Informed Consent Form (ICF).

At Randomization (Day 8±2)

21. Any post-transplant history of thrombosis, occlusion or stent placement in any hepatic arteries, hepatic veins, portal vein or inferior vena cava at any time during the run-in period prior to randomization. Absence of any graft vascular thrombosis or occlusion (by diagnostic method used at the site to assess vascular patency) must be confirmed by imaging prior to randomization.
22. Recipients with platelet count < 50,000/mm^3.
23. Recipients with an absolute neutrophil count of < 1,000/mm^3 or white blood cell count of < 2,000/mm^3.
24. Recipients with clinically significant systemic infection requiring use of IV antibiotics.
25. 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).
26. Recipients who are in a critical care setting at the time of randomization requiring life support measures such as mechanical ventilation, dialysis, requirement of vasopressor agents.
27. Recipients who are on renal replacement therapy at randomization.
28. Any episode of acute rejection or suspected rejection prior to randomization.
29. HCC participants whose explanted liver graft pathology report shows i) pTNM stage beyond T2N0M0, ii) presence of mixed carcinoma, iii) microvascular invasion despite pTNM stage.

30. Participants with body weight < 30 kg or > 180 kg.
31. Recipients with donors who had confirmed history of SARS-CoV-2 infection.

The investigator may apply no additional exclusions, in order to ensure that the study population will be representative of all eligible participants.

6 Treatment

6.1 Study treatment

6.1.1 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.

Investigational drug

- CFZ533 150 mg/1 mL vials which can be used as concentrate for solution for infusion via IV route of administration or solution for injection for SC route of administration
- CFZ533 300 mg/2 mL prefilled syringes (PFS) - solution for injection for SC route of administration.

Both the above mentioned CFZ533 vials and PFS will be supplied centrally by Novartis.

Participants will switch over from 150 mg/1mL vial to CFZ533 300 mg/2 mL PFS presentation once they have completed the M12 visit and PFS are made available. PFS is intended for self-administration and Section 6.7.2.1 provides instructions on PFS use.

Instructions for preparation and administration of CFZ533 vials will be described in a separate pharmacy manual. Instruction for administration of CFZ533 PFS will be provided in a separate Instructions for Use document.

Control and other study drugs

Concomitant immunosuppression medication will be used in this study in the combination described in the run-in and randomized treatment periods:

- Tacrolimus (TAC, Prograf® or generic equivalent) as 0.5 mg. 1.0 mg or 5.0 mg capsules/tablets or IV formulation where required. TAC will be supplied locally as part of standard of care.
- Mycophenolate mofetil (MMF, CellCept® or generic equivalent) 500 mg film-coated tablets, 250 mg capsules or 500 mg vial for IV administration.
- Corticosteroids (CS) for oral and IV administration will be purchased locally. The CS dose must be administered according to local practice.

MMF and CS for oral and IV administration will be supplied locally and will be used as per local label. TAC will be supplied locally and will be used as per local label from transplantation onwards (Arm 1).

6.1.2 Additional study treatments

No additional concomitant immunosuppressive drugs beyond study treatment (CFZ533, TAC, MMF/mycophenolates, corticosteroids) are allowed in this trial; however, treatment of acute rejection (e.g. bolus steroids or anti-T-cell antibodies) should be performed according to local practice.

6.1.3 Treatment arms/groups

Participants will be assigned to one of the following three treatment arms in a 2:3:3 ratio:

- **Arm 1 - TAC Control (n=32)**: TAC + MMF + CS up to EOS. Initial TAC target trough will be between 5-15 ng/mL during the run-in period. From randomization onwards, the TAC levels will be adjusted as per local label.
- **Arm 2 - CFZ533 600 mg regimen (n=48)**: Loading doses of 30 mg/kg IV on Day 8 (with ±2 days window), and 15 mg/kg IV on Day 15. The SC administration of 600 mg (2 injections of 2 mL CFZ533 at 150 mg/mL) every 2 weeks will begin on Day 29, in combination with MMF and CS up to EOS.
- **Arm 3 - CFZ533 300 mg regimen (n=48)**: Single loading dose of 30 mg/kg IV on Day 8 (with ±2 days window). The SC administration of 300 mg (1 injection of 2 mL CFZ533 at 150 mg/mL) every 2 weeks will begin on Day 29, in combination with MMF and CS up to EOS.

CFZ533 SC will be administered by authorized Investigator/staff at each study visit. After the Month 6 visit in-home administration may be allowed by a health care provider. PFS will be used upon availability once patient has completed M12 visit.

6.1.4 Compensation for CFZ533 loss through ascites fluid drainage

At any time during the treatment period, when the **cumulative** ascites fluid drainage volume reaches at least **4 L**, and **independently of the planned dosing schedule** (IV or SC; Section 4.3), an **additional** dose of CFZ533 will be administered intravenously to compensate for the amount of CFZ533 removed from the body through drained ascites.

- **Arm 2** (600 mg regimen): one (additional) dose of 10 mg/kg IV CFZ533, regardless of the time
- **Arm 3** (300 mg regimen)
  a. Up to Day 29: one (additional) dose of 10 mg/kg IV CFZ533,
  b. After Day 29: one (additional) dose of 5 mg/kg IV CFZ533.

In an extreme situation (massive ascites; Cirera 2000) where participants are experiencing a loss of fluid of 4 L/day, this should trigger the daily administration of an additional, compensatory CFZ533 dose, as described above.

Any additional IV dose of CFZ533, administered on top of the scheduled CFZ533 doses (IV, SC), to compensate for drug loss through ascites drainage, should be captured in the appropriate CRF.

Each time an additional/compensating intravenous CFZ533 dose (10 or 5 mg/kg IV) will be administered; a pre-dose blood sample will be taken.

6.1.5 Post-Trial Access

Participants who complete participation in this trial and continue to derive clinical benefit from the treatment based on the investigator's evaluation may receive post-trial drug access program or have the opportunity to enter a follow-up study. Details of the follow-up study will be described in a separate protocol which will require endorsement in participating countries and sites as per local laws and regulations.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

Cytomegalovirus prophylaxis

Cytomegalovirus (CMV) prophylaxis or preemptive monitoring for CMV should be according to local practice and applied uniformly for all enrolled participants at the center. However, following the guideline of the American Society of Transplantation Infectious Diseases Community of Practice to treat CMV in solid organ transplant recipients is highly recommended (Razonable RR and Humar 2019). Treatment with valganciclovir, ganciclovir, cytomegalovirus hyperimmune globulin or valacyclovir or other approved agents are permitted and will be administered according to local practice. CMV prophylaxis for at least 3 months is recommended for CMV Donor positive, Recipient negative (D+/R-) participants. CMV prophylaxis is also recommended following any antibody treatment of acute rejection episodes.

Pneumocystis jirovecii (Pneumocystis carinii pneumonia (PCP) prophylaxis

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

Hepatitis B (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. The type of HBV prophylaxis should be according to local practice. Prophylaxis should be recorded in the appropriate CRF.

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 in the appropriate CRF.

Other concomitant Medications

The investigator must instruct the participant to notify the study site about any new medications he/she takes after being enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant 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 Novartis before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

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.

6.2.2 Prohibited medication

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

Use of treatments displayed in Table 6-1 is **NOT** allowed. This is in order to avoid potential confounding factors or interaction with investigational or control treatment medication.

These non-protocol immunosuppressants are only allowed for those participants who have discontinued the randomized study treatment and switched to standard of care treatment as per local practice, and are continuing in follow up until Month 24 visit.

Table 6-1 Prohibited medication

Treatment Arm	Medication	Action to be taken
All	Cyclosporine Sirolimus Once a day tacrolimus formulations (e.g., Advagraf, Envarsus) Everolimus Azathioprine Campath Belatacept Alemtuzumab Rituximab Bortezomib Use of any antibody as an induction agent Live vaccines	Discontinue the prohibited medication immediately Keep the participant in the study Report the protocol deviation

6.2.3 Induction therapy

No antibody therapy is allowed.

6.2.4 Rescue medication

Rescue therapy is based on local center practice. Use of rescue medication must be recorded on the respective CRF.

Treatment of HCV recurrence

Only patients with sustained virologic response (at least SVR 12) are eligible for the study. Treatment for HCV recurrence is permitted, but cannot be preemptive. Investigators will be allowed to treat HCV only when recurrent HCV disease has been documented, based on histological evidence as determined by the local pathologist. Therapies used for post-transplantation HCV recurrence will be documented on the appropriate CRF. Any HCV positive participants requiring treatment with a protease inhibitor should be discussed with the sponsor.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

The participant number assigned to a participant at screening remains the unique identifier for the participant throughout the study. The participant number is composed of a site number and a sequential number. Once assigned to a participant, the participant number will not be re-used.

6.3.2 Treatment assignment, randomization

At Day 8 (randomization) visit, all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms.

A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

There is no blinding, the study is open-label to participants, investigator staff, persons performing the assessments, and the Novartis team. Furthermore, the stopping rules (Section 12.6) will be assessed by the sponsor team based on real time unblinded safety and efficacy data.

6.5 Dose modification

6.5.1 Permitted dose adjustments and interruptions of CFZ533 study treatment

CFZ533 interruption

During the first 12 months of the treatment period, only 1 dose of CFZ533 can be missed. In case of a second dose or more SC doses need to be interrupted, the investigator should contact the sponsor immediately to discuss if the participant 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 participant.

CFZ533 dose adjustments

CFZ533 dose adjustments **are not permitted except in the case of significant ascites/fluid loss** by drainage (more details in Section 4.3 and Section 6.1.4).

In case of medical needs, 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).

6.5.2 Permitted dose adjustments and interruptions of other study treatment

Tacrolimus

For Control participants (Arm 1) who are unable to tolerate the protocol-specified dosing scheme, dose adjustments and interruptions of tacrolimus are permitted in order to keep the participant 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 treatment cannot be maintained, the participant must be permanently discontinued from the randomized study treatment and be managed as per local practice.

MMF

For both CFZ533 and control participants who are unable to tolerate the protocol-specified dosing scheme, dose adjustments and interruptions of MMF are permitted in order to keep the participant on study drug.

The following guidelines must be followed:

- In the event of MMF intolerance (e.g., gastrointestinal disorders, bronchiectasis), 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 the participant may be switched to other mycophenolates (e.g., Myfortic® mycophenolic acid) and remain in the study on randomized study treatment. Alternatively, MMF may be discontinued completely and participants may remain in the study on randomized study treatment. All dose changes must be recorded on the appropriate CRFs.

Corticosteroids

Corticosteroids will be administered with dosing according to local standard practice in a way that is consistent across all participants enrolled at each site. Corticosteroids may be tapered, as per local standard practice up to a minimal daily dose of 5 mg prednisone (or equivalent dose of another oral corticosteroid) for the first 4 months of treatment. Corticosteroids may then be discontinued (after completion of Month 4 visit) according to investigator discretion. Corticosteroids doses should be recorded on the appropriate CRF.

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 dose by 50 % or more.

If there still are signs of over-immunosuppression, MMF and/or corticosteroids may be further reduced or permanently discontinued.

Participants on CFZ533 with signs of over-immunosuppression may continue on their randomized regimen. In case of persistent signs of over-immunosuppression despite mycophenolate discontinuation, or if the symptoms are severe, participant should be discontinued from CFZ533 and switched to SoC.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

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

All pre-transplant immunosuppressive drugs, such as TAC, MMF and CS will be recorded on the appropriate CRFs.

All immunosuppressive drugs administered at the time of transplantation and post-randomization doses of CFZ533, TAC, MMF (or substitute) and CS will be recorded on the appropriate CRFs.

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

TAC trough levels during the run-in period and for participants in Arm 1 until EOS 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 treatment will be entered on the appropriate CRF.

Compliance will be assessed by the investigator and/or study personnel at each visit based on information provided by the participant. This information should be captured in the source document at each visit.

6.6.2 Recommended treatment of adverse events

Acute rejection

For all 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 up to Month 24 visit), and the histological lesions will be graded according to the Banff criteria (Appendix 3). Determination of the need for treatment will be according to the local pathologist's findings and the investigator's judgement.

All episodes of acute rejection should be treated as per local practice, using for example bolus steroids, increased dose of oral steroids or tacrolimus (for control participants) as first line and anti-T-cell antibody for steroid-resistant rejections.

A steroid-resistant acute rejection episode will be defined when no stabilization and/or no improvement of liver enzymes is seen within five days after initiation of methylprednisolone, when the participant has received at least 3 bolus injections with a minimum of 500 mg/bolus, or a total of 1.5 g of methylprednisolone, or initiation of anti-T-cell antibody treatment after repetitive methylprednisolone.

Whenever possible a re-biopsy should be performed to confirm an ongoing steroid-resistant acute rejection prior to initiating anti-T-cell antibody treatment.

The specific anti-rejection treatment, corticosteroids and anti-T-cell antibody treatment must be recorded on the appropriate CRFs. Increased doses of tacrolimus applied as anti-rejection treatment will be recorded on the corresponding dose administration record CRF page

Participants requiring cyclosporine, azathioprine, everolimus, sirolimus or tacrolimus (if the participant is on a CFZ533 arm) or any other agents for anti-rejection treatment will be discontinued from the randomized study treatment but will be followed until Month 24. Any participant requiring anti-T cell antibody therapy for rejection up to Month 24 should be discontinued from CFZ533 but should continue in the study on standard of care immunosuppression. Participants requiring any of the above treatments for rejection during the extension will be discontinued from the study.

The CFZ533 dose will not be modified and no extra dosing will be administered following a rejection episode.

All episodes of acute rejection must be entered on the appropriate CRFs preferably within 24 hours.

6.7 Preparation and dispensation

Each study site will be supplied with investigational drug CFZ533, (in packaging) as described in Section 6.1.1.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of CFZ533

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 designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified in the CFZ533 Investigator's Brochure.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO 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 participant except for the medication number.

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. Participants will be asked to return all unused study treatment and packaging at the end of the study 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.

6.7.1.2 Handling of Tacrolimus, MPA and corticosteroids

If tacrolimus is sourced locally by Novartis, it 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 designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the label.

MMF and CS for oral and IV administration will be supplied locally and will be used as per local label.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of IMP directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 3-month supply. In this case, regular phone calls or virtual contacts (every 4 weeks or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, drug accountability, investigation of any adverse events, ensuring participants continue to benefit from treatment and discussion of the participant´s health status until the participants can resume visits at the study site.

6.7.2 Instruction for prescribing and taking study treatment

6.7.2.1 CFZ533 administration

The CFZ533 investigational drug will be supplied centrally by Novartis Global Clinical Supply to the investigators as open-labeled supplies.

For preparation of CFZ533, the pharmacist or designee at the investigator's site will need to log into the IRT system to identify the medication assigned number as per treatment arm. In addition, the pharmacist or designee at the investigator's site and HCP (if applicable) will prepare the medication for administration to participants based on a separate pharmacy manual.

Appropriate documentation of the participant specific dispensing process must be maintained throughout the study.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label. Immediately before drug administration or dispensing the package to the in-home health care provider, investigator staff will detach the outer part of the label from the packaging and affix it to the source documents (Drug Label Form) for that participant's unique participant number.

CFZ533 initial loading dose(s) will be administered as an IV infusion to the participant by authorized investigator staff at the visits specified in the assessment schedule.

CFZ533 SC will be administered by authorized investigator/staff at each study visit. After the Month 6 visit (at site), in-home administration may be allowed by a health care provider.

CFZ533 SC using PFS will be administered by authorized participants or person of his/her choice once qualified and trained or by the investigator/staff.

In-home drug administration

At protocol specified time points (see Table 8-1, Table 8-2 and Table 8-3), if in-home administration of CFZ533 supported by a locally contracted health care provider has been opted for, the investigator or delegated site staff will contact the participant by telephone to check his/her status (e.g., AEs, concomitant medications) prior to ordering the treatment. The

investigator or delegated site staff will then dispense via the IRT an appropriate number of CFZ533 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). 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. The site personnel should review these instructions in detail.

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

The study medication preparation and administration guidelines are described in a separate pharmacy manual.

During the COVID-19 pandemic that limits or prevents on-site study visits, in-home administration may be considered. In-home visits would be conducted by the site staff (under the responsibility of the investigator), or by a health care provider (HCP) supporting this activity beyond Month 6 visit. In such pandemic situation home-visits performed by HCP may also be considered prior to completion of the Month 6 visit, if this is in agreement with the investigator.

Use of PFS

Once available, and after completion of their Month 12 visit, participants will receive SC injections using PFS. If a participant had good safety and tolerability, with no indication of hypersensitivity or other acute reactions from the previous doses, starting from Month 12, the investigator will determine if participant (or person of his/her choice) is able to administer treatment following completion of training. Site must document training completion and site's decision.

If participant or person of his/her choice are authorized to perform the injection at home, on-site visits after M12 will only be conducted every 3 months, until EOS or discontinuation, whichever occurs earlier. The investigator or delegated site staff should contact the participant by telephone to check on his/her status (e.g., AEs, concomitant medications, pregnancy status) prior to any home dosing.

Site will provide material for self-administration (PFS kits and transportation materials). Site will dispense CFZ533 from the IRT according to the participant's storage capacity, based on Investigator determination, with a maximum stock to cover administration up to the next on-site visit. The site will instruct the participant that on the days 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 will be described in a separate manual and provided to the participants. The participants will be provided with a form to record each administration, the location, and who performed it.

Arm 2 (CFZ533 600 mg regimen)

The first dose of CFZ533 (30 mg/kg) will be administered IV on day of randomization (Day 8±2). The participant will be weighed prior to randomization and this weight value will be used for the study medication preparation and the calculation of the dose.

The second dose of CFZ533 15 mg/kg will be administered IV on Day 15. The most recent weight will serve for the dose calculation.

From Day 29 up to the EOS, participants randomized to **Arm 2** will receive two SC injections of 2 mL CFZ533 at 150 mg/mL (4 CFZ533 vials, 1 mL each, or 2 CFZ533 PFS of 2mL each) every 2 weeks in combination with MMF and CS.

Arm 3 (CFZ533 300 mg regimen)

The first dose of CFZ533 (30 mg/kg) will be administered IV on day of randomization (Day 8±2). The participant will be weighed prior to randomization and this weight value will be used for the study medication preparation and the calculation of the dose.

From Day 29 up to the EOS, participants randomized to **Arm 3** will receive every 2 weeks one SC injection of 2 mL CFZ533 at 150 mg/mL (2 CFZ533 vials, 1 mL each, or 1 CFZ533 PFS of 2mL), in combination with MMF and CS.

Administration of CFZ533 should occur **after** blood sample collection for PK/PD/immunogenicity assessments at visits specified in Table 8-1, Table 8-2 and Table 8-3 (Section 8).

All CFZ533 investigational drug kits assigned will be recorded in the IRT system.

All dosages prescribed and dispensed to the participants during the study must be recorded in the appropriate CRF, including the location of injection and person who administered it.

6.7.2.2 Tacrolimus administration

All participants need to be on a treatment regimen comprising TAC, CS and MMF at the time of randomization.

Initiating TAC before transplantation is permitted.

Initiation of tacrolimus post-transplantation

Tacrolimus will be administered as capsules orally twice daily. Tacrolimus should be initiated as soon as possible after transplantation and TAC blood trough levels should be targeted and adjusted between 5-15 ng/mL (i.e., all participants should be treated exactly according to the same local treatment protocol). The use of intravenous tacrolimus in the immediate post-operative period is permitted.

Arm 1

Participants randomized to the Control Arm 1 will continue to receive TAC, in combination with MMF and corticosteroids until EOS. TAC will be administered as p.o. capsules/tablets b.i.d. and blood trough levels will be managed according to the local approved label.

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

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

Arms 2 and 3

For the CFZ533 (Arms 2 and 3) participants; TAC dose will be progressively decreased up to Day 21 as described thereafter. At randomization, on the day of the first CFZ533 loading dose (30 mg/kg IV), the TAC dose will be reduced to achieve a TAC blood trough level of 5-8 ng/mL.

The TAC dose will be further decreased by Day 15 to reach a TAC blood trough level below 5 ng/mL. By Day 22, TAC must be completely weaned-off. If, at any time post Day 22 and for any reason, TAC is not completely withdrawn and co-administration with the randomized study treatment is ongoing, an immediate discussion will be needed between the Sponsor and the Investigator whether to keep the participant on randomized treatment; this will be assessed on a case-by-case basis.

In case a participant 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 participants who cannot swallow tablets.

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

6.7.2.3 MMF administration – Arms 1, 2 and 3

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

MMF will be initiated and administered according to the approved labeling and local practice.

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

Dose adjustment/interruption guidance for MMF is provided in Section 6.5.2.

6.7.2.4 Corticosteroids administration – Arms 1, 2 and 3

Corticosteroids will be administered immediately on or after liver transplant surgery according to local standard practice. CS doses should be recorded on the appropriate CRF. Dose adjustment/interruption guidance for CS is provided in Section 6.5.2.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB) / Independent Ethics Committee (IEC)-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent

possible given his/her understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

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 participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

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 participant informed consent and should be discussed with the participant 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 participant.

The following informed consent forms are included in this study:

- Main study consent, also including:
  - 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
  - [redacted]
  - [redacted]
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment
- As applicable, home visits consent for participants to receive CFZ533 injections at home

Women of childbearing 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 participants 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. A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval. Sexually active male participants, or the female partner, are recommended to use highly effective contraception during therapy with MMF and at least 12 weeks following discontinuation of mycophenolates (see additional information in Section 8.4.3).

8 Visit schedule and assessments

Table 8-1,Table 8-2 and Table 8-3 list all of the assessments and indicate with an “X” when the visits need to be performed. All data obtained from study assessments must be clearly documented in the participant’s source notes.

Electrocardiograms (ECGs) must be recorded after 10 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 samplings.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1, Table 8-2 and Table 8-3). Visit window of ±2 days is allowed for the randomization visit (Day 8). All other visits are expected to occur according to the study schedule based on the randomization date, or as close to the designated day/time as possible. If a visit is delayed or occur in advance, the following visit date will not be re-adjusted and will remain according to the initial schedule.

The study visit names may not match the number of days from transplant depending on the randomization date (due to the visit window of ±2 days). The injection schedule should be calculated from the date of first treatment (actual randomization date).

Screening and baseline visits may occur on same day. If these visits occur within a 48h period screening assessments do not need to be repeated at the baseline visit.

Every effort should be made to take the blood samples at the protocol specified visits and times.

Missed or rescheduled visits should not lead to automatic discontinuation.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowed by local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g., tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

All randomized participants are expected to continue in the study up to Month 24, even if they have discontinued the study treatment.

Participants who discontinue CFZ533 or control regimen prior to Month 24 should be treated according to SoC immunosuppression and return at scheduled visits to provide follow-up information. Participants who discontinue treatment prior to Month 12 should attend Month 6, Month 8, Month 10, Month 12, Month 18 and Month 24 follow-up visits. Participants who discontinue after Month 12 but before Month 24 should attend the Month 18 and Month 24 follow-up visits. 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 participant and graft status. Participants who discontinue study treatment prior to Month 24 visit will not enter the extension.

Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the EOS visit will be performed. At this EOS visit, all dispensed investigational treatment should be reconciled, and the adverse events and concomitant medications recorded on the CRF.

Participants who discontinue CFZ533 or control regimen during the extension should be scheduled for a visit as soon as possible to perform EOS visit assessments.

Table 8-1 Assessment schedule (Treatment Period 1)

Assessment schedule (Treatment Period 1) – Screening to Randomization

Period	**Screening**		**Treatment Run-in**		
Visit Name	**SCR**	**BSL/pre-LTx@**	**Randomization**		
Month					
Day	**-1 to -60**	**1**	**8±2**		
Hour (h)			**Pre**	**0**	**EOI + 1h**
Informed consent	X				
Inclusion/Exclusion	X			X	
Relevant medical History/current medical history	X				
Demographics	X				
Pregnancy test (serum)	S#	S#	S		
Pregnancy test (urine)					
IRT visit/dispensation record	S	S		S	
Transplant procedure		X			
Liver transplant background recipient/donor		X			
Hepatocellular carcinoma history		X			
Recipient/donor viral serology	X	X			
Liver imaging[1]				S	
Vital signs:					
-Height	X	X			
-Temperature/ blood pressure/ pulse/ weight	X	X		X	

Period	**Screening**		**Treatment Run-in**		
Visit Name	**SCR**	**BSL/pre-LTx@**	**Randomization**		
Month					
Day	**-1 to -60**	**1**	**8±2**		
Hour (h)			**Pre**	**0**	**EOI + 1h**
Assessments and specifications[2]	S#	S#		S	
ECG evaluation	X#	X#			
Local laboratory tests[3]	X#	X#		X	
Safety laboratory tests[4]		X		X	
A-fetoprotein assessment[4]		X		X	
MMF trough levels[4]				X	
TAC trough levels (local)			X		
CFZ533 Pharmacokinetics[5]			X		X
Pharmacodynamics sCD40[6]			X		
CFZ533 Immunogenicity[7]			X		
Ascites fluid drainage and management[8]		As required			
Administration of CFZ533 IV (Arm 2)				X	
Administration of CFZ533 IV (Arm 3)				X	
Administration of TAC (Arm 2 & Arm 3)		X		X	
CFZ533 dosage administration record				X	

Period	**Screening**		**Treatment Run-in**		
Visit Name	**SCR**	**BSL/pre-LTx@**	**Randomization**		
Month					
Day	**-1 to -60**	**1**	**8±2**		
Hour (h)			**Pre**	**0**	**EOI + 1h**
MMF and CS dosage administration records (Arm 2 & Arm 3)		X		X	
TAC, MMF and CS dosage administration records (Arm 1)		X		X	
Concomitant medications	X	X		X	
Surgical and medical procedures	X	X		X	
Liver allograft rejection				X	
Hospitalization record				X	
Graft loss				X	
EBV and CMV viral load	As required				
Dialysis log				X	
AEs / SAEs		As required			
Infections				X	
Hepatocellular carcinoma				X	
Malignancies				X	
Withdrawal of Informed Consent		As required			
M12 Period completion	Not applicable		As required		
Study completion	As required				

Assessment schedule (Treatment Period 1) – Day 15 to Month 12

Period	**Treatment**																												
Visit Name	**Treatment Period 1**																												
Month					**1**	**1.5**	**2**	**2.5**	**3**	**3.5**	**4**	**4.5**	**5**	**5.5**	**6 or FU**	**6.5**	**7**	**7.5**	**8 or FU**	**8.5**	**9**	**9.5**	**10 or FU**	**10.5**	**11**	**11.5**	**12 or FU**
Day	**15**			**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**				**225**				**281**			**323**	**337**
Hour (h)	**Pre**	**0**	**EOI +1h**																								
Pregnancy test (serum)																											
Pregnancy test (urine)					S		S		S		S		S		S		S[0]		S		S[0]		S		S[0]		S
IRT visit/dispensation record		S		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Liver allograft biopsy	As required																										
Vital signs:																											
-Weight/ temperature	X				X	X	X	X	X		X		X		X				X				X				X
-Blood pressure/pulse	X				X	X	X	X	X		X		X		X				X				X				X
Assessments and specifications[2]							S				S				S				S				S				S
ECG evaluation															X												X

Period	**Treatment**																												
Visit Name	**Treatment Period 1**																												
Month					1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6 or FU	6.5	7	7.5	8 or FU	8.5	9	9.5	10 or FU	10.5	11	11.5	12 or FU
Day	15			22	29	43	57	71	85	99	113	127	141	155	169				225				281			323	337
Hour (h)	Pre	0	EOI +1h																								
Safety laboratory tests[4]	X				X		X		X		X		X		X				X				X				X
A-fetoprotein assessment[4]	As required																										
MMF trough levels[4]					X		X				X				X				X				X				X
TAC trough levels (local)	X			X	X 10	X	X	X	X		X				X				X				X				X
CFZ533 Pharmaco-kinetics[5]	X		X		X	X	X	X	X	X	X	X	X	X	X				X				X				X
Pharmacodynamics sCD40[6]					X		X		X			X[7]			X				X				X				X
CFZ533 Immuno-genicity[7]					X		X		X			X			X				X				X				X
Ascites fluid drainage and management[8]	As required																										
Administration of CFZ533 IV (Arm 2)		X																									

Period	**Treatment**																												
Visit Name	**Treatment Period 1**																												
Month					**1**	**1.5**	**2**	**2.5**	**3**	**3.5**	**4**	**4.5**	**5**	**5.5**	**6 or FU**	**6.5**	**7**	**7.5**	**8 or FU**	**8.5**	**9**	**9.5**	**10 or FU**	**10.5**	**11**	**11.5**	**12 or FU**
Day	**15**			**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**				**225**				**281**			**323**	**337**
Hour (h)	**Pre**	**0**	**EOI +1h**																								
Administration of CFZ533 IV (Arm 3)																											
Administration of CFZ533 600 mg (Arm 2) & 300 mg (Arm 3)					X	X	X	X	X	X	X	X	X	X	X	X^0	X^0	X^0	X	X^0	X^0	X_0	X	X^0	X^0	X^0	X
Administration of TAC (Arm 2 & Arm 3)		X																									
CFZ533 dosage administration record		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TAC dosage administration. record (Arm 2 & Arm 3)		X		X																							
MMF and CS dosage administration records (Arm 2 & Arm 3)		X		X	X	X	X	X	X	X	X				X				X				X				X
TAC, MMF and CS dosage administration		X			X		X		X		X				X				X				X				X

Period	**Treatment**																														
Visit Name	**Treatment Period 1**																														
Month					**1**	**1.5**	**2**	**2.5**	**3**	**3.5**	**4**	**4.5**	**5**	**5.5**	**6 or FU**	**6.5**	**7**	**7.5**	**8 or FU**	**8.5**	**9**	**9.5**	**10 or FU**	**10.5**	**11**	**11.5**	**12 or FU**
Day	**15**			**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**				**225**				**281**			**323**	**337**
Hour (h)	**Pre**	**0**	**EOI +1h**																								
records (Arm 1)																											
Concomitant medications	Ongoing basis																										
Surgical and medical procedures	As required																										
Liver allograft rejection	As required																										
Hospitalization record	As required																										
Graft loss	As required																										
EBV and CMV viral load	As required																										
Dialysis log	As required																										
AEs / SAEs	As required																										
Infections	As required																										
Hepatocellular carcinoma	As required																										
Malignancies	As required																										
Withdrawal of Informed Consent	As required																										
M12 Period completion[9]	As required																										X

Period	**Treatment**																												
Visit Name	**Treatment Period 1**																												
Month					1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6 or FU	6.5	7	7.5	8 or FU	8.5	9	9.5	10 or FU	10.5	11	11.5	12 or FU
Day	15			22	29	43	57	71	85	99	113	127	141	155	169				225				281			323	337
Hour (h)	Pre	0	EOI +1h																								
Study completion[9]	As required																										

@ = all assessment must be completed prior to the liver transplantation procedure.

S = Assessment to be recorded in source documentation, not in CRF.

X = Assessment to be performed/evaluated and recorded in CRF if applicable.

= to be performed once in a 48-hour period if Screening and Transplantation (Day 1) occur in close proximity.

EOI = End of infusion IV (administration), EOS = End of Study, EOT = End of Treatment

0 = Assessment can be done at home for Arm 1 participants and for Arm 2 and 3 participants receiving CFZ533 at home via a health care provider.

1. Graft vascular patency must be confirmed using appropriate imaging technology (e.g. Doppler ultrasound, angiography, angio MRI). Participants with any thrombosis or occlusion of hepatic artery, veins, portal vein or inferior vena cava or participants with no confirmatory imaging study cannot be randomized.

2. Assessment and specification refers to the physical examination. See Table 8-4 for detailed list of expected physical examinations.

3. Site must perform, at minimum, all assessments needed to evaluate participant's eligibility at screening and randomization.

4. Safety laboratory tests (central) from Baseline, Day 8±2 (Randomization), and at all visits indicated will include hematology, chemistry, coagulation and urinalysis as specified in Table 8-5. A-fetoprotein will be evaluated at Baseline, Day 8±2/Randomization (for HCC subjects, only) and as needed thereafter for recurrent and *de novo* cases. MMF trough levels will be collected at all visits indicated or unscheduled visit (dose change). At the time of biopsies, a chemistry central laboratory test should be performed and thereafter until the final outcome.

5. **Arms 2 & 3 - CFZ533-treated participants only**: a blood sample is collected pre-dose at each dose administration visit (IV or SC) during the treatment period and up to EOS visit as indicated. In addition, for both arms 2 & 3, a blood sample is required after the loading dose (30 mg/kg IV on Day 8±2) 1 hr. after the end of the 30-min infusion. For participants in the Arm 2, an additional sample is required after the loading dose on Day 15 (15 mg/kg IV) 0, 1 hr. after the end of the infusion. For more details on scheduled and unscheduled PK samples refer to Appendix 6a and Appendix 6b.

6. All participants (**Control and CFZ533-treated**): all samples are taken at pre-dose. For details refer to Appendix 6a.

7. **Arms 2 & 3 - CFZ533-treated participants only**: all samples are taken at pre-dose. For details refer to Appendix 6a.

8. **Arms 2 & 3 - CFZ533-treated participants only**: at any time, if ascites fluids are drained from CFZ533-treated participants, the volume of ascites drained should be measured and recorded on the appropriate CRF. [redacted]

9. All participants are expected to continue in the study up to Month 24 regardless of whether they are on or off their randomized study treatment. If subjects discontinue the randomized study treatment prior to Month 12 they should continue in the study to Month 24 on standard of care, and come to the follow-up visit(s). In case of early study discontinuation, the appropriate CRF must be completed together with all final Month 24 assessments.

10. Participants in Arms 2 & 3 will not have TAC trough levels taken from D29. TAC trough levels will continue to be applicable only for Arm 1 patients from D29 onwards.

[redacted]

12. After a participant is switched to PFS and he/she administers at home, the participant needs to be reminded that on the days of clinic visits, CFZ533 dosing will be done after collection of PK labs which are required at pre-dose.

13. Annual extension schedule will continue if needed after Month 72 until the EOS is declared.

Table 8-2 Assessment Schedule (Treatment Period 2)

Assessment schedule (Treatment Period 2) - Month 12.5 to Month 24

Period	**Treatment**																							
Visit Name	**Treatment Period 2**																							
Month	**12.5**	**13**	**13.5**	**14**	**14.5**	**15**	**15.5**	**16**	**16.5**	**17**	**17.5**	**18 or FU**	**18.5**	**19**	**19.5**	**20**	**20.5**	**21**	**21.5**	**22**	**22.5**	**23**	**23.5**	**24 or FU**
Day						**421**						**505**						**589**						**673**
Hour (h)																								
IRT visit/dispensation record	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Pregnancy test (serum)																								S
Pregnancy test (urine)		S[0]		S[0]		S		S[0]		S[0]		S		S[0]		S[0]		S		S[0]		S[0]		
Vital Signs:																								
-Weight/ temperature						X						X						X						X
-Blood pressure/pulse						X						X						X						X
Assessments and specifications[2]						S						S						S						S
ECG evaluation												X												X
Safety laboratory tests[4]						X						X						X						X
A-fetoprotein assessment[4]	As required																							
MMF trough levels[4]												X												X

Period	**Treatment**																							
Visit Name	**Treatment Period 2**																							
Month	**12.5**	**13**	**13.5**	**14**	**14.5**	**15**	**15.5**	**16**	**16.5**	**17**	**17.5**	**18 or FU**	**18.5**	**19**	**19.5**	**20**	**20.5**	**21**	**21.5**	**22**	**22.5**	**23**	**23.5**	**24 or FU**
Day						**421**						**505**						**589**						**673**
Hour (h)																								
TAC trough levels (local)						X						X						X						X
CFZ533 Pharmacokinetics[5, 12]						X						X						X						X
Pharmacodynamics sCD40[6]						X						X						X						X
CFZ533 Immunogenicity[7]						X						X						X						X
Ascites fluid drainage and management[8]	As required																							
Administration of CFZ533 600 mg (Arm 2) & 300 mg (Arm 3)[12]	X^0	X^0	X^0	X^0	X^0	X^0	X^0	X^0	X^0	X^0	X^0	X^0	X^0	X^0	X^0	X^0	X^0	X^0	X^0	X^0	X^0	X^0	X^0	X^0
CFZ533 dosage administration record	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MMF and CS dosage administration records (Arm 2 & Arm 3)						X						X						X					X	X
TAC, MMF and CS dosage administration						X						X						X					X	X

Period	**Treatment**																							
Visit Name	**Treatment Period 2**																							
Month	**12.5**	**13**	**13.5**	**14**	**14.5**	**15**	**15.5**	**16**	**16.5**	**17**	**17.5**	**18 or FU**	**18.5**	**19**	**19.5**	**20**	**20.5**	**21**	**21.5**	**22**	**22.5**	**23**	**23.5**	**24 or FU**
Day						**421**						**505**						**589**						**673**
Hour (h)																								
records (Arm 1 only)																								
Concomitant medications	Ongoing																							
Surgical and medical procedures	As required																							
Liver allograft biopsy	Not applicable																							
Liver allograft rejection	As required																							
Hospitalization	As required																							
Graft loss	As required																							
EBV and CMV infections	As required																							
Dialysis log	As required																							
AEs/SAEs	Ongoing																							
Infections	As required																							
Hepatocellular carcinoma	As required																							
Malignancies	As required																							
Withdrawal of Informed Consent	As required																							
Month 24 Period completion[9]	As required																							X
Study completion[9]	As required																							X

For footnotes, see Table 8-1.

Table 8-3 Assessment Schedule (Extension Period)

Assessment schedule (Extension period) - Month 24.5 to end of extension

Period	**Long-term Extension**																								**End of study**
Visit Name	**Treatment period 3**																								**EOS**
Month	**24.5**	**25**	**25.5**	**26**	**26.5**	**27**	**27.5**	**28**	**28.5**	**29**	**29.5**	**30**	**30.5**	**31**	**31.5**	**32**	**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**	**41.5**	**42**	**42.5**	**43**	**43.5**	**44**	**44.5**	**45**	**44.5**	**46**	**46.5**	**47**	**47.5**	**48**	
	48.5	**49**	**48.5**	**50**	**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**	**60**	
	60.5	**61**	**61.5**	**62**	**62.5**	**63**	**63.5**	**64**	**64.5**	**65**	**65.5**	**66**	**66.5**	**67**	**67.5**	**68**	**68.5**	**69**	**69.5**	**70**	**70.5**	**71**	**71.5**	**72**[13]	
IRT visit/dispensation record						S						S						S						S	S
Pregnancy test (urine)		S[0]		S[0]		S		S[0]		S[0]		S		S[0]		S[0]		S		S[0]		S[0]		S	S
CFZ533 injection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight/ temperature						X						X						X						X	X
[redacted]																									
Assessments and specifications[2]												S												S	S
[redacted]																									
A-fetoprotein assessment[4]	As required																								
[redacted]																									
CFZ533 Drug dispensation						X						X						X						X	
TAC Drug dispensation						X						X						X						X	

Period	**Long-term Extension**																								**End of study**
Visit Name	**Treatment period 3**																								**EOS**
Month	**24.5**	**25**	**25.5**	**26**	**26.5**	**27**	**27.5**	**28**	**28.5**	**29**	**29.5**	**30**	**30.5**	**31**	**31.5**	**32**	**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**	**41.5**	**42**	**42.5**	**43**	**43.5**	**44**	**44.5**	**45**	**44.5**	**46**	**46.5**	**47**	**47.5**	**48**	
	48.5	**49**	**48.5**	**50**	**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**	**60**	
	60.5	**61**	**61.5**	**62**	**62.5**	**63**	**63.5**	**64**	**64.5**	**65**	**65.5**	**66**	**66.5**	**67**	**67.5**	**68**	**68.5**	**69**	**69.5**	**70**	**70.5**	**71**	**71.5**	**72**[13]	
MMF and CS Drug dispensation						X						X						X						X	
Concomitant medications	Ongoing																								
Liver allograft rejection	As required																								
[redacted]																									
Withdrawal of Informed Consent	As required																								
Hospitalization	As required																								
EBV and CMV infections	As required																								
Dialysis log	As required																								
Hepatocellular carcinoma	As required																								
Malignancies	As required																								
Study completion	As required																								X

For footnotes, see Table 8-1.

8.1 Screening

All participants who have signed informed consent but do not enter into the Run-in period will be classified as screen failures and need to have the screening completion CRF for the screening period, demographics, inclusion/exclusion, and any SAE data collected.

Rescreening (with a maximum of three screening attempts) is only allowed for participants who were screen failures on the initial Screening visit (due for example, to lab values out of range or no donor-organ available) but not yet transplanted. No transplanted participant can be rescreened. Rescreened participants should be assigned a new participant ID number.

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

8.1.1 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see SAE section for reporting details). If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized.

Participants who are randomized and fail to start treatment, e.g., participants randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

8.2 Participant demographics/other baseline characteristics

After informed consent has been signed and the participant's eligibility to participate in the study has been determined, baseline participant information will be obtained in accordance with local regulations, including, age, sex (with childbearing status for females), race and ethnicity. Participant'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.

In addition full relevant medical history/current medical conditions, information on liver transplant procedure, recipient and donor viral serology will be obtained.

The hepatocellular carcinoma (HCC) CRF should be completed for participants with a diagnosis of HCC pre-transplant or in whom HCC is discovered incidentally in the peri-transplant period.

Liver Doppler Ultrasound, angiography or angio MRI must be performed and allograft vessels must be patent prior to randomization.

Country specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

8.3 Efficacy

8.3.1 Suspected Acute Rejection/Biopsy Proven Acute Rejection (BPAR)

All episodes of acute rejection must be recorded on the appropriate CRF. Recording should be done within 24 h of occurrence, to ensure timely information sharing to the 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 biopsy proven acute rejection (BPAR) is defined as an acute rejection confirmed by biopsy with a rejection activity index (RAI) score ≥ 3, Appendix 3. For all suspected rejection episodes, a liver biopsy must be performed preferably within 24 hours, latest within 48 hours whenever clinically possible, regardless of initiation of anti-rejection treatment.

The liver biopsies will be read by a local pathologist according to the Banff criteria (Appendix 3) and will be used to guide participant management. The results of the biopsy read by the local pathologist must be recorded on the appropriate CRF.

In addition, up to Month 24 visit completion, biopsy specimen slides from these for "cause biopsies" will be sent to an independent central pathologist for blinded review. The efficacy analysis will rely on the central pathologist's evaluations and will be based on acute rejection confirmed by a biopsy. Central laboratory chemistry tests should be performed at the time of suspected BPAR and thereafter until the final clinical outcome. Lactate dehydrogenase (LDH) test results, if available locally, should also be captured in the eCRF

Every suspected acute rejection event must be recorded on the appropriate CRF with full details including whether or not a liver biopsy was performed (if not, reason should be provided, e.g. abnormal coagulation test) and the primary clinical diagnosis.

Suspected acute rejection episodes ultimately diagnosed to be other conditions should also be recorded with the final diagnosis on the appropriate CRF.

For any diagnosis of acute rejection, the treatment given and the final clinical outcome of the event must be recorded on the appropriate CRF.

8.3.2 Treated Biopsy Proven Acute Rejection (tBPAR)

A treated biopsy proven acute rejection will be considered BPAR as defined in Section 8.3.1 which is treated with anti-rejection therapy.

8.3.3 Graft loss

The allograft will be presumed to be lost on the day the participant becomes newly listed for a liver allograft or the day the participant is re-transplanted or dies due to liver failure. This, in addition to the reason for graft loss, will be reported on the appropriate CRF.

Graft Loss will lead to discontinuation from the study and be reported on the appropriate CRF page:

- on Month 12 visit CRF if occurs prior this time point,
- on Month 24 visit CRF if it occurs between Month 12 and Month 24,
- on EOS visit CRF if it occurs during the extension,

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 as a Serious Adverse Event (SAE) and should be reported as a SAE report to the Novartis Chief Medical Office and Patient Safety (CMO & PS) department within 24 hours.

8.3.4 Death

In the event of participant death, the SAE leading to death should be reported to the Novartis CMO & PS department within 24 hrs. The events leading to the death should be entered on the appropriate CRF capturing Adverse Events. The death as reason for discontinuing study should be indicated on the Study Completion CRF.

8.3.5 Appropriateness of efficacy assessments

The composite efficacy endpoint of BPAR, graft loss, and death is standard in the transplantation indication. This approach is consistent with the most recent Health Authorities guidance ([CHMP/EWP/263148/06], effective February 2009).

The endpoint represents an attempt to assess the clinical balance between having sufficient immunosuppression to prevent rejection while minimizing toxicity.

8.4 Safety

Safety assessments are specified below with the assessment schedule (Table 8-1, Table 8-2 and Table 8-3) detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to section AE.

Table 8-4 Assessments & Specifications

Assessment	Specification
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, and extremities, vascular and neurological systems. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams will 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 signing informed consent which meet the definition of an adverse event must be recorded as AE.
Vital sign	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 participants at each site).

Assessment	Specification
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 as specified in Table 8-1, Table 8-2 and Table 8-3. Body mass index (BMI) will be calculated using the following formula: BMI = Body weight (kg) / [Height (m)]^2

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowed by local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g., tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

8.4.1 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 are provided in the laboratory manual.

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 be contacted.

Clinically notable laboratory findings are defined in Appendix 1.

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 participant to continue in the study.

Local laboratory results will be used to assess inclusion/exclusion criteria at Screening and Randomization (Day 8). It is not mandatory to perform locally all assessments listed in Table 8-5, but at a minimum those assessments required to confirm participant's eligibility. For randomization, local laboratory assessments can be performed up to 3 days prior to randomization. Local serum creatinine results (most recent value available by the time of randomization or any time thereafter if not available at the central laboratory) will be recorded in the appropriate CRF page.

As per Section 4.6 during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site for protocol specified safety lab assessments, collection can be performed at home by an health care provider or an alternative lab (local) collection site may be used.

Table 8-5 Laboratory Assessments

Test Category	Test Name
Hematology	Platelets, hematocrit, hemoglobin, red blood cell (RBC), white blood cell (WBC) and differential count (e.g., neutrophils, basophils, eosinophils, monocytes and lymphocytes).
Chemistry	Albumin, alkaline phosphatase, total bilirubin, bicarbonate, calcium, total cholesterol, chloride, creatinine(*), CPK, gamma-GT, (fasting plasma) glucose, HbA1c, HDL, LDL, ratio of total cholesterol to HDL, ratio to LDL to HDL, inorganic phosphorus, lipase, amylase, magnesium, potassium, total Immunoglobulin G (IgG), total protein, AST, ALT, sodium, triglycerides, blood urea nitrogen (BUN) and uric acid. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated. (*) Serum creatinine (local) prior to the time of randomization or anytime thereafter if not available at the central laboratory.
Urinalysis	Protein, creatinine, albumin, glucose; proteinuria and albuminuria will be estimated from spot protein/creatinine and albumin/creatinine ratios. If the (macroscopic panel) dipstick result is positive for protein, nitrite, leucocytes and/or blood the sample will be sent for microscopic analysis of WBC, RBC and casts.
Coagulation	International normalized ratio (INR), prothrombin time (PT), partial thromboplastin (PTT) and activated partial thromboplastin time (aPTT).
[redacted]	
Viral serology	Qualitative viral serology for donors/recipients evaluated for screening and/or baseline will be performed by local laboratories. It includes: • Hepatitis serology: hepatitis B surface antigen (HBsAg), antibodies to hepatitis B virus (anti-HBc and anti-HBs) and antibody to hepatitis C virus (anti-HCV). • Human immunodeficiency virus (HIV). • Qualitative viral serology tests for cytomegalovirus (CMV) and Epstein Barr virus (EBV) (IgG and IgM). Quantitative viral serology test for EBV and CMV will be assessed locally if active infection is suspected. It is highly recommended to quantify the EBV and CMV viremia and record the results on the corresponding CRF pages (number of copies/mL and method used). Qualitative and/or quantitative HCV-RNA and HBV-DNA (using PCR) will be performed locally for those participants who are tested anti-HCV positive and HBsAg positive, respectively.
Additional tests:	A-fetoprotein, MMF trough levels, PK, PD (soluble CD40) and immunogenicity (anti-CFZ533 antibodies) blood samplings.
Pregnancy Test	Serum (local laboratory)/Urine.

8.4.2 Electrocardiogram (ECG)

In this study, local ECG will be used. ECGs must be recorded after 10 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 appropriately signed, must be collected and archived at the study site.

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

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

8.4.3 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 locally at the screening, baseline, randomization and Month 24 visits. Monthly local urine pregnancy tests will be performed as indicated in Table 8-1, Table 8-2 and Table 8-3. To fulfill inclusion criteria the local pregnancy test must be negative at the screening, baseline and randomization visits. In case treatment is discontinued prior to Month 24 visit, urine pregnancy test will be performed during follow-up visits (Month 6, 8, 10, 12, 18 and 24, whichever are applicable). A positive urine pregnancy test result needs to be confirmed via a serum β-hCG test.

Urine pregnancy test can be evaluated at home between on-site visits (refer to Table 8-1, Table 8-2 and Table 8-3) for participants in Arm 1; for Arm 2 and 3 participants same rule applies after the Month 6 visit, if treatment administration is performed at home via a health care provider. If any urine pregnancy test performed at home is positive, participant must immediately inform the clinical site.

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 childbearing potential (see exclusion criteria definitions, Section 5.2).

As per Section 4.6 during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site for protocol specified safety lab assessments, collection can be performed at home by an health care provider or an alternative lab (local) collection site may be used.

Recommendations for female participants taking CFZ533

In consideration of the participant population and overall CFZ533 benefit-risk 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 on Section 4.2.1, Figure 4-1).

Recommendations for female and male participants taking MMF (Cellcept)

MMF is a confirmed teratogen associated with an increased rate of spontaneous abortion and congenital malformation compared with other immunosuppressant. Therefore, investigators should ensure that female and male participants taking MMF understand the risk of harm to the baby, the need for effective contraception, and the need to consult immediately 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 participants

- Female participants who could become pregnant must use an effective method of contraception with CellCept®. This includes before start taking CellCept®, during the entire treatment period with CellCept® and for 6 weeks after the last dose of CellCept®.
- Two forms of contraception applied simultaneously are preferable, as this will reduce the risk of unintended pregnancy.
- Female participants should not donate blood during therapy with MMF or for at least 6 weeks following discontinuation of mycophenolate.

b. Recommendations for male participants

- The available evidence does not indicate an increased risk of malformations or miscarriage if the father takes mycophenolate. However, risk cannot be completely excluded.
- Sexually active male participants, or the female partner, are recommended to use highly effective contraception during therapy with MMF and at least 12 weeks following discontinuation of mycophenolate.

c. Additional precautions

- Male participants should not donate blood during therapy with mycophenolate mofetil or for at least 6 weeks following discontinuation of mycophenolate. Men should not donate semen during therapy or 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 child-bearing 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, FSH testing is required of any female participant regardless of reported reproductive/menopausal status at screening/baseline.

8.4.4 Other safety evaluations

Renal function

Renal function will be assessed at each visit by measuring serum creatinine and utilized to calculate the estimated glomerular filtration rate (eGFR) using the MDRD-4 formula.

New onset diabetes mellitus

New onset diabetes mellitus is defined as:

All of the following should be true (no diabetes mellitus pre-transplantation):

- Diabetes was not included in the medical history.
- Glucose (random) <11.1 mmol/L (200 mg/dL) at the time of transplantation.
- Diabetes was not recorded as reason for any medication given prior to transplantation.
- HbA1c <5.7% at the time of transplantation.

And at least one of the following should be true (diabetes onset after randomization):

- 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 Day 85 forward).
- Diabetes reported as an AE that is prevalent after Day 29.
- Any concomitant medication with Anatomical Therapeutic Chemical (ATC) level 2 code "A10" (drugs used in diabetes), if prevalent after Day 29.

Definitions for diabetic related diagnoses are according to the American Diabetes Association 2013 and [WHO-ADA criteria].

Hepatic Artery Thrombosis

Hepatic Artery Thrombosis (HAT) are frequent in this population and will be recorded as Adverse Events or Serious Adverse Events as appropriate. The treatments given should be recorded on the Concomitant Medications and/or the Surgical and Medical Procedures CRF (e.g., re-anastomosis, stent, etc.) as appropriate.

Malignancies

For participants on study treatment and in follow-up, any type of malignancy (including skin neoplasms, leukemia, post-transplantation proliferative disorder (PTLD)) should be reported as a SAE and recorded on the appropriate CRFs. A SAE report should be completed for malignancies occurring until the last visit (for participants in follow-up) or for 14 weeks after the last dose of study treatment taken, (for participants in the treatment period or who completed the treatment period).

Hepatocellular carcinoma (HCC) recurrence

Participants transplanted for HCC or with HCC diagnosed at the time of transplantation should be monitored for HCC recurrence according to local practice. For example routine laboratory monitoring/tests, tumor markers, hepatic ultrasound, computed tomography scans (CAT, CT) or Magnetic Resonance Imaging (MRI) (especially Fe-MRI) on regular basis as per local practice. A-fetoprotein will be regularly evaluated at the central laboratory, Table 8-1, Table 8-2 and Table 8-3.

All cases of HCC recurrence or de novo HCC, diagnosed post-randomization should be recorded on the appropriate CRF. Details of method of diagnosis, location (hepatic and/or extrahepatic) of lesions, number/size of lesions, tumoral invasion of major vessels or biliary system and any treatment given should be recorded on the CRFs. In addition, a SAE report should be completed.

In the event of HCC recurrence, the slides from the explant liver graft biopsy will be sent to the independent central pathologist for evaluation.

For recurrent and *de novo* cases of HCC, α-fetoprotein will be monitored as needed.

Dialysis

All instances of renal replacement therapy (including hemodialysis, hemodiafiltration, hemofiltration and peritoneal dialysis) occurring post transplantation should be recorded on the appropriate CRF giving the method used. Reason for dialysis, the start and end dates and the total number of sessions should also be recorded.

Infections

Infections should be recorded with start and end date, type of infection, and medications used on the CRF capturing Adverse Events. If medications are used to treat the infection, the name of the medication must be entered on the appropriate CRF. If the participant is hospitalized a SAE report must be completed and reported.

Viral infections (CMV, EBV)

Quantitative EBV and CMV viral load will be assessed locally if active infection is suspected.

CMV

Suspected CMV infections will be recorded as an infection on the CRF capturing Adverse Events and on the CMV-specific CRF.

CMV-infection is identified by assessments of laboratory and/or clinical sign/symptoms:

- Laboratory-defined CMV (Antigenemia-positive, PCR-positive).
- CMV syndrome (Fever for the last 2 days, neutropenia, leucopenia, viral syndrome).
- CMV disease (Organ involvement).

EBV

EBV infections will be recorded as an infection on the CRF capturing Adverse Event and on the EBV-specific CRF.

EBV-infection should be identified by assessments of laboratory and/or clinical sign/symptoms and these should be entered on the EBV CRF.

8.4.5 Appropriateness of safety measurements

The safety laboratory assessments selected are standard for the liver transplant population. The assessment of (serious) adverse events, including infections, graft loss, death, malignancies and details of opportunistic viral infections (CMV, EBV) allow proper assessment of safety related outcomes and side effects in this population.

8.5 Additional assessments

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site for protocol specified safety lab assessments, collection can be performed at home by an health care provider or an alternative lab (local) collection site may be used. [redacted]

[redacted]

8.5.2 Pharmacokinetics

Free CFZ533 plasma concentrations will be measured in all CFZ533-treated participants (Arms 2 and 3 only).

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein (opposite to the site of the IV administration on Day 8 or Day 15). Details of sample processing, handling, storage and shipment will be described in a separate laboratory manual. All samples will be given a unique sample and collection number. The actual sample collection date and time will be entered on the appropriate CRF.

Free CFZ533 plasma concentrations will be determined using a validated target-based sandwich enzyme-linked immunosorbent assay (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.

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

The following PK parameters will be determined: Ctrough at steady state and Cmax will be directly derived from the bioanalytical data and listings. Additional PK parameters may be determined if data permit.

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.

8.5.3 Pharmacodynamics

Soluble CD40

Blood samples collected for free (pre-treatment) or total (post-treatment) soluble CD40 in plasma (to inform the biology of the target and target engagement) will be obtained from all participants and all arms (Control and CFZ533-treated participants; all samples will be analyzed). Assessment is not mandatory at Month 4.5 visit for arm 1 participants on TAC treatment.

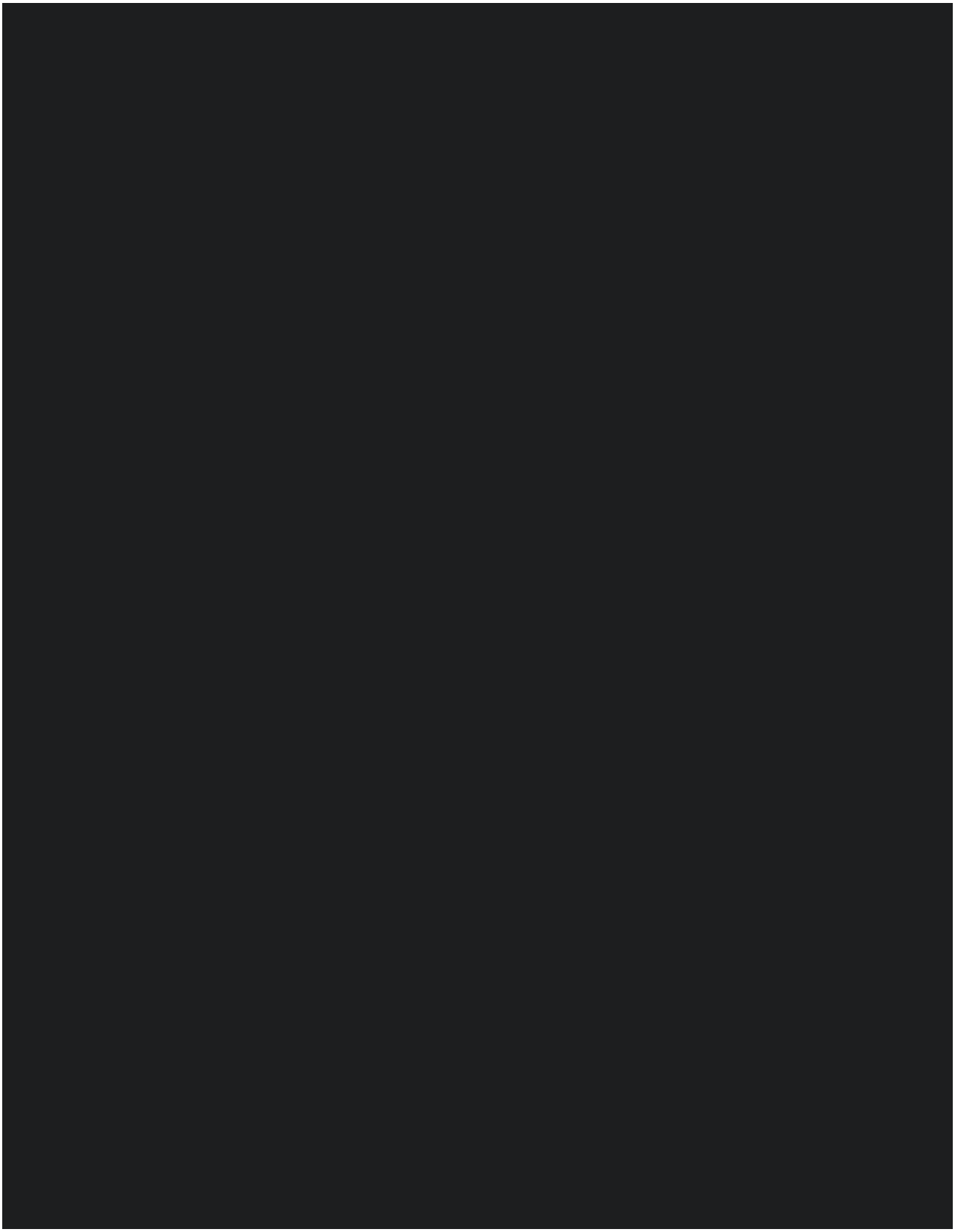
All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein (opposite to the site of the IV administration on Day 8 or Day 15). Details of sample processing, handling, storage and shipment will be described in a separate laboratory manual. All samples will be given a unique sample number (as listed in the blood log Appendix 6a). The actual sample collection date and time will be entered on the appropriate CRF. The detailed methods and analysis will be described in the Bioanalytical Data Report.

8.5.4 Immunogenicity

The presence of anti-CFZ533 antibodies will be determined in all CFZ533-treated participants 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 (opposite to the site of the IV administration on Day 8 or Day 15). 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 6a). The detailed methods and analysis will be described in the Bioanalytical Data Report.

The actual sample collection date and time will be entered on the appropriate CRF.



[redacted]

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

Discontinuation of study treatment for a participant occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the participant or the investigator. Study treatment can be discontinued for different reasons including:

- Adverse event
- Lack of efficacy
- Technical problems
- Participant/guardian decision
- Loss to follow-up
- Death
- Graft loss
- Pregnancy
- Any situation in which study participation might result in a safety risk to the participant
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the participant's overall status, prevents the participant from continuing participation in the study

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdrawn of informed consent Section 9.1.2). Where possible, they should return for the assessments indicated in the assessment schedule (Table 8-1 and Table 8-2).

Participants who discontinue treatment prior to Month 12 should attend all follow up visits (Month 6, Month 8, Month 10, Month 12 and Month 18) until Month 24. Participants who discontinue after Month 12 but before Month 24 should attend Month 18 and Month 24 follow-up visits. Participants who discontinue treatment after Month 24 visit will leave the study and complete the EOS visit.

They should remain in the study on local standard of care and return at the subsequent follow-up scheduled visits to obtain follow-up information.

Information will be collected on graft loss/re-transplant, rejection episodes, and vital signs, hospitalizations, central and/or local laboratory samples (serum creatinine), AEs/SAEs, malignancies, opportunistic infections (especially CMV, EBV) and immunosuppressive therapy.

The dosage administration records for CFZ533, MMF and tacrolimus will be used to record when a participant has discontinued study treatment.

Appropriate CRF for Treatment Completion should also be completed, giving the date and primary reason for stopping the study treatment.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant as specified in the lost to follow-up Section 9.1.3. This telephone contact should preferably be done according to the study visit schedule (Table 8-1 and Table 8-2).

Every effort should be made to contact the participant or a knowledgeable informant by telephone to determine the information on survival status, graft loss/re-transplant, rejection episodes, malignancies, adverse events, opportunistic infections, and immunosuppressive therapies. Since participants will be followed even after discontinuation of study medication, the appropriate CRF for Study Completion should only be completed at Month 24 or earlier if the participant can no longer be followed, e.g., death, loss to follow-up, withdrawal of consent.

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

No study drug will be provided for participants who discontinue the study treatment.

Pregnancy

Participants who become pregnant while in the study must be discontinued from the study medication and from the study and should attend a visit at the clinical site as soon as possible. For participants who are discontinued prior to Month 12, assessments for Month 12 visit should be completed. For participants who are discontinued after Month 12 but before Month 24, assessments for Month 24 visit should be completed. For participants who are discontinued after Month 24, assessments for EOS will be completed. Please also refer to Section 10.1.4 – Pregnancy reporting.

Graft loss

Participants who experienced graft loss will be discontinued from study treatment as well as from the study and should attend a visit at the clinical site as soon as possible. For participants who are discontinued prior to Month 12, assessments for Month 12 visit should be completed. For participants who are discontinued after Month 12 but before Month 24, assessments for Month 24 visit should be completed. For participants who are discontinued after Month 24, assessments for EOS will be completed.

9.1.2 Withdrawal of informed consent

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

- Does not want to participate in the study anymore,

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

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

Where consent to the use of personal and coded data is not required, participant therefore cannot withdraw consent. They still retain the right to object to the further use of personal data.

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 participant 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 participant's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation (including any data resulting from the analysis of a participant's samples until the time of withdrawal) according to applicable law.

For United States: 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 informed consent form.

For EU and Rest of World (RoW): 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.

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study 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 participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the time point of his/her planned end of study visit has passed.

9.1.4 Replacement of early withdrawals or discontinuations

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

9.1.5 Study stopping rules

Until Month 24, stopping rules for the incidence of BPAR and serious infections will be applied. These rules are designed to ensure that they trigger if there is high probability (>90%) that the true BPAR (RAI ≥6, evaluated by central reader) or serious infection rate is greater than 20%.

Infections declared as "Life-threatening" by the investigator or with fatal outcome will be considered as serious infections for the purpose of this stopping rule.

Based on this stopping rule and depending on the number of participants randomized to a treatment arm at a given point in time, the number of participants that experienced a BPAR or a serious infection in this arm that would first trigger the stopping criterion are given in Table 12-1.

In case the stopping rule is reached for a treatment arm, recruitment to that arm will be stopped and all available data reviewed. The decision to continue or permanently stop the treatment arm or adjust study procedures will be taken based on a thorough evaluation of the available data.

No stopping rules will be assessed during the long-term extension.

9.1.6 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study.
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data.
- Discontinuation of study drug development.
- Practical reasons.
- Regulatory or medical reasons (including slow enrollment).

In taking the decision to terminate, Novartis will always consider the participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. 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 participant's interests. The investigator or sponsor depending on the local regulation will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

9.2 Study completion and post-study treatment

Information on the participant'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 participant's study completion (EOS) and/or discontinuation.

The investigator must provide follow-up medical care for all participants 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 participants randomized to the CFZ533 arms. In case a CFZ533 participant is switched to a TAC-based regimen, TAC should be initiated at the lowest daily dose, e.g., 0.5 mg b.i.d., 4 weeks after last

CFZ533 dose. 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. Subsequently, TAC trough levels will be managed as per local practice and local label.

For all participants, a safety follow-up will be conducted during 14 weeks from the last CFZ533 injection or 12 weeks from last TAC dose. Any serious adverse event occurring during this period should be communicated to Novartis to be collected in the safety database, refer to Section 10.1.3.

At the study level, study completion will occur when the last participant finishes the end of study visit (EOS) and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision. End of Study will occur when the last participant completes 3 years in the long-term extension period or at the time of an early study termination.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 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 clinical investigation participant after providing written informed consent for participation in the study. Considering that the screening period may be up to 2 months long, recording of AEs will start from Baseline/LTx date onwards. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product. Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

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 investigator has the responsibility for managing the safety of individual participants and identifying adverse events.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

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

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 non-typical in participant with underlying disease. Investigators have the responsibility for managing the safety of individual participant and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Adverse events must be recorded under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

- 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 and other investigational treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e., progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant.
- 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 10.1.2 for definition of SAE) and which seriousness criteria have been met
- action taken regarding with study 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
- participant hospitalized/participant's hospitalization prolonged (see Section 10.1.2 for definition of SAE)
- its outcome - not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; fatal; or unknown

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued until EOS visit. After EOS, only the SAEs will be reported to the Novartis safety database for a period of 14 weeks from the last CFZ533 injection.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), 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.

Information about adverse drug reactions already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the participant informed consent and should be discussed with the participant 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 participant.

The investigator must also instruct each participant to report any new adverse event (beyond the protocol observation period) that the participant, or the participant'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.

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 participant with the underlying disease. Alert ranges for some key laboratory parameters and other test abnormalities are included in Appendix 1.

10.1.2 Serious adverse events

A 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:

- fatal
- life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires in-patient hospitalization or prolongation of existing hospitalization, **unless** hospitalization is for:
    - initial hospitalization for the transplant procedure

- 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 (e.g., liver allograft biopsy, hospitalization for rejection treatment, revision of an incisional hernia, etc..)
- 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 participant's general condition
- liver biopsy for a suspected rejection
- treatment for acute rejection, unless the rejection is unusually severe or unusual in nature

- is medically significant, e.g., defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

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 participant 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 participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered "medically significant". 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 [ICH-E2D Guideline]).

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

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

All report of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant's safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 14 weeks following the last administration of study treatment (CFZ533 participants, Arms 2 & 3) and until 12 weeks for TAC participants (Arm 1) must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed

instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

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. A 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.

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 CMO & PS 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.

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

10.1.4 Pregnancy reporting

Pregnancies

All pre-menopausal women who are not surgically sterile will have a serum β-hCG test (serum pregnancy test) performed at the screening/baseline/randomization/Month 24 visits, and monthly local urine pregnancy tests as indicated in Table 8-1, Table 8-2 and Table 8-3. 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 pregnancy is confirmed the trial participant must be asked to read and sign pregnancy consent form to allow the study doctor ask about her pregnancy.

To ensure participant's safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported. Information will be collected at three time points after the estimated date of delivery and for a period of 12 months.

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.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (European Medicines Agency (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 recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with a SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

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

For more information on AE and SAE definition and reporting requirements, please see the, respective sections.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

There has been no safety signal for liver toxicity with CFZ533 to date in all participants and healthy volunteers 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.

10.2.2 Renal safety monitoring

The available data does not suggest a risk of renal injury with CFZ533. Kidney function is an important component in the liver transplantation indication and participant'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 participant's 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.

10.2.3 Data Monitoring Committee

This study will include a DMC which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify, or terminate a trial.

An independent DMC will be established to monitor the safety of the treatment regimens. The DMC will be an independent board comprised of a group of physicians with experience in liver 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 first data cutoff for DMC reviews is approximately 6 months after First Patient First Visit (FPFV) provided at least five participants/arm have been randomized at that time.

All visits occurring up to and including this cut-off date for all participants will be included in the DMC analysis. The DMC will then meet approximately every 6 months and the cut-off date used for each DMC analysis shall be the last cut-off date used plus 6 months.

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

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, and provides guidelines for stopping rules. 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 enrolment of participants in the study, continuing the participants on the study drug and/or the study. Such information and recommendations will be used in the best interest of the participants 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 Standard Operating Procedures (SOPs).

10.2.4 Steering Committee

The steering committee has been established comprising investigators participating in the trial, not being members of the DMC, and Novartis/sponsor representatives from the Clinical Trial Team.

The steering committee will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The

steering committee will review initial protocol and protocol amendments as appropriate. Together with the clinical trial team, the steering committee will also develop recommendations for publications of study results including authorship rules.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the CRFs. The CRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the Electronic Data Capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the CRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data entered into the CRF are complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

11.2 Database management and quality control

Novartis personnel (or designated Clinical Research Organization (CRO)) will review the data entered by investigational 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 EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

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

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 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 capture requirements 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 participant records, the accuracy of data capture / data entry, 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 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 Clinical Research Associate (CRA) organization. Additionally, a central analytics organization may analyze data & 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 participant 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 participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. 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 participants will be disclosed.

12 Data analysis and statistical methods

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

The primary analysis will be performed after all participants have completed the Month 12 visit (or prematurely discontinued study before Month 12). Another analysis will be performed after all participants have completed the Month 24 visit. A final analysis will be performed at the end of the extension.

12.1 Analysis sets

The screened set (SCR) consists of all participants who signed the informed consent.

The full analysis set (FAS) will include all participants who are transplanted and randomized, excluding mis-randomized participants. Mis-randomized participants are defined as cases where IRT contacts were made by the Investigator/qualified site staff either prematurely or inappropriately for confirmation of subject's final randomization eligibility and treatment was

not administered to the participant. Following the intention-to-treat (ITT) principle, participants will be analyzed according to their treatment assignment at randomization.

The safety set (SAF) consists of all participants who received at least one dose of study drug (i.e., at least one dose of TAC after randomization in the control arm and at least one dose of CFZ533 in the CFZ533 arms). Participants will be analyzed according to the treatment they actually received.

All safety analyses will be performed on the SAF. The safety will be presented separately for the treatment and follow-up periods.

The PK analysis set will include all participants with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

12.2 Participant demographics and other baseline characteristics

Data for background and demographic variables, including disease characteristics, will be summarized by treatment arm based on the FAS. 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 labelled “missing” when appropriate).

Relevant medical histories and current medical conditions at baseline will be summarized by treatment arm, system organ class and preferred term.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

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 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 dose interruption) will be presented by reason for change.

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 participants who prematurely discontinue study medication will be summarized by reason for discontinuation.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the ATC classification system, by treatment arm.

The average daily dose of CFZ533, MMF, TAC and CS will be summarized by treatment arm.

12.4 Analysis of the primary endpoint

The primary objective is to evaluate the rate of composite efficacy failure (BPAR, graft loss or death) with CFZ533 600 mg and 300 mg compared to TAC Control at Month 12 post-transplantation. Analysis will be on the FAS.

In addition the number of BPAR is used to evaluate the stopping rules during the conduct of the study given in Section 9.1.5.

12.4.1 Definition of primary endpoint

The primary efficacy endpoint is occurrence of composite efficacy failure (BPAR, graft loss, or death) at 12 months post-transplantation based on central pathologist evaluation. If the central pathologist's evaluation is not available, the local pathologist's reading will be used. The estimand is:

1. Population: full analysis set
2. Endpoint: composite efficacy failure at 12 months
3. Intercurrent events: regardless of treatment or study discontinuation, loss to follow-up, or ascites-based dosing adjustment
4. Summary measure: the difference in the proportion of participants with composite efficacy failure in a CFZ533 arm compared to control

Note that ascites-based dosing adjustment is not considered a rescue medication because the occurrence of ascites is not due to lack of efficacy. Accordingly, administering CFZ533 to compensate for drug loss caused by ascites cannot be considered rescue medication. In addition, this unscheduled administration will not result in exposure higher than that seen in participants with no ascites.

12.4.2 Statistical model, hypothesis, and method of analysis

The efficacy analysis at Month 12 evaluates whether at least one of the two CFZ533 treatment arms meets the pre-defined success criterion.

The number of participants with composite efficacy failure is assumed to follow a binomial distribution, i.e.,$r_{\mathrm{i}} \sim \mathrm{Binomial}(n_i, \theta_i)$, where r_i is the number of participants with composite efficacy failure in treatment group i, n_i is the number of participants in treatment group i and θ_i is the probability of composite efficacy failure.

A CFZ533 arm is considered successful if the composite efficacy failure rate difference between this CFZ533 arm and the control arm is less than 15% with probability >80%:

$$P(\theta_{\mathrm{CFZ533}} - \theta_{\mathrm{control}} < 0.15|\mathrm{data}) > 0.8.$$

The required posterior probabilities will be estimated from simulations of the posterior distributions of $\theta_{\mathrm{CFZ533}} - \theta_{\mathrm{control}}$ and compared to the threshold for level of proof. The prior distributions will be assumed to be non-informative. The posterior mean composite efficacy failure rates for each treatment arm and for the difference in mean response rates between CFZ533 treatment arms and control will be presented together with 95% credible intervals.

The posterior probability of the primary decisions rule will be derived and in addition posterior probabilities of the composite efficacy failure rates for each treatment arm and the treatment difference being above various thresholds such as 10%, 15%, and 20% will also be presented.

12.4.3 Handling of missing values not related to intercurrent event

The primary analysis is based on the FAS, i.e., all observations whether on- or off-treatment. Since participants continue to be followed after early study drug discontinuation, the number of missing values is expected to be limited. Any participant who is lost to follow-up or does not attend the Month 12 visit after treatment discontinuation will be counted as failure. A lost-to-follow-up participant is one who did not experience BPAR, graft loss, or death and whose last day of contact is prior to the day of the lower limit of the (Month 12) visit window.

12.4.4 Supportive analyses

As a supportive analysis, a Poisson distribution rather than binomial will be applied for the number of subjects with composite failures. Specifically, the number of composite efficacy failure events in group i will be assumed to follow a Poisson distribution , i.e., $y_i \sim \text{Poisson}\ (\mu_i)$, where μ_i is the expected number of events in group i, with $\mu_i = \lambda_{i,T} * t_{i,T}$, $t_{i,T}$ being the total follow up time in group i in years, thus incomplete follow up of subjects due to early discontinuation is adjusted for. The follow up time will be calculated as [Treatment start date – min (lower limit of the Month 12 visit window, lost-to-follow-up date)].

For the purposes of analysis, time of discontinuation of study drug will be determined by date of last study drug administration as follows:

- Arm 1: earliest date of discontinuation of study drug (TAC or MMF)
- Arms 2 and 3: CFZ533 study drug discontinuation date + 14 days to account for the dosing interval

If a subject discontinues before randomization, the rules of Arm 1 apply.

The exposure-adjusted treatment difference in composite efficacy failure rates between a CFZ533 arm and control at Month 12 will then be evaluated as for the primary endpoint.

In addition, Kaplan-Meier estimates of time to composite efficacy failure and BPAR censored at Month 12 will be respectively constructed and presented graphically. In this analysis, subjects who have not experienced composite efficacy failure, are lost to follow-up, or do not attend the Month 12 visit after treatment discontinuation will be censored with the censoring time defined by the last contact day.

Impact of COVID-19 or any other pandemic on the primary endpoint will be assessed. Details will be presented in SAP.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy endpoint(s)

Secondary efficacy endpoints include:

1. Composite of BPAR, graft loss, death
2. Composite of BPAR, graft loss, death, lost to follow-up

3. Treated BPAR (tBPAR)
4. Acute rejection (AR)
5. Treated AR
6. Antibody-mediated rejection (AMR)
7. Steroid resistant, steroid treated, and antibody treated AR
8. Steroid resistant, steroid treated, and antibody treated BPAR
9. Graft loss
10. Death
11. Graft loss and death

Simple event rates (proportions of events) will be presented. In addition, the event rates will be estimated with Kaplan-Meier estimates. Greenwood's formula will be used to estimate the variance and to derive 2-sided 95% Z-test based confidence intervals for the difference between a CFZ533 and control arm.

The confidence interval will be constructed as:

$$\left(r_{T_i} - r_C\right) \pm Z_{\alpha/2} * \mathrm{SE}_{d_i},$$

where

r_{T_i} = Kaplan-Meier estimate of the failure rate for CFZ533 arm up to 12 months, $i = 1, 2,$

r_C = Kaplan-Meier estimate of the failure rate for the control arm up to 12 months,

$\mathrm{SE}_{d_i} = \sqrt{\mathrm{SE}_{T_i}^2 + \mathrm{SE}_C^2}, i = 1, 2,$

SE_{T_i} = Estimated standard error for CFZ533 arm based on Greenwood's formula, $i = 1, 2,$

SE_C = Estimated standard error for the control arm based on Greenwood's formula, and

$\alpha = 0.05$.

12.5.2 Safety endpoints

12.5.2.1 Renal function

The key secondary objective is to evaluate renal function (eGFR) at Month 12. GFR will be estimated using the MDRD formula described in Section 16.4.

Central laboratory serum creatinine values will be used for all renal function data analysis. If the central lab value is missing, then the local creatinine value will be used, if available.

The estimand is:

1. **population**: Full analysis set (FAS)
2. **endpoint**: change from randomization in eGFR at 12 months post-transplant
3. **intercurrent events**: regardless of missing assessments, discontinuation of study treatment, graft loss, or loss-to-follow-up

4. **summary measure**: the difference in mean eGFR on CFZ533 at 12 months post-transplant as compared to control

The mean change for each arm will be obtained through covariate-adjusted treatment effects using MMRM. The model will contain treatment arm, visit, treatment arm*visit, and randomization GFR with unstructured covariance matrix. The estimand will be evaluated in the FAS population by comparing the difference in mean change between each CFZ533 arm and control.

Renal function at Month 24 measured by eGFR will also be evaluated following the same analyses strategy.

Hypothesis testing

The objective is to demonstrate that either CFZ533 treatment arm is superior to the control arm with respect to mean change in eGFR at 12 months post-transplant.

The null hypothesis: the mean change from randomization in eGFR for a CFZ533 treatment arm is not superior to that in the control arm.

The alternative hypothesis: the mean change from randomization in eGFR for a CFZ533 treatment arm is superior to that in the control arm.

The null hypothesis will be tested at a significance level of 10% against a one-sided alternative hypothesis, and the test statistic will be the estimated difference in Month 12 least squares means from the mixed effects model to allow for adjustment for correlations between time points within participants.

Handling of missing values/censoring/discontinuations

The primary analysis is based on the FAS, i.e., all observations whether on- or off-treatment. Since participants continue to be followed after early study drug discontinuation, the number of missing values is expected to be limited.

1. For participants with graft loss or death, a value of 0 will be imputed after the time of graft loss.
2. Participants who are lost to follow-up with a functioning graft, or have missing assessments will have missing values assessed via MMRM.

Supportive analyses

The analysis of eGFR (MDRD-4) will be repeated with assessments occurring after discontinuation of study medication counting as missing in the MMRM model (an “on-treatment” analysis).

12.5.2.2 General safety

For all other safety analyses, the safety set will be used. Adverse events (AEs) will be presented and summarized for all treatment-emergent events, with a start date after randomization, whether on- or off-treatment. In addition, a separate summary for death including on treatment and post treatment deaths will be provided. General safety summaries (tables, figures) will

include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries).

For CFZ533, the on-treatment period lasts from the date of first administration of study treatment to 14 days after the date of the last actual administration. For TAC, it lasts to the day of the last actual administration.

Adverse events

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

The number and percentage of participants with treatment emergent adverse events and serious adverse events (events started after the first dose of study medication or events present prior to start of treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment.

In addition, the proportion of participants with infections will be summarized as follows:

1. Infections by type of infection (viral, fungal, bacterial, others) and microorganism of infection
2. Serious infections by type of infection (viral, fungal, bacterial, others) and microorganism of infection

The incidence rate of infection by type and micro-organism will be tabulated for each treatment arm. The key safety parameter is serious infections. The number of serious infections will be used to evaluate the stopping rule as outlined in Section 9.1.5.

AEs and infections data will be analyzed as a whole under the heading of AEs for each treatment arm. If a participant has multiple occurrences of an AE, the participant will only be counted once in the corresponding AE category. If participant has multiple AEs within a SOC, the participant will be counted only once for that SOC. If a participant has multiple severity ratings for an AE, the participant will be counted under the maximum rating.

New onset of diabetes mellitus (NODM)

The new onset diabetes mellitus is defined in Section 8.4.4

If any of the criteria for diabetes prior transplantation is unknown (e.g., lab values) and all other criteria are true, the subject will be considered to have no diabetes pre-transplant.

The proportion of participants developing new onset diabetes mellitus after transplantation (NODM) will be summarized by treatment arm. The probabilities of developing NODM will be compared between treatment arms at Month 12 and at Month 24 post-transplantation using logistic regression models with treatment arm and HbA1c levels at randomization as explanatory variables. Death, graft loss, or loss to follow up without NODM before Month 12

(or 24) will not be counted as developing NODM. This analysis will be performed using participants in the FAS population who do not have diabetes mellitus at randomization.

Vital signs

Summary statistics will be provided by treatment and visit/time.

12-lead ECG

All ECG data will be listed by treatment arm, participant and visit/time. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

Summary statistics (mean, standard deviation, minimum, median, maximum) of quantitative lab variables, including change from randomization, will be provided by parameter, treatment, and visit.

Renal function will be plotted over time.

12.5.2.3 Other safety evaluations

Immunogenicity

Blood samples for immunogenicity testing will be collected from all CFZ533-treated participants only, at selected time points, as defined in the assessment schedule (Table 8-1, Table 8-2 and Table 8-3). 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 ADA will be applied. The consequences of an immune response to CFZ533 may be correlated with a loss of exposure (free CFZ533 measures), a loss of target engagement (sCD40 measures), and/or the appearance of immune related adverse events.

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

12.5.3 Pharmacokinetics

CFZ533 plasma concentration data will be listed by treatment, participant, 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.

Summary statistics will include mean (arithmetic and geometric), SD, 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.

Summary statistics and graphical analysis (e.g. Box-plot) will be provided to compare steady-state PK before and after introduction of PFS in the study.

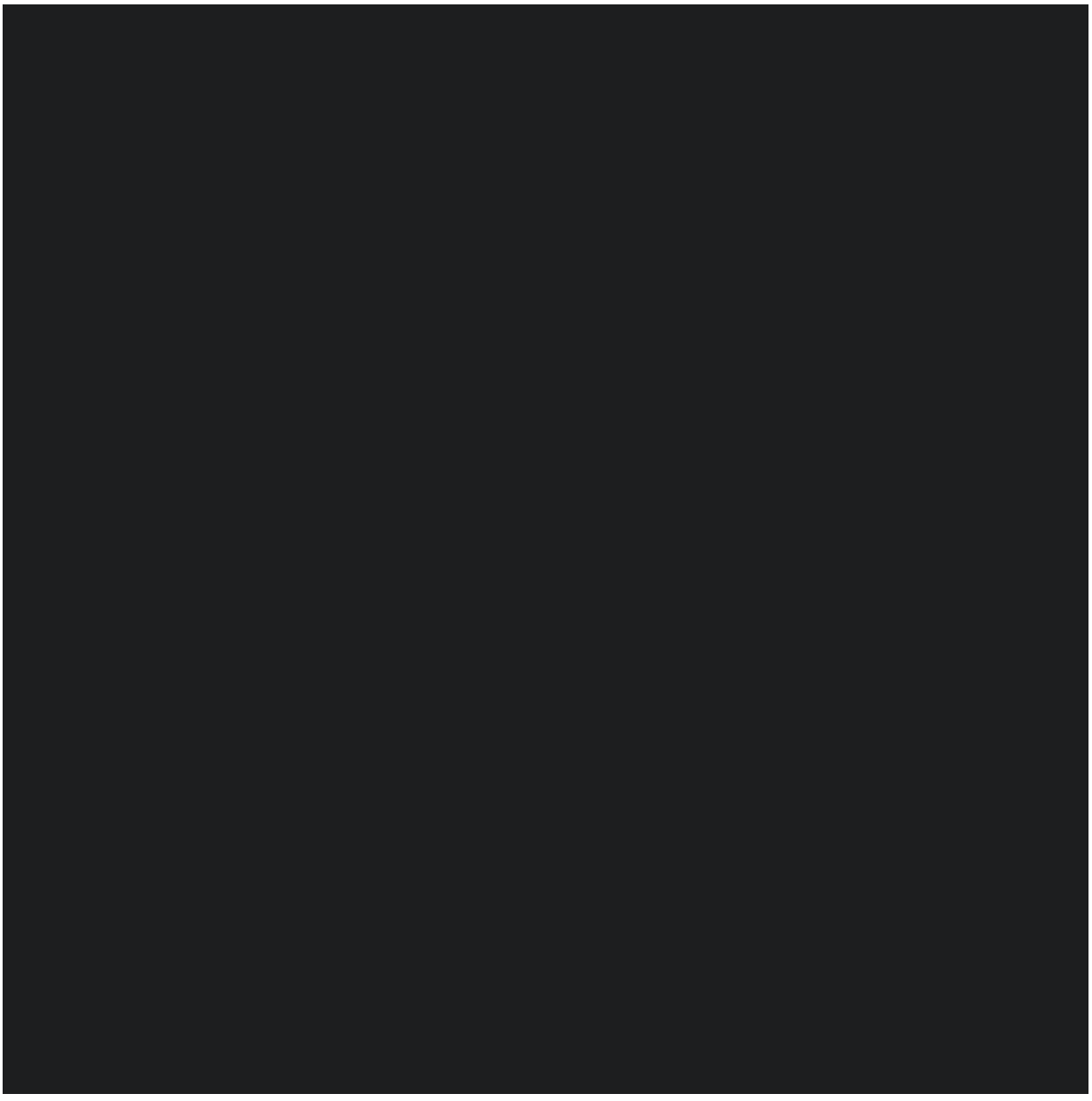
If data permit, PK parameters will be calculated as described in Section 8.5.1 and will be listed by treatment and participant. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum.

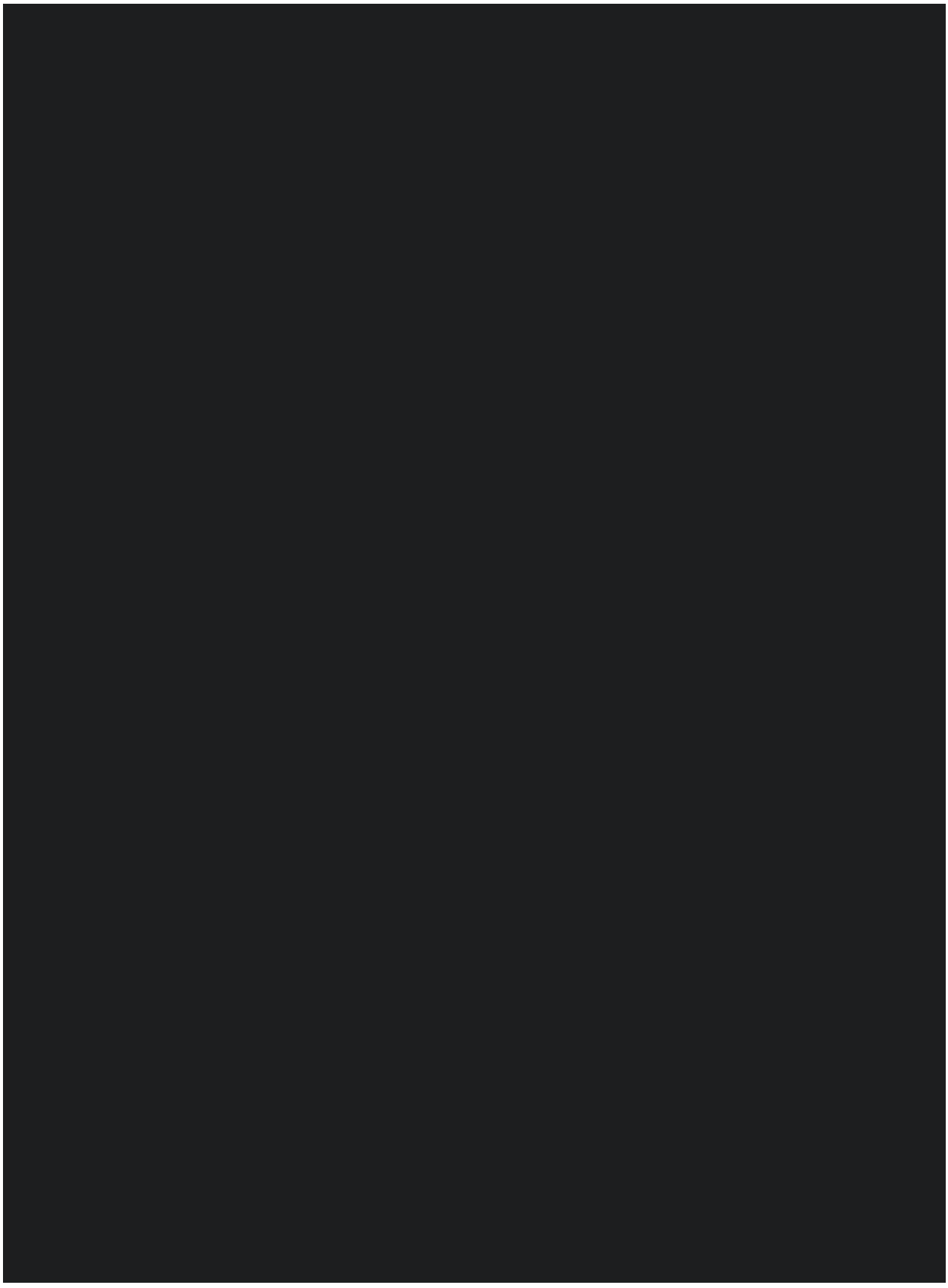
[redacted]

12.5.4 PK/PD relationships

The relationship between PK (CFZ533 concentration) and PD (total soluble CD40; target engagement) will be explored graphically. Modeling of PK/PD (e.g., BPAR or eGFR) data using a population approach may be performed if appropriate, and reported in a standalone report.

[redacted]





12.7 Sample size calculation

The sample size justification considers the probability of success of the study based on the success criterion for the planned sample size. The success criterion for one CFZ533 treatment arm (see Section 12.4.2) is reached if

$$P(\theta_{\text{CFZ533}} - \theta_{\text{control}} < 0.15|\text{data}) > 0.8,$$

where θ is the composite efficacy failure rates, and the prior is Beta(1/3, 1/3).

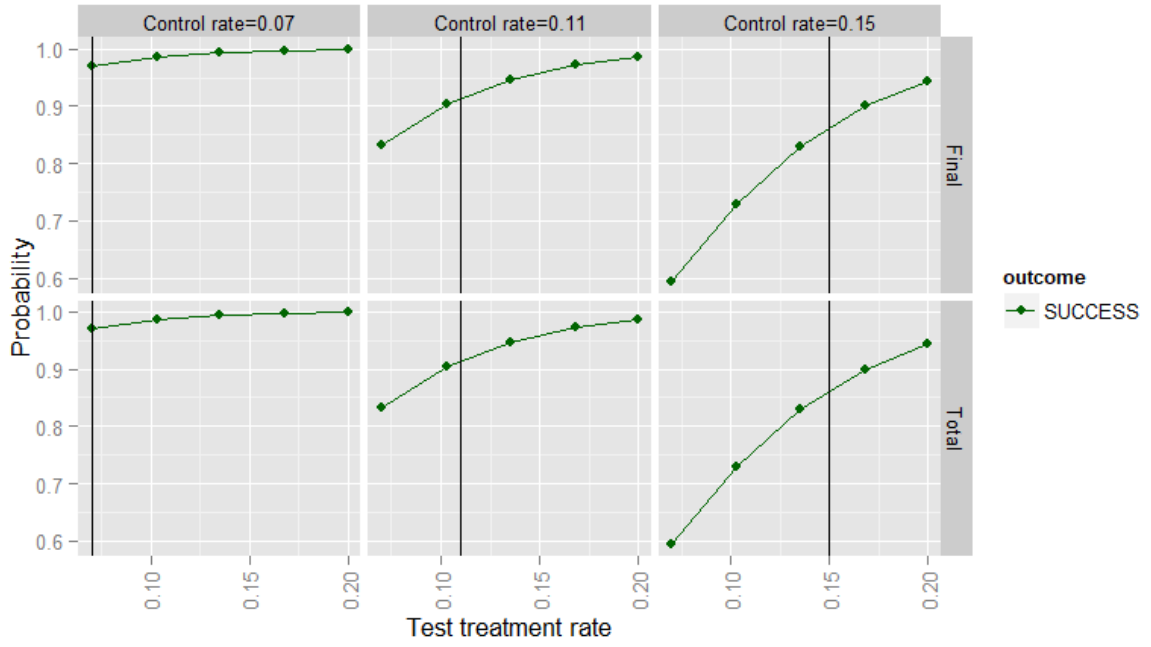
Table 12-2 and Figure 12-2 show the probability of success of the study for a sample size of 48 participants in the CFZ533 arm and 32 participants in the control arm for a range of underlying event rates for composite efficacy failure and serious infections in the CFZ533 treatment arm and in the control arm. A control rate of 10% at Month 12 is expected based on (Levitsky et al 2016), which examined a large registry of deceased donor liver transplant participants from Scientific Registry of Transplant Recipients (SRTR) and internal Novartis studies (RAD001 Study H2304 and AEB071 Study B2203).

Table 12-2 Probability of success under different event rates for 48 participants of CFZ533 arm and 32 participants of control arm

θ_{CFZ533}	θ_{control}	Probability of success
0.07	0.070	0.971
0.07	0.103	0.986
0.07	0.135	0.993

0.07	0.168	0.997
0.07	0.200	0.999
0.11	0.070	0.833
0.11	0.103	0.904
0.11	0.135	0.947
0.11	0.168	0.973
0.11	0.200	0.987
0.15	0.070	0.594
0.15	0.103	0.729
0.15	0.135	0.830
0.15	0.168	0.900
0.15	0.200	0.944

Figure 12-2 Probability of success under different event rates for 48 participants of CFZ533 arm and 32 participants of control arm



Power for key secondary variable

The primary analysis of renal function is based on the FAS. Participants continue to be followed after study drug discontinuation and participants with graft loss or death will have their Month 12 values imputed as described in Section 12.5.2.1. For treatment comparisons, there will be a randomized sample of 48 and 32 participants in the CFZ533 and control arms respectively after 12 months. Assuming a common standard deviation of 16 mL/min and one-sided α=0.10, there is 63, 73, or 81% power to detection a difference of 6, 7, or 8 mL/min/1.73m^2 respectively. If the standard deviation is 20, there is 51, 59, or 67% power respectively.

13 Ethical considerations and administrative procedures

13.1 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 with the ethical principles laid down in the [Declaration of Helsinki].

13.2 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, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. 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.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g., Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, 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.

14 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 participants 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 prohibition, 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.

14.1 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 required for participant safety 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 expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

16.1 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 (ASAT)	≥3 × ULN	≥3 × ULN
SGPT (ALAT)	≥3 × ULN	≥3 × ULN
Bilirubin	>2 × ULN	>2 × ULN
Alkaline Phosphatase	≥5 × ULN	≥5 × ULN
GGT	≥5 × ULN	≥5 × ULN
Renal function, metabolic and electrolyte variables		
Urea	≥5 × ULN	≥5 × ULN
Creatinine	After Day 8±2: ≥3 mg/dL	After Day 8±2: ≥265 µmoFl/L
	OR	OR
	>30% above value from preceding visit	>30% above value from preceding visit
Uric acid	M ≥12 mg/dL	M ≥714 µmol/L
	F ≥9 mg/dL	F ≥535 µmol/L
Glucose	<45 mg/dL	<2.5 mmol/L
	>250 mg/dL	>13.9 mmol/L
Cholesterol	≥350 mg/dL	≥9.1 mmol/L
Triglycerides	≥750 mg/dL	≥8.5 mmol/L
CK (MB)	None	None
Potassium	≤3.0 mEq/L	≤3 mmol/L
	≥6.0 mEq/L	≥6 mmol/L
Calcium	≤6 mg/dL	≤1.5 mmol/L
	≥13 mg/dL	≥3.2 mmol/L
Magnesium	< 1.0 mg/dL	< 0.4 mmol/L
	> 3.6 mg/dL	> 1.5 mmol/L
Amylase	≥ 2 x ULN	≥ 2 x ULN
Lipase	≥ 2 x ULN	≥ 2 x ULN
Hematology variables		
Hemoglobin	<7 g/dL	<4.39 mmol/L
Platelets (thrombocytes)	<50 k/mm^3	<50 × 10^9/L
	≥700 k/mm^3	≥700 × 10^9/L
Leukocytes (WBCs)	≤2.0 k/mm^3	≤ 2.0 × 10^9/L
	≥16 k/mm^3	≥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
Vital sign variables	**Notable criteria**	
Systolic BP (mm/Hg)	160 or higher (hypertension stage 2)	
Diastolic BP (mm/Hg)	110 or higher (hypertension stage 2)	

16.2 Appendix 2: Milan criteria

The United Network of Organ Sharing (UNOS) decided to prioritize allocation of organs to those HCC participants who met the tumor criteria recognized in the Milan experience to have the best outcomes (TNM = T2N0). The Milan criteria is based on tumor burden and limit prioritization for OLT to those who have either a single tumor 5 cm or less in diameter with a single hepatocellular carcinoma, and those with no more than 3 nodules, and each 3 cm or less in diameter, without evidence of metastatic disease or vascular invasion. The Milan criteria provide a simple means of selecting participants with HCC for transplantation who are at low risk (˜10%) for recurrence.

Modified Tumor Node Metastases (pTNM) Classification of HCC

pT0	Tumor not found
pT1	1 nodule ≤ 1.9 cm
pT2	1 nodule 2.0 – 5.0 cm; 2 or 3 nodules, all ≤ 3.0 cm
pT3	1 nodule > 5.0 cm; 2 or 3 nodules, at least one > 3.0 cm
pT4a	4 or more nodules, any size
pT4b	pT2, pT3 or pT4 plus gross intraphepatic portal or hepatic vein involvement as indicated by CT, MRI, or US
N1	Regional (portal hepatitis) nodes, involved
M1	Metastatic disease, including extrahepatic portal or hepatic vein involvement
Stage I	T1
Stage II	T2
Stage III	T3
Stage IVA1	T4a
Stage IVA2	T4b
Stage IVB	Any N1, any M1

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16.3 Appendix 3: Banff classification of liver allograft rejection

REJECTION ACTIVITY INDEX (RAI)

Criteria which can be used to score liver allograft biopsies with acute rejection, as defined by the World Gastroenterology Consensus Document.

Category	Criteria	Score
Portal Inflammation	Mostly lymphocytic inflammation involving, but not noticeably expanding, a minority of the triads	1
	Expansion of most or all of the triads, by a mixed infiltrate containing lymphocytes with occasional blasts, neutrophils and eosinophils	2
	Marked expansion of most or all of the triads by a mixed infiltrate containing numerous blasts and eosinophils with inflammatory spillover into the periportal parenchyma	3
Bile Duct Inflammation Damage	A minority of the ducts are cuffed and infiltrated by inflammatory cells and show only mild reactive changes such as increased nuclear:cytoplasmic ratio of the epithelial cells	1
	Most or all of the ducts infiltrated by inflammatory cells. More than an occasional duct shows degenerative changes such as nuclear pleomorphism, disordered polarity and cytoplasmic vacuolization of the epithelium	2
	As above for 2, with most or all of the ducts showing degenerative changes or focal lumenal disruption	3
Venous Endothelial Inflammation	Subendothelial lymphocytic infiltration involving some, but not a majority of the portal and/or hepatic venules	1
	Subendothelial infiltration involving most or all of the portal and/or hepatic venules	2
	As above for 2, with moderate or severe perivenular inflammation that extends into the perivenular parenchyma and is associated with perivenular hepatocyte necrosis	3

Total RAI Score = _/9

Reference: (Demetris et al 1997)

Grading of Acute Liver Allograft Rejection

Global assessment of rejection grade made on a review of the biopsy and after the diagnosis of rejection has been established.

*Global Assessment	Criteria
Indeterminate	Portal inflammatory infiltrate that fails to meet the criteria for the diagnosis of acute rejection (see reference below)
Mild	Rejection infiltrate in a minority of the triads, that is generally mild, and confined within the portal spaces
Moderate	Rejection infiltrate, expanding most or all of the triads
Severe	As above for moderate, with spillover into periportal areas and moderate to severe perivenular inflammation that extends into the hepatic parenchyma and is associated with perivenular hepatocyte necrosis

* Verbal description of mild, moderate or severe acute rejection could also be labeled as Grade I, II and III, respectively.

Reference: (Demetris et al 1997)

16.4 Appendix 4: Abbreviated MDRD formula for eGFR

The abbreviated MDRD formula used for eGFR calculation is as follows, quoted from quoted from Levey et al (2006):

eGFR 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,

R=1.212 when race is black, otherwise R=1.

16.5 Appendix 5: American Diabetes Association criteria for Diabetes

As defined by the American Diabetes Association:

Diabetes is diagnosed when any of the following are present:

- Symptoms of diabetes, plus casual plasma glucose ≥ 200 mg/dL (11.1 mmol/L).
- Two consecutive fasting plasma glucose (post-transplantation) ≥ 126 mg/dL (7.0 mmol/L)
- 2-hour post-load plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during a 75 gram (g) oral glucose tolerance test.
- HbA1c ≥ 6.5% post-transplantation.

Results obtained by each method must be confirmed on a different day unless definite symptoms of hyper glycemia are present.

- Impaired fasting glucose is a fasting plasma glucose 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L).
- Impaired glucose tolerance is a 2-hour post-load plasma glucose 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) during a 75 g glucose tolerance test.

Reference: Diagnosis and Classification of Diabetes Mellitus, American Diabetes Association (2013), Diabetes Care 2013; 36 Suppl 1:S11.

16.6 Appendix 6a: Blood log for PK, PD, Immunogenicity and other assessments sampling

Arm 1 (TAC regimen) - Blood collection log for pharmacodynamics (sCD40 in plasma).

Study Day	Month	PD (sCD40) Sample Number[d, c] (V = 2 mL)	Other assessments Sample Number
8	0	400	920
29	1	401	921
57	2	402	922
85	3	403	923
127	4.5	404	924
169	6	405	925
225	8	406	926
281	10	407	927
337	12	408	928
421	15	409	929
505	18	410	920
589	21	411	921
673	24	412	922
[redacted]			

Arm 2 (CFZ533 600 mg regimen) - Blood collection log for pharmacokinetics (CFZ533 in plasma), pharmacodynamics (sCD40 in plasma) and immunogenicity (anti-CFZ533 in plasma).

Study Day	Month	Time Point	Dose Reference ID #1	Dose Reference ID #2	PK (CFZ533) Sample Number[b] (V = 3 mL)	PD (sCD40) Sample Number[d, c] (V = 2 mL)	Immuno-genicity Sample Number[b, c] (V = 3 mL)	Other assessments Sample Number
8	0	Pre-dose	1	1	100	200	300	900
		1 hr post dose [a]	1	1	101			
15	0.5	Pre-dose	1	2	102			
		1 hr post dose [a]	1	2	103			
29	1	Pre-dose	1	3	104	201	301	901
43	1.5	Pre-dose	1	4	105			
57	2	Pre-dose	1	5	106	202	302	902
71	2.5	Pre-dose	1	6	107			

Study Day	Month	Time Point	Dose Reference ID #1	Dose Reference ID #2	PK (CFZ533) Sample Number[b] (V = 3 mL)	PD (sCD40) Sample Number[d, c] (V = 2 mL)	Immuno-genicity Sample Number[b, c] (V = 3 mL)	Other assessments Sample Number
85	3	Pre-dose	1	7	108	203	303	903
99	3.5	Pre-dose	1	8	109			
113	4	Pre-dose	1	9	110			
127	4.5	Pre-dose	1	10	111	204	304	904
141	5	Pre-dose	1	11	112			
155	5.5	Pre-dose	1	12	113			
169	6	Pre-dose	1	13	114	205	305	905
225	8	Pre-dose	1	17	115	206	306	906
281	10	Pre-dose	1	21	116	207	307	907
337	12	Pre-dose	1	25	117	208	308	908
421	15	Pre-dose	1	31	118	209	309	909
505	18	Pre-dose	1	37	119	210	310	910
589	21	Pre-dose	1	43	120	211	311	911
673	24	Pre-dose	1	48	121	212	312	912
[redacted]								

[a] 1 Hour **after the <u>end</u>** of 30-min infusion

[b] CFZ533-treated participants only

[c] Samples are taken at pre-dose

[d] All arms (CFZ533-treated and Control)

Arm 3 (CFZ533 300 mg regimen) - Blood collection log for pharmacokinetics (CFZ533 in plasma), pharmacodynamics (sCD40 in plasma) and immunogenicity (anti-CFZ533 in plasma)

Study Day	Month	Time Point	Dose Reference ID #1	Dose Reference ID #2	PK (CFZ533) Sample Number [b] (V = 3 mL)	PD (sCD40) Sample Number [d, c] (V = 2 mL)	Immuno-genicity Sample Number [b, c] (V = 3 mL)	Other assessments Sample Number
8	0	Pre-dose	1	1	150	250	350	950
		1 hr post dose [a]	1	1	151			
29	1	Pre-dose	1	2	152	251	351	951
43	1.5	Pre-dose	1	3	153			
57	2	Pre-dose	1	4	154	252	352	952
71	2.5	Pre-dose	1	5	155			
85	3	Pre-dose	1	6	156	253	353	953
99	3.5	Pre-dose	1	7	157			
113	4	Pre-dose	1	8	158			
127	4.5	Pre-dose	1	9	159	254	354	954
141	5	Pre-dose	1	10	160			
155	5.5	Pre-dose	1	11	161			
169	6	Pre-dose	1	12	162	255	355	955
225	8	Pre-dose	1	16	163	256	356	956
281	10	Pre-dose	1	20	164	257	357	957
337	12	Pre-dose	1	24	165	258	358	958
421	15	Pre-dose	1	30	166	259	359	959
505	18	Pre-dose	1	36	167	260	360	960
589	21	Pre-dose	1	42	168	261	361	961
673	24	Pre-dose	1	47	169	262	362	962
[redacted]								

[a] 1 Hour **after the <u>end</u>** of 30-min infusion

[b] CFZ533-treated participants only

[c] Samples are taken at pre-dose

[d] All arms (CFZ533-treated and Control)

[#] End of study

16.7 Appendix 6b: Blood log for unscheduled PK sampling

Applicable when an additional/compensatory IV dose of CFZ533 is administered, independently of the planned dosing regimen.

Limited to up to Month 12

Each time an additional/compensating intravenous CFZ533 dose (10 or 5 mg/kg; see protocol for instructions) will be administered, **a pre-dose blood sample** will be taken to assess the CFZ533 concentration in plasma (PK sample).

The blood collection log for these **unscheduled** pharmacokinetic samples (to assess CFZ533 in plasma) is described below.

For each participant a *unique sample number* will be given and the *timing* of blood sample will be recorded.

- Arm 2 (CFZ533 600 mg regimen)

Unique PK sample number: 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, etc ...

Dose Reference ID: 1, for all samples

- Arm 3 (CFZ533 300 mg regimen)

Unique PK sample number: 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, etc ...

Dose Reference ID: 1, for all samples

Ascites collection log for unscheduled ascites samples

Limited to up to Month 12

From Day 1 and at any time during the study, if ascites fluids are drained from CFZ533-treated participants, the **total daily volume of drained ascites** will be measured and recorded on the ascites page of the CRF.

An aliquot of ascites fluid will be collected from 1 bag and stored in frozen conditions.

For each participant a *unique sample number* will be given and the *timing* of the ascites sample will be recorded.

- Arm 2 (CFZ533 600 mg regimen)

Unique sample number: 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, etc ...

- Arm 3 (CFZ533 300 mg regimen)

Unique sample number: 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, etc ...