NOVARTIS

Clinical Development

CFZ533A / Iscalimab

CFZ533A2202 / 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)

Statistical Analysis Plan (SAP) Amendment 3

Author:	Statistician, [redacted]

Document type:	SAP Documentation
Document status:	Final
Release date:	24 November 2023
Number of pages:	48

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
14 Oct 2019	Prior to DB lock	Creation of final version	N/A – First version	N/A
16 June 2020	Prior to DB lock	Creation of Amendment 1	Modifications reflecting Protocol Amendment 1 and 2 updates. See change history of the protocol.	All sections
			Updated supportive analyses for primary objective.	Section 2.4.4
			Updated definition of AR, NODM, etc.	Section 2.7.1, 5.4
8 Oct 2021	Prior to DB lock	Creation of Amendment 2	Modifications reflecting Protocol Amendment 3 and 4 updates. See change history of the protocol.	All sections
			Removed description of compensation for CFZ533 due to ascites.	Section 2.1
			Updated the estimand framework and handling of missing data for primary and secondary endpoints.	Section 2.4, 2.5
			Updated sensitivity and supplementary analyses for primary objective.	Section 2.4.4
			Updated general rules for safety analysis.	Section 2.7
			Updated summary of virology.	Section 2.7.3
			Updated summary of pharmacokinetic endpoints regarding PFS application.	Section 2.8
			Added COVID-19 related summaries and analyses at the end of the extension.	Section 2.12
			Updated IA plans and reorganized sections regarding sample size and stopping rules.	Section 2.13, 3

10 Apr 2023	Prior to DB lock	Creation of Amendment 3	Modified the analysis plan following IA due to the study termination.	All sections
			Updated analysis visit window.	Section 5.1
			Updated details for derivation of efficacy endpoints and statistical models.	Section 5.4, 5.5
			Updated analysis for AE.	Section 2.7.1

Table of contents

List of abbreviations

AE	adverse event
AMR	antibody-mediated rejection
AR	acute rejection
ATC	Anatomical Therapeutic Classification
BMI	body mass index
BP	blood pressure
BPAR	biopsy proven acute rejection
CMV	cytomegalovirus
CNI	calcineurin inhibitor
CS	corticosteroids
CSR	clinical study report
CV	coefficient of variation
DAR	dose administration record
DMC	Data Monitoring Committee
EBV	Epstein Barr virus
FAS	full analysis set
eCRF	electronic Case Report Form
eCRS	eletronic Case Retrieve Strategy
eGFR	estimated glomerular filtration rate
EOS	end of study
EP	endpoint
GFR	glomerular filtration rate
IA	interim analysis
ITT	Intention to treat
i.v. / IV	intravenous
LLOQ	lower limit of quantification
LTx	liver transplantation
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MMF	mycophenolate mofetil
MMRM	mixed model of repeated measures
NODM	new onset diabetes mellitus
PD	pharmacodynamic
PK	pharmacokinetics
PT	preferred term or prothrombin time
Q2W	every 2 weeks
RAI	Rejection activity index
SAF	safety set
SAP	Statistical Analysis Plan
s.c. / SC	subcutaneous
sCD40	soluble CD40
SCR	screened set
SD	standard deviation

SE	standard error
SMQ	standard MedDRA query
SNOMED	systematized nomenclature of medicine
SOC	System Organ Class
TAC	tacrolimus
tAR	treated acute rejection
tBPAR	treated biopsy proven acute rejection
TFLs	tables, figures, listings
Tx	transplantation
UPCR	urine protein creatinine ratio

List of tables

List of figures

1 Introduction

This document presents the detailed statistical analysis plan (SAP), for Study CFZ533A2202, "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)".

The study was terminated in September 2022 after the planned Interim Analysis (IA) which led to a decision that the risk-benefit was no longer favorable to continue clinical development in the disease area. Given the decision to terminate the study early, an abbreviated clinical study report (CSR) will be created for this study. Analyses covered in the original SAP and Amendment 1 and 2 have been reduced or simplified accordingly.

1.1 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 1-1).
- 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 corticosteroids (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 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 maintenance 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 1-1).

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 in the Protocol for dose rationale). Participants who do not meet the randomization criteria will be designated screen failures. The screen-failed 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 and will continue up to 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 in the Protocol.

CFZ533 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 or intolerance (see Section 6.5.2 in the Protocol).

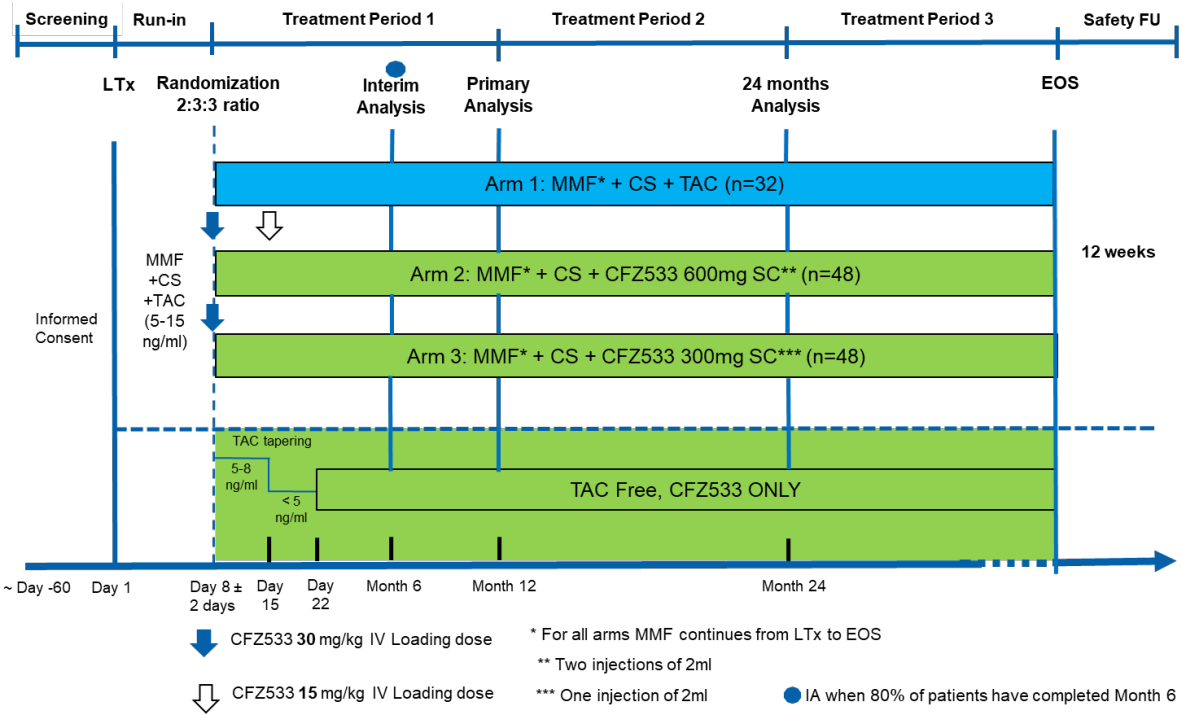
For all participants after the last study visit (EOS), there will be a 12-week safety follow-up period.

MMF and corticosteroid doses will be administered according to local practice. Corticosteroid use is mandatory until Month 4 has been completed but the initiation and dose are 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 1-1 Study design



1.2 Study objectives and endpoints

Table 1-1 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 in the Protocol).
Key Secondary Objective • 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 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.	**Endpoint(s) for Secondary Objective(s)** • Mean change in eGFR from randomization to Month 12. • BPAR as above, Death, Graft Loss and Study completion/disposition datasets.

Objective(s)	Endpoint(s)
• 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 to Month 24 post-transplantation.	• To evaluate eGFR values and change from randomization over time.
• 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 in the Protocol) • 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]	

2 Statistical methods

2.1 Data analysis general information

Due to the early termination of the study, the analysis plan has been modified and may be different from the Protocol.

The primary analysis will be performed after all participants have completed the Month 12 visit, or prematurely discontinued study before Month 12. These analyses will be performed by a Contract Research Organization, ICON. Interim analyses, detailed in Section 2.13, will be performed also by ICON.

The following general data conventions will apply:

- Cut-off day is defined as the latest study day before or up to which data will be used in the analysis. Note that safety data collected during the Safety Follow-up period after EOS is reported to Novartis/Safety and will be included in relevant analyses.
- Descriptive statistics will be calculated based on observed values. Missing values will be presented separately for each parameter or category. Categorical data will be presented as frequencies and percentages. For continuous data, n (sample size), mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.
- BPAR will be based on centrally blinded adjudicated data. All other efficacy [redacted] endpoints will also be based on central lab data.
- AE, SAE, Infection, Serious Infection (including malignancies), CMV information, and EBV information will be summarized based on all eligible collected events.
- All lab and vital sign tables will include data since baseline (liver Tx) but changes are calculated based on the day of randomization. All summaries are based on central lab data.

- Efficacy and liver function analyses are based on all available data including those after study medication discontinuation or as a supportive analysis based only on on-treatment values. Participants are censored for the time-to-event analyses if they do not have an event. For on-treatment analysis, the censoring day is the date of discontinuation of study treatment (defined in Section 2.1.1); for the all-data analysis (regardless of on-treatment or off-treatment), the censoring day is the last contact day.
- Listings will only be provided for variables explicitly indicated in this SAP. Listings will include all available data.

Details about the definition of efficacy and safety events, data handling conventions including "re-aligned" visit windows, imputation of missing dates, and other details about study concepts and terms can be found in Section 5. Note that the visits defined in the protocol are used to guide investigators whereas the "re-aligned" visit windows (Table 5-1) (simply referred to as visit windows hereafter) will be used for the analyses.

2.1.1 General definitions

For the purposes of statistical analysis, "study treatments" are and will be displayed in the outputs as CFZ533 300mg + MMF, CFZ533 600mg + MMF, and TAC + MMF. "Baseline" is defined as the last assessment, including unscheduled assessments, performed prior to liver Tx. All assessments obtained after liver Tx are considered as post-baseline unless otherwise specified. Only centrally adjudicated data will be used for efficacy [redacted] analyses and laboratory (including vital signs).

In the event that a participant only takes one of the three treatments, the following definitions apply:

- Start of study treatment:
  a. CFZ533 arms: day of the first loading dose of CFZ533 on Day 8±2 post-LTx.
  b. Control arm: Day 8 post LTx.
- End of study treatment:
  a. CFZ533 arms: day of the last dose of CFZ533 +14 days. If a participant in CFZ533 arms discontinues treatment before Day 8±2 (first dose of CFZ533), the rules of control arm apply.
  b. Control arm: day of the last dose of TAC.

In calculating the duration of treatment, days of permitted interruption of study medication (CFZ, TAC, and MMF) for any reason will be included (see Section 6.5 in the Protocol for details on permitted dose interruption). The entire treatment period is divided into three parts: Treatment Period 1, 2, and 3 (see Section 1.1).

2.1.2 Analysis sets

The screened set (SCR) consists of all participants who signed the informed consent. The screened set includes only uniquely screened participants, i.e., in the case of re-screened participants, only the chronologically last screened data is counted. Screening phase disposition will be based on the SCR.

The randomized set (RND) consists of all participants who signed the informed consent and were randomized, including misrandomizations.

The full analysis set (FAS) will include all participants who were 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 to confirmation of the participant'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. Participant demographics, baseline characteristics, efficacy and renal function measured by GFR will be performed on the FAS.

The safety set (SAF) consists of all participants in FAS 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, including renal function parameters other than GFR, will be performed on the SAF using on-treatment (between start and end of treatment defined in Section 2.1.1) data unless otherwise specified.

The PK analysis set (PKS) 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, e.g. if a dose was taken more than 7 days after the planned date.

The total screened participants and each analysis population above will be summarized in terms of the frequencies and percentages. Listings of randomized participants and of the participants excluded from analysis sets will be provided.

Rules for exclusion from analysis sets is in Table 5-9.

2.1.3 Subgroup of interest

No subgroup is defined.

2.2 Participant disposition, demographics and other baseline characteristics

Data for background and demographic variables 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, 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).

The following demographics and baseline characteristics will be reported by treatment arm:

- Recipient demographics: age, age group (< 60 years and ≥ 60 years), gender, race (Asian, White, Black or African American, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other), height, weight, body mass index (BMI), and region (North America, Europe, and Rest of the world).

- Recipient baseline characteristics: HbA1c level at the time of transplantation, renal function measured by eGFR (MDRD4) (< 30, [30, 55), [55, 70), [70, 90), and ≥ 90 $mL/min/1.73m^2$), diabetic status* (Y/N) prior to transplantation, HCV status (pos/neg), ratio of spot urine protein to creatinine categories**, and evidence and treatment of HCC prior to transplantation (Y/N).
- Donor background information: age, gender, race, weight, allograft weight, donor characteristics (standard criteria donor (SCD), expanded criteria (EXD)), donor category (deceased heart beating, deceased non heart beating), cause of death, ABO blood group/type, RH type, and hypotension prior to procurement (Y/N/unknown).
- Recipient liver transplant background information: end stage disease leading to transplantation, MELD score summary and by-category (≤ 14,[15, 19], [20, 24], [25, 29], and ≥ 30), UNOS classification (Status 1A, Status1B, and Status Non 1), CHILD classification (Status A, Status B, and Status C), and ABO match (Identical and Compatible).
- Recipient and donor viral serology for: CMV, EBV, HCV, HBsAg Anti-Hep B Surface, Anti-Hep B Core, and HIV. CMV donor/recipient constellation (D+R+ / D-R- / D+R- / DR+) is included.
- Liver transplantation procedure information: cold ischemia time summary and by category (≤ 6, (6, 12], and > 12 hours).

* A patient is identified as not having diabetes prior to transplantation if all of the following are true:

1. Diabetes was not included in the medical history.
2. Glucose (random) < 11.1 mmol/L (200 mg/dL) at the time of transplantation.
3. Diabetes was not recorded as reason for any medication given prior to transplantation.
4. HbA1c < 5.7% at the time of transplantation.
5. If any of the above criteria is unknown (e.g., lab values), the participant will be considered to have no diabetes pre-transplant if all other criteria are true.

** Ratio of spot urine protein to creatinine will be categorized as < 30 mg/g, [30, 500) mg/g, [500, 1000) mg/g, [1000, 3000) mg/g, and ≥ 3000 mg/g.

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

Demographics, baseline characteristics, and recipient liver transplant background information, will be provided in the listings.

2.2.1 Medical history

Relevant medical history/current medical conditions will be summarized by primary system organ class, preferred term, and treatment arm. Frequencies and percentages of participants in the FAS in each treatment arm will be presented.

Relevant ongoing medical history/current medical conditions data will be listed.

2.2.2 Participant disposition

The number and percentage of participants who prematurely discontinued from study medication and from study (by primary reasons), and who completed treatment periods (12-month and 24-month), respectively and cumulatively, will be provided by treatment based on the FAS.

A listing of participant disposition and randomization information and a listing of primary reasons and date/study day for premature discontinuation of the randomized study treatment will be provided. Discontinuation of study medication reasons are from Disposition CRFs.

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

The SAF will be used for the analyses below. All study treatment summaries will be presented by treatment arm. Categorical data will be summarized as frequencies and percentages. For continuous data, n, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

2.3.1 Study treatment / compliance

Administration of study drug (CFZ533, MMF, TAC, and CS)

The duration of exposure (in days and participant-years) to CFZ533, MMF and TAC will be summarized continuously, in addtion n and percentages of participants in each exposure category in days (as defined in Table 2-1) will be summarized.

The duration of exposure 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 considered (i.e., 14 days after the last dose of CFZ533, see Section 2.1.1). In calculating the duration of treatment, days of temporary interruption of study medication (CFZ533, TAC, and MMF) for any reason will be included. For CS, the total duration will be the sum of each individual CS duration. The list of CS will undergo a medical review prior to the analysis and medications which are not considered CS will be removed (e.g., Basiliximab, Ceftriaxone, Mycophenolate (any type), and Tacrolimus (any type)). Further, the frequency of dose changes (including dose interruption) will be presented by reason for change.

In addition, the dose administration records for CFZ533, MMF, TAC and CS will be provided in the listings.

Table 2-1 Exposure duration categories for study treatment

TAC, MMF		CFZ533		
Start	End	Start	End	Days
		0	14	
0	28	15	28	14
		29	42	14
29	56	43	56	14
		57	70	14

TAC, MMF		CFZ533		
Start	End	Start	End	Days
57	84	71	84	14
		85	98	14
85	112	99	112	14
		113	126	14
113	140	127	140	14
		141	154	14
141	168	155	168	28, 14
169	224	169	224	56
225	280	225	280	56
281	336	281	336	56
337	420	337	420	84
421	504	421	504	84
505	588	505	588	84
589	672	589	672	84
673	756	673	756	84
757	840	757	840	84
841	924	841	924	84
925	1008	925	1008	84
1009	1092	1009	1092	84
1093	1176	1093	1176	84
1177	1260	1177	1260	84
1261	1344	1261	1344	84
1345	1428	1345	1428	84
1429	1512	1429	1512	84
1513	1596	1513	1596	84
1597	1680	1597	1680	84
1681	1764	1681	1764	84
1765	1848	1765	1848	84
1849	1932	1849	1932	84
1933	2016	1933	2016	84
2017	2100	2017	2100	84
2100	EOT	2100	EOT	

Dose change, interruption, and discontinuation

The number and percentage of participants with dose changes (MMF and TAC), dose interruptions (only in cases of ascites drainage; see Section 4.3 in the Protocol), and permanent discontinuation will be summarized by reason for change.

Average daily dose of study drug

The average daily dose of each study drug (CFZ533, TAC, and MMF) will be presented by treatment and by visit window from baseline. In calculating average dose, zero daily dose will be used for periods of temporary interruption.

Corticosteroids dosage

The average daily dose and the daily body weight-adjusted prednisone equivalent dosages [mg/kg/day] will be summarized using descriptive statistics by treatment. Steroids administered after the discontinuation of randomized study medication will be ignored. To adjust the dose, the body weight measured closest to the start of a steroid dose will be used.

The averages will only include corticosteroids given for "Rejection prophylaxis" purpose. Steroids (p.o. or i.v.) used for the treatment of rejection episodes will be presented separately. Inhaled, intra-nasal, and topical corticosteroids will not be included in either analysis.

For conversion factors to prednisone equivalent dosages see Table 5-8.

2.3.2 Prior, concomitant and post therapies

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

All medications recorded on the concomitant medications and significant non-drug therapies eCRF page will be classified as *prior* or *concomitant* medications and grouped by Anatomical Therapeutic Classification (ATC) codes and preferred terms (PT). Number and percentage of participants using each medication (by ATC and PT) will be presented by treatment.

Prior medications will be drugs taken prior to the start of study treatment regardless of whether they continue thereafter; any medication given at least once between the start and the end of study treatment was a concomitant medication, including those started before randomization and continued into the treatment period. The start and the end of study treatment is defined in Section 2.1.1.

Immunosuppressive therapies taken after discontinuation of study drug will be summarized separately from study drug therapies. Immunosuppressive therapies are defined as by the investigator in the CRF.

Rules for imputing incomplete dates are described in Section 5.2.

2.4 Analysis of the primary objective

The primary objective is to evaluate the rate of composite efficacy failure (BPAR, graft loss, or death) with CFZ533 600 mg and 300 mg Q2W maintenance regimen compared to TAC Control at Month 12 post-transplantation. Analysis will be on the FAS.

The analysis of the primary objective has been modified due to the early termination of the study.

2.4.1 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 (graft loss and death will be from local evaluation). The estimand is:

- Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted population.
- Endpoint: composite efficacy failure at Month 12 post-transplantation, defined as BPAR, graft loss, or death.
- Treatment of interest: the randomized treatment, CFZ533 300 mg + MMF, CFZ533 600 mg + MMF, and TAC+MMF, regardless of treatment or study discontinuation, loss to follow-up, ascites-based dosing adjustment, or administration of CS (treatment policy).
- Summary measure: the difference in the proportion of participants with composite efficacy failure in CFZ533 arms at 12 months post-transplantation as compared to control.

BPAR is defined as an acute rejection confirmed by biopsy within 48 hours of the suspected rejection (preferably within 24 hours) with a rejection activity index (RAI) score ≥ 3. Events of rejection which were discovered incidentally during the study (e.g., via optional Month 12 biopsy or standard of care biopsy) with no clinical suspicion of acute rejection will not be included in the assessment of the primary endpoint. 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 drug loss caused by ascites cannot be considered rescue medication. In addition, this unscheduled administration aims not to result in exposure higher than that seen in participants with no ascites.

2.4.2 Statistical hypothesis, model, and method of analysis

A Poisson distribution will be assumed for the number of participants with composite efficacy 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 $\mu_i = \lambda_{i,T} t_{i,T}$, with $t_{i,T}$ being the total on-treatment time in group i in years up to $T = 12$ months, thus incomplete follow-up of participants due to early discontinuation is adjusted for. The follow-up time will be calculated as [min(upper limit of the Month 12 visit window, date of treatment discontinuation, date of lost-to-follow-up) – date of randomization]. The probability of a composite event occurring before T can the be derived as $\theta_i = 1 - \exp\ (-\lambda_{i,T})$.

For the purposes of analysis, time of discontinuation of study drug will be determined by the 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.

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 estimand.

Specifically, a CFZ533 arm will be considered successful if the annualized composite efficacy failure rate difference between this CFZ533 arm and the Control arm is less than 15% with probability greater than 80%:

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

The required posterior probabilities will be estimated from simulations of the posterior distributions of $\theta_{\text{CFZ533}} - \theta_{\text{control}}$ and compared to the threshold for the level of proof. The prior distributions of $\lambda_{i,T}$ will be assumed to be non-informative (specifically, Gamma(0.001, 0.001)). 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 decision rule $P(\theta_{\text{CFZ533}} - \theta_{\text{control}} < 0.15|\text{data})$ will be derived. 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, i.e. $P(\theta_{\text{CFZ533}} - \theta_{\text{control}} < \theta_0|\text{data})$, where θ_0= 0.1, 0.12, 0.15, and 0.2.

2.4.3 Handling of missing values/censoring/discontinuations

Participants continued to be followed until Month 12 visit, early study drug discontinuation, or lost to follow-up, whichever first. If no event is observed, the partcipant is considered as censored and will still contribute to the analysis as described above.

2.4.4 Sensitivity analyses

No sensitivity analysis is planned.

2.4.5 Supplementary analyses

Kaplan-Meier (KM) estimates of events rates of composite efficacy failure and BPAR censored at Month 12 will be respectively summarized and presented graphically. In addition, participants 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.

For 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 arm and the Control arm. The confidence interval will be constructed as:

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

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,

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

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

$\mathrm{SE}_C =$ Estimated standard error for the control arm based on Greenwood's formula, and

$\alpha = 0.05.$

Summaries of the composite efficacy failure and its individual components will be provided. Acute rejection events will be summarized by treatment and severity for central and local assessment, respectively. Histological evidence and pathological assessment of liver allograft biopsies will be provided in the listings for central and local assessment, respectively.

2.5 Analysis of the key secondary objective

2.5.1 Key secondary endpoint

The key secondary objective is to evaluate renal function (eGFR) at Month 12. GFR will be estimated using the MDRD formula (Levey et al 2006):

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

where

C is the serum concentration of creatinine [mg/dL],

A is age [years],

$G = 0.742$ when gender is **female**, otherwise $G = 1$, and

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

Central laboratory serum creatinine values will be used for all renal function data analysis. Summary statistics for central eGFR change from randomization will be produced.

The estimand is:

- Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted population.
- Endpoint: change from randomization in eGFR at 12 months post-transplant
- Treatment of interest: the randomized treatment, CFZ533 300mg + MMF, and CFZ533 600mg + MMF, TAC+MMF, regardless of treatment or study discontinuation, loss to follow-up, ascites-based dosing adjustment, or administration of CS (treatment policy).
- Summary measure: the difference in mean eGFR on CFZ533 arms at 12 months posttransplantation as compared to control.

The mean change for each arm will be obtained through covariate-adjusted treatment effects using MMRM where visit is treated as a categorical variable. The model will contain treatment arm, visit, treatment arm*visit interaction, and eGFR at randomization with unstructured covariance matrix. In case of a convergence issue with the MMRM model, Compound Symmetry structure will be used for the covariance matrix. If convergence issue still persists,

an ANCOVA model will be used for Month 12 visit. The estimand will be evaluated in the FAS population by comparing the difference in mean change between each CFZ533 arm and control.

2.5.2 Statistical hypothesis, model, and method of analysis

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-transplantation.

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

The alternative hypothesis is that 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 treatment difference at Month 12 based on least squares means from either the MMRM to allow for adjustment for correlations between time points within participants or the ANCOVA model in case of convergence issue.

2.5.3 Handling of missing values/censoring/discontinuations

The primary analysis is based on the FAS. Since participants continue to be followed after early study drug discontinuation, the number of missing values is expected to be limited. In case of missing values,

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

2.5.4 Supplementary 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).

2.6 Analysis of secondary efficacy objectives

Not applicable as this is removed from the abbreviated CSR.

2.7 Safety analyses

The SAF will be used for safety analyses unless otherwise specified. General safety summaries (tables, figures, etc.) 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), unless otherwise specified. For CFZ533 arms, 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 the Control arm, it lasts to the day of the last actual administration of TAC.

2.7.1 Adverse events (AEs)

Adverse events (AEs) will be presented and summarized for all treatment-emergent events, with a start date after randomization and covering until 14 weeks after the last administration of CFZ533 for CFZ533 arms and 12 weeks after that of TAC for TAC arm. In addition, a separate summary for death will be provided. Malignancies are summarized under SAEs.

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/or preferred term
- by treatment, primary system organ class, preferred term and/or maximum severity

Separate summaries will be provided for AEs leading to treatment discontinuation.

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

- Infections by type of infection (viral, fungal, bacterial, others) and severity.
- Serious infections by type of infection (viral, fungal, bacterial, others) and severity.

The incidence rate of infection by type (viral, bacterial, fungal, and others) 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 in Protocol.

Data collected on AE CRFs will be coded with the MedDRA dictionary that gives preferred term (PT) and system organ class (SOC) information. 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.

Incidence rates of safety topics of interests from eCRS will be summarized by risk categories. Safety topics of interests are defined in Table 2-2.

Table 2-2 Safety topics of interests

Safety topics of interests	Search strategy
Infections	MedDRA search strategy SOC “Infections and infestations” [10021881] and HLGT “Microbiology and serology investigations” [10027529].
Malignancies including Lymphoproliferative disorder	SMQ Malignant or unspecified tumours (Narrow) (20000091), SMQ Malignancy related therapeutic and diagnostic procedures (20000093) and SMQ Tumour markers (20000094)
Thrombosis	MedDRA search strategy SMQ “Embolic and thrombotic events (SMQ)” [20000081] and HLT “Coagulation and bleeding analyses” [10009728].

Immunogenicity	PT: Drug specific antibody present [10013745] SMQ: Hypersensitivity (Narrow), (20000214)
Vaccination failure	Therapeutic product ineffective (10060769) Therapeutic response changed (10074941) Therapeutic response decreased (10043414) Therapeutic response delayed (10053181) Therapy non-responder (10051082) Antibody test abnormal (10061425) Antibody test negative (10061426) Immunology test abnormal (10061214) Vaccination failure (10046862) Vaccine breakthrough infection (10067923) Absence of immediate treatment response (10081766) Drug effect less than expected (10083365)

The AE, SAE, infections, and serious infections summarized as above will also be provided in corresponding listings.

New onset of diabetes mellitus (NODM)

New onset diabetes mellitus is defined as:

a. All of the following should be true (no diabetes pre-transplantation):
   1. Diabetes was not included in the medical history.
   2. Glucose (random) < 11.1 mmol/L (200 mg/dL) at the time of transplantation.
   3. Diabetes was not recorded as reason for any medication given prior to transplantation.
   4. HbA1c < 5.7% at the time of transplantation
   5. If any of the above criteria is unknown (e.g. lab values), the participant will be considered to have no diabetes pre-transplant if all other criteria are true;

   AND

b. At least one of the following should be true (diabetes onset after transplantation):
   1. Two consecutive fasting plasma glucose (FPG) ≥ 126 mg/dL (7.0 mmol/L) any day after Day 29 or a random plasma glucose (RPG) ≥ 200 mg/dL (11.1 mmol/L).
   2. HbA1c ≥ 6.5% (only from Day 85 onward).
   3. Diabetes reported as an AE that is prevalent after Day 29.
   4. Any concomitant medication with ATC level 2 code “A10” (drugs used in diabetes), if prevalent after Day 29. Here “prevalent after Day 29” means the described drug has been consecutively used for at least 30 days since Day 29.

Note that participants with steroid-induced diabetes are excluded. The date of onset is the earliest date when any of the conditions in Criterion b above is met. The proportion of participants developing new onset diabetes mellitus (NODM) after transplantation will be summarized by treatment group. Death, graft loss, or loss to follow up without NODM before Month 12 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 the time of transplantation according to Criterion a.

Disclosure reporting

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

If for a participant, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

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

2.7.2 Deaths

In addition to the output required for disclosure, the number of deaths will be tabulated by treatment.

2.7.3 Laboratory data

Analyses of laboratory data include data since baseline (liver Tx) but changes are calucated based on the day of randomization. Summary statistics (mean, standard deviation, minimum, median, maximum, and 25% and 75% percentiles) of quantitative lab variables, including change from randomization, will be provided by parameter, treatment, and visit. Similarly, proportion of notable abnormalities of key laboratory tests (Table 5-4) by parameter, treatment, and visit and its listing will be provided. Shift tables using the normal/abnormal classification will be used to compare randomization to the worst on-treatment value.

The following lab parameters will be presented: liver function (AST, ALT, GGT, ALP, and total bilirubin), renal function (eGFR, creatinine, and urine protein/creatinine ratio), lipids, and hematology (WBC, neutrophils, and lymphocytes). eGFR will also be summarized by CKG stages (< 15, [15, 30), [30, 45), [45, 60), [60, 90), and ≥ 90) by treatment arm and by visit.

Liver events will be presented as defined in Table 5-6.

Virology monitoring

Average duration of infection-free period will be presented by treatment. The frequency of following categories will also be summarized by treatment:

- EBV: > 2000 copies/mL;
- CMV: ≤ 5000, (5000, 1000], and > 10000 copies/mL;

For CFZ533 participants, the counts will be provided separately for participants who remain on CFZ533 vs. those who switch from CFZ533 to discontinuation or to SOC. In participants who switch from CFZ533, summary statistics of the mean time from the end of switch to viral load elevation (EBV > 2000 copies/mL, CMV > 10000 copies/mL) will be provided. A listing of participants above the thresholds will be provided by treatment and visit. The day of end of switch is the same as the day of discontinuation of CFZ533 (defined in Section 2.1.1).

2.7.4 Other safety data

2.7.4.1 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, 8-2, and 8-3 in the Protocol). The presence of anti-CFZ533 antibodies will be assessed using screening and confirmatory assays. An integrated PK/PD and immunogenicity approach, focusing on the clinical and functional consequences of anti-drug antibodies 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), or the appearance of immune related adverse events.

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

2.7.4.2 ECG and cardiac imaging data

ECG data will be listed by treatment arm, participant, and visit.

2.7.4.3 Vital signs

Vital signs will be listed by treatment arm, participant, and visit.

2.8 Pharmacokinetic endpoints

CFZ533 plasma concentration data will be listed by treatment, participant, and visit/sampling time point using PKS. Concentrations will be given in mass per volume units. 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, maximum, and 25% and 75% percentiles. 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. PK is considered steady after 10 weeks since PFS introduction.

If data permit, PK parameters will be calculated as described in Section 8.5.2 in Protocol and will be listed by treatment and participant. Descriptive summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, maximum, and 25% and 75% percentiles.

In addition, CFZ533 concentration will be measured in any collected/drained ascites. The detailed methods and analysis will be described in the Bioanalytical Data Report.

In the zz.xpt file in GPSII (merge file), PK concentration (free CFZ533 in plasma) will be expressed in unit 'microgram/mL' (in addition to 'nanogram/mL'), and time will be expressed in unit 'day' (in addition to 'hours').

a. Two variables for the elapsed time (*e.g.* EACLTM_1 and EACLTM_2) will be provided: elapsed time since first dose: EACLTM_1 is calculated using the Dose Reference ID provided in the Blood Log under Dose Reference ID series #1,
b. EACLTM_2 is calculated using using the Dose Reference ID provided in the Blood Log under Dose Reference ID series #2; e.g. for Arm 2 (600 mg Q2W regimen) a Dose Reference ID of 17 for pre-dose PK Sample 115 on Day 225 (17ith dose of CFZ533) means that the elapsed time is calculated with reference to timing of 17ith dose of CFZ533 (and is negative).

The zz.xpt file in GPSII will combine PK data (free CFZ533 in plasma) as well as sCD40 data in plasma (PD). Similar to PK output, elapsed time variables (EACLTM_1 and EACLTM_2) will be generated.

2.9 PD and PK/PD analyses

The relationship between PK (CFZ533 concentration in plasma; Section 2.8) and PD (total soluble CD40 in plasma; target engagement) will be explored graphically. All participants with evaluable PK and PD parameters will be included in the data analysis.

Total soluble CD40 for all participants in the PKS will be listed by treatment, participant, and visit/sampling time point. Total soluble CD40 concentrations will be given in mass per volume units (in nanogram/mL). 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.

The zz.xpt file in GPSII will combine PK data (free CFZ533 in plasma) as well as sCD40 data in plasma (PD) (Section 2.8).

2.10 Participant-reported outcomes

Not applicable.

[redacted]

2.13 Interim analysis

An interim analysis is planned after 80% participants have reached the Month 6 visit (or have prematurely discontinued the study before Month 6) where all endpoints are analyzed as in the full CSR using on-treatment data with exceptions as described below.

Efficacy data of all participants available at the cutoff date, including data beyond Month 6 and participants not yet reaching Month 6, will be included. The primary endpoint (the composite efficacy failure rate) will be analyzed based on a Poisson model to adjust for different follow-up time of participants at the cutoff date (see Section 2.4.4 for details). Other primary comparisons not using Poisson model, including the key secondary endpoint [redacted], will be based on data up to Month 6 visits to maximize the sample size. All summaries by visits will include all visits, including those beyond Month 6. Safety analyses, including AE, SAE, infections, serious infections, death, and safety topics of interests, will be analyzed for participants who complete Month 6 and for all participants based on exposure adjusted rates, respectively.

The primary objective of the interim analysis 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.

3 Sample size calculation

3.1 Study stopping rules

The stopping rules will be evaluated by the clinical team and the DMC will review data at regular intervals as described in the Section 10.2 in the Protocol and the DMC charter. 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.

Stopping rules for the incidence of centrally read moderate to severe BPARs (RAI ≥ 6) 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 or serious infection rate is greater than 20%. In other words, a trial is to be stopped if:

$$P(\theta_i > 0.2|\text{data}) > 0.9,$$

where θ_i is referring to the event rate of arm i, and the prior is Beta(1/3, 1/3).

Based on these stopping rules 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 3-1.

Table 3-1 Stopping rules per number of events

Number of participants randomized to the treatment arm (N)	Number of participants with observed event in the treatment arm that would lead to stopping the treatment arm (n)	Observed event rate (n/N)
3	2	67%
4	2	50%
5	3	60%
6	3	50%
7	3	43%
8	4	50%
9	4	44%
10	4	40%
11	5	45%
12	5	42%
13	5	38%
14	5	36%
15	6	40%
16	6	38%
17	6	35%
18	6	33%
19	7	37%
20	7	35%
21	7	33%

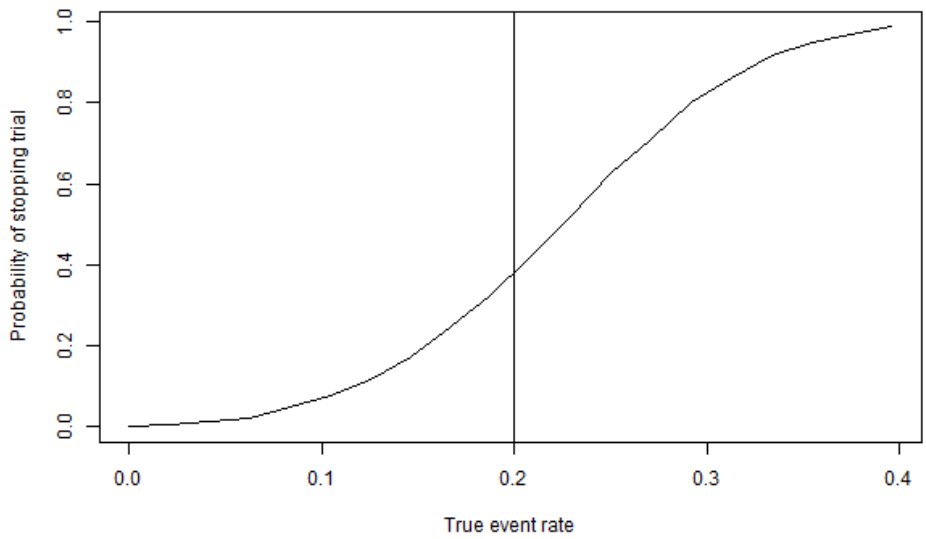
Number of participants randomized to the treatment arm (N)	Number of participants with observed event in the treatment arm that would lead to stopping the treatment arm (n)	Observed event rate (n/N)
22	7	32%
23	8	35%
24	8	33%
25	8	32%
26	8	31%
27	9	33%
28	9	32%
29	9	31%
30	9	30%
31	10	32%
32	10	31%
33	10	30%
34	10	29%
35	11	31%
36	11	31%
37	11	30%
38	11	29%
39	12	31%
40	12	30%
41	12	29%
42	12	29%
43	13	30%
44	13	30%
45	13	29%
46	13	28%
47	14	30%
48	14	29%

Properties of stopping rule

The stopping rules as defined in Section 3.1 are designed to ensure that enrollment in a treatment arm will be stopped if there is a high probability (> 90%) that the true BPAR or serious infection rate is greater than 20%.

Figure 3-1 indicates the probability of stopping enrollment in a treatment arm for various true BPAR or serious infection rates. The thresholds for the stopping rules ensure that the chance of stopping enrollment in an arm is sufficiently high for true high BPAR or serious infection rates, while remaining appropriately low when the true rates are low.

Figure 3-1 Probability of stopping a cohort for various event rates for up to 48 participants per arm



3.2 Power for primary endpoint

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 2.4.2) is reached if

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

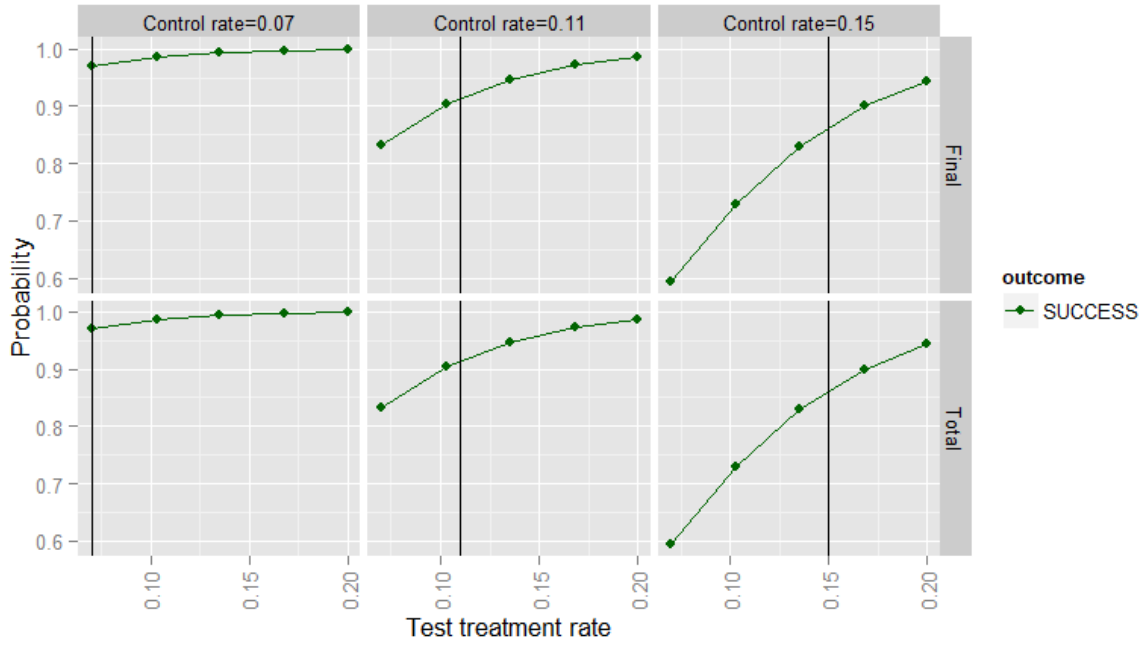
where θ is the composite efficacy failure rates, and the prior is Beta(1/3, 1/3).

Table 3-2 and Figure 3-2 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 2017), 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 3-2 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 3-2 Probability of success under different event rates for 48 participants of CFZ533 arm and 32 participants of control arm



3.3 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 2.5.3. 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 $\alpha = 0.10$, there is 63, 73, or 81% power to detect 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. The power calcuation is completed by nQuery 8.4 based on two-sample t-test with equal variance.

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Analysis visit windows

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

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

Table 5-1 Analysis visit windows

Re-aligned visit	Visit window (relative to date of Tx)	Relative to first treatment date		
		Start day of Visit window	Midpoint	End day of visit window
1	Screening	Day of informed consent		Day of transplant - 1
2	Baseline	Day of Tx		Day of Tx
3	Randomization	Day of Tx +1		Start of study drug# = Day 1
4	Day 15	2	8	11
5	Day 22	12	15	18
6	Day 29	19	22	29
7	Month 1.5	30	36	43
8	Month 2	44	50	57
9	Month 2.5	58	64	71
10	Month 3	72	78	85
11	Month 3.5	86	92	99
12	Month 4	100	106	113

Re-aligned visit	Visit window (relative to date of Tx)	Relative to first treatment date		
		Start day of Visit window	Midpoint	End day of visit window
13	Month 4.5	114	120	127
14	Month 5	128	134	141
15	Month 5.5	142	148	155
16	Month 6	156	162	190
17	Month 8	191	218	246
18	Month 10	247	274	302
19	Month 12	303	330	372 (358*)
20	Month 15	373	414	456
21	Month 18	457	498	540
22	Month 21	541	582	624
23	Month 24	625	666	708
24	Month 27	709	750	792
25	Month 30	793	834	876
26	Month 33	877	918	960
27	Month 36	961	1002	1044
28	Month 39	1045	1086	1128
29	Month 42	1129	1170	1212
30	Month 45	1213	1254	1296
31	Month 48	1297	1338	1380
32	Month 51	1381	1422	1464
33	Month 54	1465	1506	1548
34	Month 57	1549	1590	1632
35	Month 60	1633	1674	1716
36	Month 63	1717	1758	1800
37	Month 66	1801	1842	1884
38	Month 69	1885	1926	1968
39	Month 72	1969	2010	End of study

Day 1 = randomization day if a participant was randomized but did not receive study drug.
* For all Month 12 analyses, the end of visit window of Month 12 visit is Day 358, instead of Day 372.

Under this window schema, multiple records of a participant are re-aligned into the same visit as follows:

- For post-randomization continuous values (except for CFZ533, TAC, and MMF trough level measurements and liver tests), for a given participant, if multiple numeric measurements for a given variable are reported in the same visit window (e.g., Month 6), then the measurement closest to the target visit day will be taken; if tie, take the earlier measurement. For screening visit, the target day is day of transplant – 1; for baseline, day of transplant; for randomization, start of study drug (Day 1); for other visits, the midpoint of the visit window.
- For trough levels, the last value observed within a visit window is taken.

- For liver tests (bilirubin, SGOT, SGPT, GGT, and alkaline phosphatase), the following algorithm is applied:
  a. If an acute rejection occurs within a visit window with multiple liver tests reported, the time of the event is the date rejection first suspected, and the liver test to be summarized are the closest to that event (if tie, take the earlier one)
  b. If no rejection occurs, the assessment closest to the target day is taken.
- For categorical values, the worst value of all records observed in the visit window is used.

For parameters which are not collected at every scheduled visit [redacted], visit windows defined in Table 5-1 will be combined using the following rules for an applicable visit post randomization: "lower limit" of the combined window= "upper limit of prior applicable visit" + 1, "upper limit" of the combined window = "target day of current visit" + integer part of [("target day of next applicable visit" – "target day of current visit")/2]. For example, if a parameter is measured only at Randomization, Day 29 (Month 1), Month 3, Month 6, and Month 12, the combined Day 29 (Month 1) visit window will be from Day 2 to Day 50 (= Day 22 + interger part of [(78 - 22)/2]), Month 3 will extend from Day 51 to Day 120 (= Day 78 + interger part of [(162 - 78)/2]), etc.. If more than one assessment falls into the combined window, the rules defined above handling multiple records are applied.

5.2 Imputation rules

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

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

5.2.1 Study drug

Not applicable.

5.2.2 AE date imputation

This algorithm is expressed in the Variable Source Derivation column as **#IMPUTAEV(*event*)** where *event* is the partial start date of the adverse event.

Table 5-2 explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

Note, if the imputed AE (or CM) start is after AE (or CM) end date, then set AE (or CM) start equal to AE (or CM) end date. Missing AE end dates will not be imputed.

Table 5-2 Imputation logic for partial AE dates

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

The following matrix explains the logic behind the imputation.

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

The following table is the legend to the logic matrix.

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

(E) After Treatment Start	01JANYYYY

5.2.3 Concomitant medication date imputation

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

Table 5-3 Imputation logic for partial concomitant medication dates

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

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

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

(C) Before/After Last contact date	31DECYYYY

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

5.3 Laboratory parameters derivations

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

Table 5-4 Clinically notable lab abnormalities

Laboratory variable	Standard units	SI units
Liver function and related variables		
AST (SGOT)	≥3 × ULN	≥3 × ULN
ALT (SGPT)	≥3 × ULN	≥3 × ULN
Bilirubin	>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 OR >30% above value from preceding visit	After Day 8±2: ≥265 µmol/L OR >30% above value from preceding visit
Uric acid	M ≥12 mg/dL F ≥9 mg/dL	M ≥714 µmol/L F ≥535 µmol/L
Glucose	<45 mg/dL >250 mg/dL	<2.5 mmol/L >13.9 mmol/L
Cholesterol	≥350 mg/dL	≥9.1 mmol/L
Triglycerides	≥750 mg/dL	≥8.5 mmol/L
CK (MB)	None	None
Potassium	≤3.0 mEq/L ≥ 6.0 mEq/L	≤3 mmol/L ≥ 6 mmol/L
Calcium	≤ 6 mg/dL ≥ 13 mg/dL	≤ 1.5 mmol/L ≥ 3.2 mmol/L
Magnesium	< 1.0 mg/dL > 3.6 mg/dL	< 0.4 mmol/L > 1.5 mmol/L
Amylase	≥ 2 × ULN	≥ 2 × ULN
Lipase	≥ 2 × ULN	≥ 2 × ULN
Hematology variables		
Hemoglobin	<7 g/dL	<4.39 mmol/L
Platelets (thrombocytes)	<50 k/mm^3 ≥700 k/mm^3	<50 × 10^9/L ≥700 × 10^9/L
Leukocytes (WBCs)	≤2.0 k/mm^3 ≥16 k/mm^3	≤ 2.0 × 10^9/L ≥16 × 10^9/L
Hematology variables: differential		

Granulocytes (poly, neutrophils)	≤1,000/mm^3	≤1 x 10^9/L
Eosinophils	≥12%	≥12%
Lymphocytes	≤1,000/mm^3	≤1× 10^9/L

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

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

Laboratory Variable	Standard Unit	Conversion Factor*	SI Unit
Platelets	%	1	%
Hematocrit	%	1	%
Hemoglobin	g/dL	0.6206	mmol/L
RBC	10^6/mm^3	1	10^{12}/L
WBC	10^3/mm^3	1	10^9/L
Sodium	mEq/L	1	mmol/L
Potassium	mEq/L	1	mmol/L
Chloride	mEq/L	1	mmol/L
Calcium	mg/dL	0.2495	mmol/L
Magnesium	mg/dL	0.4114	mmol/L
	mEq/L	0.5	mmol/L
Inorganic phosphate	mg/dL	0.3229	mmol/L
Urea**	Urea[mg/dL]	0.1665	mmol/L
Creatinine	mg/dL	88.4	µmol/L
Glucose	mg/dL	0.05551	mmol/L
HbA1c	%	1	%
Uric acid	mg/dL	0.05948	mmol/L
AST (SGOT)	U/L	1	U/L
ALT(SGPT)	U/L	1	U/L
Alkaline phosphatase	U/L	1	U/L
GGT	U/L	1	U/L
Total bilirubin	mg/dL	17.1	umol/L
Total cholesterol	mg/dL	0.02586	mmol/L
High Density Lipoprotein(HDL)	mg/dL	0.02586	mmol/L
Low Density Lipoprotein(LDL)	mg/dL	0.02586	mmol/L
Triglycerides	mg/dL	0.01129	mmol/L
Creatinine phosphokinase (CK)	U/L	1	U/L
Lipase	U/L	1	U/L
Amylase	U/L	1	U/L
Albumin	g/dL	10	g/L
Protein	g/dL	10	g/L
Urinary protein:creatinine	mg/g	0.113	mg/mmol

Table 5-6 displays the liver events to be displayed. Refer to the internal Novartis “Analysis plan for liver safety data” for more information.

Table 5-6 Newly occurring liver enzyme abnormalities

Safety set
Timepoint: *Week xx/Endpoint/*Any time post-baseline

	Active dose A N=xxx n/m (%)	Active dose B N=xxx n/m (%)	Placebo N=xxx n/m (%)
ALT > 3x ULN	xx/xxx (xx.x)	xx/xxx (xx.x)	xx/xxx (xx.x)
ALT > 5x ULN	xx/xxx (xx.x)	xx/xxx (xx.x)	xx/xxx (xx.x)
ALT > 8x ULN	xx/xxx (xx.x)	xx/xxx (xx.x)	xx/xxx (xx.x)
ALT > 10x ULN	xx/xxx (xx.x)	xx/xxx (xx.x)	xx/xxx (xx.x)
ALT > 20x ULN	xx/xxx (xx.x)	xx/xxx (xx.x)	xx/xxx (xx.x)
ALT or AST > 3x ULN	xx/xxx (xx.x)	xx/xxx (xx.x)	xx/xxx (xx.x)
ALT or AST > 5x ULN	xx/xxx (xx.x)	xx/xxx (xx.x)	xx/xxx (xx.x)
ALT or AST > 8x ULN	*xx/xxx (xx.x)*	*xx/xxx (xx.x)*	*xx/xxx (xx.x)*
ALT or AST > 10x ULN	xx/xxx (xx.x)	xx/xxx (xx.x)	xx/xxx (xx.x)
ALT or AST > 20x ULN	xx/xxx (xx.x)	xx/xxx (xx.x)	xx/xxx (xx.x)
ALT or AST > 3x ULN & TBL > 1.5x ULN	xx/xxx (xx.x)	xx/xxx (xx.x)	xx/xxx (xx.x)
ALT or AST > 3x ULN & TBL > 2x ULN	xx/xxx (xx.x)	xx/xxx (xx.x)	xx/xxx (xx.x)
ALT or AST > 5x ULN & TBL > 2x ULN	xx/xxx (xx.x)	xx/xxx (xx.x)	xx/xxx (xx.x)
ALT or AST > 8x ULN & TBL > 2x ULN	xx/xxx (xx.x)	xx/xxx (xx.x)	xx/xxx (xx.x)
ALT or AST > 10x ULN & TBL > 2x ULN	xx/xxx (xx.x)	xx/xxx (xx.x)	xx/xxx (xx.x)
ALT or AST > 20x ULN & TBL > 2x ULN	xx/xxx (xx.x)	xx/xxx (xx.x)	xx/xxx (xx.x)
ALT or AST > 3x ULN & INR > 1.5x ULN	xx/xxx (xx.x)	xx/xxx (xx.x)	xx/xxx (xx.x)
ALP > 1.5x ULN	xx/xxx (xx.x)	xx/xxx (xx.x)	xx/xxx (xx.x)
ALP > 2x ULN	*xx/xxx (xx.x)*	*xx/xxx (xx.x)*	*xx/xxx (xx.x)*
ALP > 3x ULN	xx/xxx (xx.x)	xx/xxx (xx.x)	xx/xxx (xx.x)
ALP > 5x ULN	*xx/xxx (xx.x)*	*xx/xxx (xx.x)*	*xx/xxx (xx.x)*
TBL > 1x ULN	*xx/xxx (xx.x)*	*xx/xxx (xx.x)*	*xx/xxx (xx.x)*
TBL > 1.5x ULN	*xx/xxx (xx.x)*	*xx/xxx (xx.x)*	*xx/xxx (xx.x)*
TBL > 2x ULN	xx/xxx (xx.x)	xx/xxx (xx.x)	xx/xxx (xx.x)
TBL > 3x ULN	xx/xxx (xx.x)	xx/xxx (xx.x)	xx/xxx (xx.x)
ALP > 3x ULN & TBL > 2x ULN	*xx/xxx (xx.x)*	*xx/xxx (xx.x)*	*xx/xxx (xx.x)*
ALP > 5x ULN & TBL > 2x ULN	*xx/xxx (xx.x)*	*xx/xxx (xx.x)*	*xx/xxx (xx.x)*
ALT or AST > 3x ULN & TBL > 2x ULN & ALP < 2x ULN	xx/xxx (xx.x)	xx/xxx (xx.x)	xx/xxx (xx.x)
(ALT or AST > 3x ULN & TBL > 2x ULN & ALP < 2x ULN) or reported Hy's Law case	xx/xxx (xx.x)	xx/xxx (xx.x)	xx/xxx (xx.x)
ALT or AST > 3x ULN & (nausea or vomiting or fatique or general malaise or abdominal pain or (rash and eosinophilia))	xx/xxx (xx.x)	xx/xxx (xx.x)	xx/xxx (xx.x)

Newly occurring: Subjects not meeting criterion at baseline and meeting criterion post-baseline
m = Number of subjects at risk (subjects having a baseline measurement not meeting the criterion or missing but at least one post-baseline measurement for the laboratory test(s) *<and timeframe>* under consideration)
n = Number of subjects at risk who satisfy the criterion *<at post-baseline visit, endpoint, or any time> post-baseline*

Notes:
1. "Hy's law case" is a lower level term in MedDRA (10070546) and may be reported as AE. Only new onsets will be considered.
2. The event which combines lab information and signs/symptoms information is derived using LB and the liver events eCRF, but is not using the AE dataset. Even if in the FDA 2009, they added as a PT anorexia, the choice was to kept it out from our definition as too unspecific.
3. Black (mandatory): Those mentioned in the FDA guidance (section 2). The last one is mandatory if liver eCRFs are used.
4. Black (mandatory) and italic: Additional criteria mentioned in the Novartis Hepatotox guideline (section 5.1).

5.3.1 Clinically notable vital signs

Table 5-8 presents the criteria that define notable abnormalities of vital signs data.

Table 5-7 Clinically notable vital signs

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)

5.3.2 Steroid conversion factors

Steroids will be displayed using prednisone equivalent body weight adjusted doses. The doses displayed in the following table are considered equivalent. To determine prednisone equivalent doses, doses will be multiplied by the conversion factor shown in Table 5-8. To adjust the dose, the body weight measured closest to the start of a steroid dose will be used (from vital signs eCRF).

Table 5-8 Steroids conversion factors

WHO drug code	Preferred Term Corticosteroid	Equivalent Dose [mg]	Conversion Factor
000447xx	Prednisone	5	1
000162xx	Prednisolone	5	1
000496xx	Methylprednisolone	4	1.25
012428xx	Meprednisone	4	1.25
001867xx	Prednylidene	5 5/7	0.875
000319xx	Triamcinolone	4	1.25
000146xx	Cortisone	25	0.2
000286xx	Hydrocortisone	20	0.25
002131xx	Fludrocortisone	2	2.5
000085xx	Betamethasone	0.75	20/3
000664xx	Paramethasone	2	2.5
000160xx	Dexamethasone	0.75	20/3
008827xx	Deflazacort	6	5/6

5.4 Definition/Derivation of Efficacy Variables

All efficacy endpoints regarding biopsy described will be summarized based on the **central** pathologists' evaluation of all biopsy readings. If the central pathologist's evaluation is missing, then the local evaluation will be used.

All acute rejections determined by local biopsy reading are recorded in the clinical database on the Liver allograft rejection and Liver allograft biopsy eCRFs. Central pathological reading will be electronically trasnferred.

5.4.1 Efficacy endpoint derivations based on central readings

Humoral rejection/AMR

A rejection is considered as a humoral rejection if:

- MI.MITEST = "AAMR" and MI.MIRESC = "Y" ; **AND**
- Reason for biopsy = "Suspicion of rejection" on Liver Allograft Biopsy eCRF page.

Date of AMR will be MI.MIDAT_RAW when MI.MITEST = "AAMR" and MI. MIRESC= "Y".

AR

A rejection is considered an AR if:

- Antibody-mediated rejection (see above); **OR**
- MI.MITEST = "ATCELL" and MI. MIRESC = "Y" ; **AND**
- Reason for biopsy = "Suspicion of rejection" on Liver Allograft Biopsy eCRF page.

Date of AR will be min(MI.MIDAT_RAW when MI.MITEST = "AAMR", MI.MIDAT_RAW when MI.MITEST = "ATCELL") when MI. MIRESC= "Y".

BPAR

A rejection is considered a BPAR if:

- AR (see above); **AND**
- MI.MITEST = "RAITOT" and MI.MIRESN ≥ 3; **AND**
- Reason for biopsy = "Suspicion of rejection" on Liver Allograft Biopsy eCRF page.

Date of BPAR will be date of MI.MIDAT_RAW when MI.MITEST = "RAITOT" and MI.MIRESN ≥ 3.

Steroid resistant AR

A rejection is considered a steroid resistant AR if

- AR (see above); **AND**
- Was the rejection steroid resistant = "Yes" from Liver Allograft Rejection eCRF page

Date of steroid resistant AR will be the date of AR (see above).

Antibody treated AR

A rejection is considered an antibody treated AR if

- AR (see above); **AND**
- Was antibody treatment administered = "Yes" from Liver Allograft Rejection eCRF page

Date of antibody treated AR will be the date of AR (see above).

Steroid treated AR

A rejection is considered an steroid treated AR if

- AR (see above); **AND**
- Were steroids administered = "Yes" from Liver Allograft Rejection eCRF page

Date of steroid treated AR will be the date of AR (see above).

Steroid resistant BPAR

A rejection is considered a steroid resistant BPAR if

- BPAR (see above); **AND**
- Was the rejection steroid resistant = "Yes" from Liver Allograft Rejection eCRF page

Date of steroid resistant BPAR will be the date of BPAR (see above).

Antibody treated BPAR

A rejection is considered an antibody treated BPAR if

- BPAR (see above); **AND**
- Was antibody treatment administered = "Yes" from Liver Allograft Rejection eCRF page

Date of antibody treated BPAR will be the date of BPAR (see above).

Steroid treated BPAR

A rejection is considered an steroid treated BPAR if

- BPAR (see above); **AND**
- Were steroids administered = "Yes" from Liver Allograft Rejection eCRF page

Date of steroid treated BPAR will be the date of BPAR (see above).

5.4.2 Efficacy endpoint derivations based on local readings

AR

A rejection is considered an AR if:

- Primary clinical diagnosis = "Acute rejection" or "Acute and chronic rejection from Liver Allograft Rejection eCRF page.

Date of AR will be "date rejection was first suspected" from the Liver Allograft Rejection eCRF, or if missing, the first available date of the biopsy of the particular rejection episode from the Liver Allograft Biopsy eCRF page.

Treated AR (tAR)

A rejection is considered a tAR if:

- Acute rejection (see above); **AND**
- Was anti-rejection therapy administered = "yes" from Liver Allograft Rejection eCRF page

Date of tAR will be the date of the corresponding AR (note: tAR is the subset of AR).

BPAR

A rejection is considered a BPAR if:

- Histological Evidence of Acute Rejection = "Yes" and of Acute and Chronic Rejection = "Yes" from Liver Allograft Biopsy eCRF page; **AND**
- Total RAI score ≥ 3 and Reason for biopsy = "Suspicion of rejection" from Liver Allograft Biopsy eCRF page.

Date of BPAR will be the date of the corresponding AR (note: BPAR is a subset of AR).

Treated BPAR (tBPAR)

A rejection is considered a tBPAR if:

- Biopsy-proven acute rejection (BPAR) (see above) **AND**
- Was anti-rejection therapy administered = "yes" from Liver Allograft Rejection eCRF page

Date of tBPAR will be the date of the corresponding AR (note: tBPAR is the subset of AR).

Death

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

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

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.

Graft losses will be identified from Graft Loss CRF page.

Loss to follow-up

A lost-to-follow-up participant is one who discontinued the study and 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 or 24) visit window. The date of loss to follow-up is the last contact date.

Composite efficacy failure

The date of composite efficacy failure will be the earliest non-missing date among the individual components of the composite endpoint.

For the composite endpoints and each individual endpoint, if the date of the event is not available, then the event will be included in listings and the simple proportion efficacy tables, but excluded from survival analysis.

5.5 Statistical models

Randomization seed for random functions utilized in all analyses is set to 5332202.

For the posterior probability simulation, the number of iteration is set to 10000.

For Kaplan-Meier estimates and related analyses, the censoring day is the last day of the associated analysis visit window.

5.5.1 Exposure-adjusted incidence rate and 100(1 - α)% confidence interval

Exposure-adjusted incidence rates is presented per 100 participant-years. Participant-years is calculated as a sum of individual participant durations in days divided by 365.25.

It will be assumed that for each of n participants in a clinical trial the time $t_j, (j = 1, \dots, n)$ to the first occurrence of a certain treatment emergent event is observed, or if the event was not experienced, the (censored) time to the end of the observation period or EOT, whichever occurs earlier. The sequence of first occurrences of an event will be modeled to follow approximately a Poisson process with constant intensity θ. The rate parameter θ will be estimated as $\lambda = D/T$, where $T = \sum_{j=1}^{n} t_j$ and D is the number of participants with at least one event. Conditionally on T, an exact $100(1-\alpha)\%$ confidence interval for a Poisson variable with parameter θT and observed value D can be obtained based on (Garwood, 1936), from which an exact $100(1-\alpha)\%$ confidence interval for $\lambda = D/T$ will be derived as follows (Sahai, 1993; Ulm, 1990):

Lower confidence limit $L = \frac{0.5\chi_{\frac{\alpha}{2},2D}}{T}$ for $D > 0$, and $= 0$ otherwise;

Upper confidence limit $U = \frac{0.5\chi_{1-\frac{\alpha}{2},2D+2}}{T}$.

where $\chi_{\alpha,k}$ is the α-th quantile of the Chi-square distribution with k degrees of freedom.

5.6 Rule of exclusion criteria of analysis sets

Table 5-9 displays the criteria for exclusions from analysis sets.

Table 5-9 Participant Classification

Analysis Set	PD ID that cause participants to be excluded	Non-PD criteria that cause participants to be excluded
SCR	INCL01	Not having informed consent; Not having screening epoch disposition page
FAS	INC03, OTH03, OTH10	Not randomized; Not transplanted; Mis-randomized
SAF	NA	No study drug taken

Analysis Set	PD ID that cause participants to be excluded	Non-PD criteria that cause participants to be excluded
PK	NA	No study drug taken; PD with relevant impact on PK; no valid PK concentration measurement

6 Reference

Garwood, F (1936). Fiducial limits for the Poisson distribution. Biometrika, 46; 441–453.

Levey AS, Coresh J, Greene T, et al (2006) Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med; 145:247-54.

Levitsky J, Goldberg D, Smith AR, Mansfield SA, Gillespie BW, Merion RM, Lok ASF, Levy G, Kulik L, Abecassis M, and Shaked A (2017). Acute Rejection Increases Risk of Graft Failure and Death in Recent Liver Transplant Recipients; Clinical Gastroenterology and Hepatology 15: 584-593.

Sahai H, Khurshid Anwer (1993). Confidence intervals for the mean of a poisson distribution: a review. Biom J, 35 (7); 857-867

Ulm K (1990). A simple method to calculate the confidence interval of a standard mortality ratio. American Journal of Epidemiology, 131(2); 373-375