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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Iscalimab (CFZ533)

Trial Indication(s)

Liver transplant

Protocol Number

CCFZ533A2202

Protocol 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 additionalr follow-up and a long-term extension (CONTRAIL I)

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase II

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Study Start/End Dates

Study Start Date: October 07, 2019 (Actual)
Primary Completion Date: April 20, 2023 (Actual)
Study Completion Date: April 20, 2023 (Actual)

Reason for Termination (If applicable)

The study was terminated following less favorable efficacy by Iscalimab (CFZ533) in liver transplant patients compared to tacrolimus.

Study Design/Methodology

This was a multicenter, open-label, active-controlled study to evaluate the efficacy, safety, tolerability, PK and PD of two CFZ533 maintenance doses in de novo liver transplant recipients. The study was designed as a randomized, 36-month clinical trial comprised of:

- A screening period (up to 2 months) starting from informed consent, screening visit, and including successful liver transplantation (LTx).
- A run-in treatment period following successful transplantation that ended 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.
- The long-term extension period (Treatment Period 3) starting post Month 24 until the end of the study (EOS).

A minimum 12-week safety follow-up period for all patients after EOS.

Centers

29 centers in 10 countries: Germany(4), Spain(4), Czech Republic(1), Italy(1), France(4), Belgium(1), Hungary(1), United States(9), Netherlands(1), Argentina(3)

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Objectives:

Primary objective

- 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.

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 objectives

- To assess the safety and tolerability of CFZ533 regimens compared to TAC control at Month 12 and Month 24.

Test Product (s), Dose(s), and Mode(s) of Administration

CFZ533 at 150 mg/mL was administered by IV infusion or SC injection to the patient by authorized Investigator staff.

Statistical Methods

The number of composite (BPAR, graft loss, death) events was assumed to follow a Poisson distribution. For the purposes of analysis, a CFZ533 arm was considered successful if the annualized composite efficacy failure rate difference between this CFZ533 arm and the Control arm was less than 15% with probability greater than 80%. 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 were presented together with 95% credible intervals.

Only one key secondary objective was evaluated, renal function (eGFR) at Month 12. Being a close-out CSR, other secondary endpoints were removed.

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Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:

Screening period up to liver transplantation:

- Written informed consent obtained before any assessment.
- Male or female patients 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.
- Transplantation to occur within defined screening period following informed consent signature.

At randomization (Day 8 +/- 2):

- Recipients with no active HCV and HBV replication.
- 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 m2 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 tested negative for Epstein Barr virus (EBV) within 28 days prior to baseline visit.
- 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 was evidence of local recurrence or metastases.
- Hepatocellular carcinoma that did 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).
- Patients who have received a live vaccine within four weeks prior to transplantation.
- Recipients with HIV positive donor.
- Recipients with donors HBsAg positive.
- Recipients who were 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/mm3.
- Recipients with an absolute neutrophil count of < 1,000/mm³ or white blood cell count of < 2,000/mm³.
- Recipients with clinically significant systemic infection requiring use of intravenous (IV) antibiotics.
- Evidence of active tuberculosis (TB) infection.
- 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 were on renal replacement therapy at randomization.
- Any episode of acute rejection or suspected rejection prior to randomization.
- HCC patients whose explanted liver graft pathology report shows (i) pathologic Tumor-Node-Metastasis (pTNM) stage beyond T2N0M0, (ii) presence of mixed carcinoma, (iii) microvascular invasion despite pTNM stage.
- Patients with body weight < 30 kg or > 180 kg.

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Participant Flow Table

Overall Study

	CFZ533 300 mg regimen (CFZ533 300 mg + MMF)	CFZ533 600 mg regimen (CFZ533 600 mg + MMF)	TAC Control (TAC + MMF)	Total
Arm/Group Description	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 started on Day 29, in combination with MMF and CS up to EOS.	Loading doses of 30 mg/kg IV on Day 8 (with +/- 2 days window), and 15 mg/kg IV on Day 15. The subcutaneous (SC) administration of 600 mg (2 injections of 2 mL CFZ533 at 150 mg/mL) every 2 weeks started on Day 29, in combination with MMF and CS up to EOS.	Tacrolimus (TAC) + Mycophenolate mofetil (MMF) + Corticosteroids (CS) up to End of Study (EOS). Initial TAC target trough were between 5-15 ng/mL during the run-in period. From randomization onwards, the TAC levels were adjusted as per local label.	
Started	48	48	32	128
Safety Set (SAF)	48	47	32	127
Completed	0	0	0	0
Not Completed	48	48	32	128
Study terminated by sponsor	39	34	25	98
Adverse Event	3	6	3	12
Physician Decision	2	0	1	3
Withdrawal by Subject	2	3	3	8
Death	1	4	0	5
Lost to Follow-up	1	1	0	2

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Baseline Characteristics

	CFZ533 300 mg regimen (CFZ533 300 mg + MMF)	CFZ533 600 mg regimen (CFZ533 600 mg + MMF)	TAC Control (TAC + MMF)	Total
Arm/Group Description	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 started on Day 29, in combination with MMF and CS up to EOS.	Loading doses of 30 mg/kg IV on Day 8 (with +/- 2 days window), and 15 mg/kg IV on Day 15. The subcutaneous (SC) administration of 600 mg (2 injections of 2 mL CFZ533 at 150 mg/mL) every 2 weeks started on Day 29, in combination with MMF and CS up to EOS.	Tacrolimus (TAC) + Mycophenolate mofetil (MMF) + Corticosteroids (CS) up to End of Study (EOS). Initial TAC target trough were between 5-15 ng/mL during the run-in period. From randomization onwards, the TAC levels were adjusted as per local label.	
Number of Participants [units: participants]	48	48	32	128
Baseline Analysis Population Description				
Age Continuous (units: Years) Analysis Population Type: Participants Mean ± Standard Deviation				
	56.7±9.94	56.2±6.98	54.0±9.90	55.8±8.92
Sex: Female, Male (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)				
Female	11	15	8	34
Male	37	33	24	94
Race/Ethnicity, Customized (units: Participants)				

Analysis Population Type: Participants
Count of Participants (Not Applicable)

White	45	46	29	120
Black or African American	3	2	2	7
Unknown	0	0	1	1

Primary Outcome Result(s)

Percentage of patients with composite event (Biopsy Proven Acute Rejection (BPAR), Graft Loss or Death) over 12 months

Description	The occurrence of biopsy proven acute rejection (BPAR) was evaluated based on central pathologist evaluation. Graft loss and death was evaluated as per local evaluation.
Time Frame	Baseline to Month 12
Analysis Population Description	Full Analysis Set (FAS)

	CFZ533 300 mg regimen (CFZ533 300 mg + MMF)	CFZ533 600 mg regimen (CFZ533 600 mg + MMF)	TAC Control (TAC + MMF)
Arm/Group Description	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 started on Day 29, in combination with MMF and CS up to EOS.	Loading doses of 30 mg/kg IV on Day 8 (with +/- 2 days window), and 15 mg/kg IV on Day 15. The subcutaneous (SC) administration of 600 mg (2 injections of 2 mL CFZ533 at 150 mg/mL) every 2 weeks started on Day 29, in combination with MMF and CS up to EOS.	Tacrolimus (TAC) + Mycophenolate mofetil (MMF) + Corticosteroids (CS) up to End of Study (EOS). Initial TAC target trough were between 5-15 ng/mL during the run-in period. From randomization onwards, the TAC levels were adjusted as per local label.

Number of Participants Analyzed [units: participants]	48	48	32
Percentage of patients with composite event (Biopsy Proven Acute Rejection (BPAR), Graft Loss or Death) over 12 months (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	8 (16.67%)	12 (25%)	3 (9.38%)

Statistical Analysis

Groups	CFZ533 300 mg regimen (CFZ533 300 mg + MMF), TAC Control (TAC + MMF)
Type of Statistical Test	Non-Inferiority
Non-Inferiority/Equivalence Test	The primary objective would be demonstrated, if the composite efficacy failure rate difference between any of the two CFZ533 arms and the TAC arm is less than the pre-defined non-inferiority margin (0.15) with probability >80%.
Other Rate difference	0.0759
95 % Confidence Interval 2-Sided	-0.0729 to 0.2165

Statistical Analysis

Groups	CFZ533 600 mg regimen (CFZ533 600 mg + MMF), TAC Control (TAC + MMF)
Type of Statistical Test	Non-Inferiority
Non-Inferiority/Equivalence Test	The primary objective would be demonstrated, if the composite efficacy failure rate difference

	between any of the two CFZ533 arms and the TAC arm is less than the pre-defined non-inferiority margin (0.15) with probability >80%.
Other Rate difference	0.1696
95 % Confidence Interval 2-Sided	0.0072 to 0.3276

Secondary Outcome Result(s)

Mean change in estimated Glomerular Filtration Rate (eGFR) from randomization to Month 12

Description	Renal function as measured by estimated Glomerular Filtration Rate (eGFR) was evaluated using the MDRD formula: eGFR = 175 x (serum concentration of creatinine (SCr))-1.154 x (age)-0.203 x 0.742 [if female] x 1.212 [if Black].
Time Frame	Baseline to Month 12
Analysis Population Description	Full Analysis Set (FAS)

	CFZ533 300 mg regimen (CFZ533 300 mg + MMF)	CFZ533 600 mg regimen (CFZ533 600 mg + MMF)	TAC Control (TAC + MMF)
Arm/Group Description	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 started on Day 29, in combination with MMF and CS up to EOS.	Loading doses of 30 mg/kg IV on Day 8 (with +/- 2 days window), and 15 mg/kg IV on Day 15. The subcutaneous (SC) administration of 600 mg (2 injections of 2 mL CFZ533 at 150 mg/mL) every 2 weeks started on Day 29, in combination with MMF and CS up to EOS.	Tacrolimus (TAC) + Mycophenolate mofetil (MMF) + Corticosteroids (CS) up to End of Study (EOS). Initial TAC target trough were between 5-15 ng/mL during the run-in period. From randomization onwards, the TAC levels were adjusted as per local label.

Number of Participants Analyzed [units: participants]	48	48	32
Mean change in estimated Glomerular Filtration Rate (eGFR) from randomization to Month 12 (units: mL/min/1.73 m^2)	**Mean (Full Range)**	**Mean (Full Range)**	**Mean (Full Range)**
	2.05 (-60.4 to 71.5)	-9.31 (-55.8 to 28.7)	-14.74 (-104.0 to 20.6)

Number of Participants with Treatment Emergent Adverse Events

Description	The distribution of adverse events was done via the analysis of frequencies for treatment emergent Adverse Event (TEAEs), Serious Adverse Event (TESAEs), Deaths due to AEs and TEAEs leading to discontinuation, through the monitoring of relevant clinical and laboratory safety parameters.
Time Frame	Baseline up to 14 weeks after last dose of study medication (CFZ533 participants) and until 12 weeks for TAC participants, up to approx. 184 weeks.
Analysis Population Description	Safety Set (SAF)

	CFZ533 300 mg regimen (CFZ533 300 mg + MMF)	**CFZ533 600 mg regimen (CFZ533 600 mg + MMF)**	**TAC Control (TAC + MMF)**
Arm/Group Description	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 started on Day 29, in combination with MMF and CS up to EOS.	Loading doses of 30 mg/kg IV on Day 8 (with +/- 2 days window), and 15 mg/kg IV on Day 15. The subcutaneous (SC) administration of 600 mg (2 injections of 2 mL CFZ533 at 150 mg/mL) every 2 weeks started on Day 29, in combination with MMF and CS up to EOS.	Tacrolimus (TAC) + Mycophenolate mofetil (MMF) + Corticosteroids (CS) up to End of Study (EOS). Initial TAC target trough were between 5-15 ng/mL during the run-in period. From randomization onwards, the TAC levels were adjusted as per local label.
Number of Participants Analyzed [units: participants]	48	47	32

Number of Participants with Treatment Emergent Adverse Events (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
TEAEs	48 (100%)	44 (93.62%)	32 (100%)
TESAEs	30 (62.5%)	29 (61.7%)	20 (62.5%)
Fatal TESAEs	1 (2.08%)	4 (8.51%)	0 (%)
TEAEs leading to discontinuation	14 (29.17%)	17 (36.17%)	8 (25%)

Percentage of patients with dose interruptions and permanent discontinuation of study treatment

Description	The number and percentage of participants with dose changes (MMF and TAC), dose interruptions (only in cases of ascites drainage), and permanent discontinuation was summarized. In the CFZ533 arms, during the immediate peri and post-transplant period, TAC was given to provide immunological coverage but TAC needed to be completely weaned off by Day 22.
Time Frame	Baseline to Month 24
Analysis Population Description	Safety Set (SAF)

	CFZ533 300 mg regimen (CFZ533 300 mg + MMF)	**CFZ533 600 mg regimen (CFZ533 600 mg + MMF)**	**TAC Control (TAC + MMF)**
Arm/Group Description	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 started on Day 29, in combination with MMF and CS up to EOS.	Loading doses of 30 mg/kg IV on Day 8 (with +/- 2 days window), and 15 mg/kg IV on Day 15. The subcutaneous (SC) administration of 600 mg (2 injections of 2 mL CFZ533 at 150 mg/mL) every 2 weeks started on Day 29, in combination with MMF and CS up to EOS.	Tacrolimus (TAC) + Mycophenolate mofetil (MMF) + Corticosteroids (CS) up to End of Study (EOS). Initial TAC target trough were between 5-15 ng/mL during the run-in period. From randomization onwards, the TAC levels were adjusted as per local label.

Number of Participants Analyzed [units: participants]	48	47	32
Percentage of patients with dose interruptions and permanent discontinuation of study treatment (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
CFZ533: Subjects with dose interrupted	8 (16.67%)	5 (10.64%)	(NaN%)
CFZ533: Subjects with permanent discontinuation of study treatment	2 (4.17%)	3 (6.38%)	(NaN%)
TAC: Subjects with dose interrupted	3 (6.25%)	3 (6.38%)	6 (18.75%)
TAC: Subjects with permanent discontinuation of study treatment	4 (8.33%)	8 (17.02%)	4 (12.5%)
MMF: Subjects with dose interrupted	18 (37.5%)	23 (48.94%)	15 (46.88%)
MMF: Subjects with permanent discontinuation of study treatment	9 (18.75%)	5 (10.64%)	1 (3.13%)

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

All collected deaths

Description	On-treatment deaths were reported from first dose of study treatment to 14 weeks after last dose of study medication (CFZ533 participants) and until 12 weeks for TAC participants, up to approx. 184 weeks. Post-treatment deaths were collected in the post treatment period from 15 weeks after last dose of study medication (CFZ533 participants, Arms 2 & 3) and from 13 weeks for TAC participants (Arm 1), up to approx. 184 weeks. These are not considered Adverse Events.
Time Frame	On-treatment deaths: Up to approximately 184 weeks. Post-treatment deaths: Up to approximately 184 weeks.

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Analysis Population Description: Safety Set (SAF)

	CFZ533 300 mg regimen (CFZ533 300 mg + MMF)	CFZ533 600 mg regimen (CFZ533 600 mg + MMF)	TAC Control (TAC + MMF)
Arm/Group Description	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 started on Day 29, in combination with MMF and CS up to EOS.	Loading doses of 30 mg/kg IV on Day 8 (with +/- 2 days window), and 15 mg/kg IV on Day 15. The subcutaneous (SC) administration of 600 mg (2 injections of 2 mL CFZ533 at 150 mg/mL) every 2 weeks started on Day 29, in combination with MMF and CS up to EOS.	Tacrolimus (TAC) + Mycophenolate mofetil (MMF) + Corticosteroids (CS) up to End of Study (EOS). Initial TAC target trough were between 5-15 ng/mL during the run-in period. From randomization onwards, the TAC levels were adjusted as per local label.
Number of Participants Analyzed [units: participants]	48	47	32
All collected deaths (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
On-treatment deaths	1 (2.08%)	3 (6.38%)	0 (%)
Post-treatment deaths	0 (%)	1 (2.27%)	0 (%)
All deaths	1 (2.08%)	4 (8.51%)	0 (%)

Safety Results

Time Frame	On-treatment adverse events and deaths were reported from first dose of study treatment to 14 weeks after last dose of study medication (CFZ533 participants) and until 12 weeks for TAC participants, up to approx. 184 weeks. Post-treatment deaths were collected in the post treatment period from 15 weeks after last dose of study medication (CFZ533 participants) and from 13 weeks for TAC participants, up to approx. 184 weeks. These are not considered Adverse Events.
Additional Description	Any sign or symptom that occurred during the conduct of the trial and safety follow-up. The safety analysis were done on the safety population, which included all randomized subjects who received at least one dose of study medication.
Source Vocabulary for Table Default	MedDRA (26.0)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	CFZ533 300 mg regimen (CFZ533 300 mg + MMF) (On-Treatment) N = 48	**CFZ533 600 mg regimen (CFZ533 600 mg + MMF) (On-Treatment) N = 47**	**TAC Control (TAC + MMF) (On-Treatment) N = 32**	**CFZ533 300 mg regimen (CFZ533 300 mg + MMF) (Post-Treatment) N = 47**	**CFZ533 600 mg regimen (CFZ533 600 mg + MMF) (Post-Treatment) N = 44**	**TAC Control (TAC + MMF) (Post-Treatment) N = 32**
Arm/Group Description	Single loading dose of 30 mg/kg IV on Day 8 (with +/- 2 days window). The subcutaneous (SC) administration of 300 mg (1 injection of 2 mL CFZ533 at 150	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	Tacrolimus (TAC) + Mycophenolate mofetil (MMF) + Corticosteroids (CS) up to End of Study (EOS). Initial TAC target trough were between 5-15 ng/mL during the run-in period.	Deaths collected in the post-treatment follow-up period (starting 15 weeks after last dose of study medication (CFZ533 participants, Arms 2 & 3) and until 13 weeks for TAC	Deaths collected in the post-treatment follow-up period (starting 15 weeks after last dose of study medication (CFZ533 participants, Arms 2 & 3) and until 13 weeks for TAC	Deaths collected in the post-treatment follow-up period (starting 15 weeks after last dose of study medication (CFZ533 participants, Arms 2 & 3) and until 13 weeks for TAC

	mg/mL) every 2 weeks started on Day 29, in combination with MMF and CS up to EOS.	weeks started on Day 29, in combination with MMF and CS up to EOS.	From randomization onwards, the TAC levels were adjusted as per local label.	participants (Arm 1)). No AEs were collected during this period.	participants (Arm 1)). No AEs were collected during this period.	participants (Arm 1)). No AEs were collected during this period.
Total Number Affected	1	3	0	0	1	0
Total Number At Risk	48	47	32	47	44	32

Serious Adverse Events

Time Frame	On-treatment adverse events and deaths were reported from first dose of study treatment to 14 weeks after last dose of study medication (CFZ533 participants) and until 12 weeks for TAC participants, up to approx. 184 weeks. Post-treatment deaths were collected in the post treatment period from 15 weeks after last dose of study medication (CFZ533 participants) and from 13 weeks for TAC participants, up to approx. 184 weeks. These are not considered Adverse Events.
Additional Description	Any sign or symptom that occurred during the conduct of the trial and safety follow-up. The safety analysis were done on the safety population, which included all randomized subjects who received at least one dose of study medication.
Source Vocabulary for Table Default	MedDRA (26.0)
Collection Approach for Table Default	Systematic Assessment

	CFZ533 300 mg regimen (CFZ533 300 mg + MMF) (On-Treatment) N = 48	**CFZ533 600 mg regimen (CFZ533 600 mg + MMF) (On-Treatment) N = 47**	**TAC Control (TAC + MMF) (On-Treatment) N = 32**	**CFZ533 300 mg regimen (CFZ533 300 mg + MMF) (Post-Treatment) N = 0**	**CFZ533 600 mg regimen (CFZ533 600 mg + MMF) (Post-Treatment) N = 0**	**TAC Control (TAC + MMF) (Post-Treatment) N = 0**

Arm/Group Description	Single loading dose of 30 mg/kg IV on Day 8 (with +/- 2 days window). The subcutaneous (SC) administration of 300 mg (1 injection of 2 mL CFZ533 at 150 mg/mL) every 2 weeks started on Day 29, in combination with MMF and CS up to EOS.	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 started on Day 29, in combination with MMF and CS up to EOS.	Tacrolimus (TAC) + Mycophenolate mofetil (MMF) + Corticosteroids (CS) up to End of Study (EOS). Initial TAC target trough were between 5-15 ng/mL during the run-in period. From randomization onwards, the TAC levels were adjusted as per local label.	Deaths collected in the post-treatment follow-up period (starting 15 weeks after last dose of study medication (CFZ533 participants, Arms 2 & 3) and until 13 weeks for TAC participants (Arm 1)). No AEs were collected during this period.	Deaths collected in the post-treatment follow-up period (starting 15 weeks after last dose of study medication (CFZ533 participants, Arms 2 & 3) and until 13 weeks for TAC participants (Arm 1)). No AEs were collected during this period.	Deaths collected in the post-treatment follow-up period (starting 15 weeks after last dose of study medication (CFZ533 participants, Arms 2 & 3) and until 13 weeks for TAC participants (Arm 1)). No AEs were collected during this period.
Total # Affected by any Serious Adverse Event	30	29	20	0	0	0
Total # at Risk by any Serious Adverse Event	48	47	32	0	0	0
Blood and lymphatic system disorders						
Febrile neutropenia	1 (2.08%)	0 (0.00%)	0 (0.00%)			
Leukopenia	2 (4.17%)	0 (0.00%)	0 (0.00%)			
Neutropenia	1 (2.08%)	0 (0.00%)	0 (0.00%)			
Pancytopenia	0 (0.00%)	1 (2.13%)	0 (0.00%)			
Cardiac disorders						
Arteriosclerosis coronary artery	1 (2.08%)	0 (0.00%)	0 (0.00%)			
Atrioventricular block	1 (2.08%)	0 (0.00%)	0 (0.00%)			
Sinus arrhythmia	0 (0.00%)	0 (0.00%)	1 (3.13%)			

Supraventricular extrasystoles	0 (0.00%)	0 (0.00%)	1 (3.13%)
Tachycardia	1 (2.08%)	0 (0.00%)	1 (3.13%)
Gastrointestinal disorders			
Abdominal pain	2 (4.17%)	0 (0.00%)	1 (3.13%)
Abdominal pain upper	1 (2.08%)	0 (0.00%)	0 (0.00%)
Appendicitis noninfective	1 (2.08%)	0 (0.00%)	0 (0.00%)
Ascites	2 (4.17%)	0 (0.00%)	2 (6.25%)
Diaphragmatic hernia	0 (0.00%)	1 (2.13%)	0 (0.00%)
Diarrhoea	0 (0.00%)	1 (2.13%)	0 (0.00%)
Enteritis	0 (0.00%)	0 (0.00%)	1 (3.13%)
Gastritis	0 (0.00%)	1 (2.13%)	0 (0.00%)
Gastrointestinal haemorrhage	0 (0.00%)	1 (2.13%)	0 (0.00%)
Haematochezia	0 (0.00%)	1 (2.13%)	0 (0.00%)
Ileus	1 (2.08%)	0 (0.00%)	0 (0.00%)
Incarcerated umbilical hernia	0 (0.00%)	0 (0.00%)	1 (3.13%)
Inguinal hernia strangulated	1 (2.08%)	0 (0.00%)	0 (0.00%)
Large intestine perforation	0 (0.00%)	0 (0.00%)	1 (3.13%)
Pancreatitis acute	1 (2.08%)	0 (0.00%)	0 (0.00%)
Salivary gland calculus	1 (2.08%)	0 (0.00%)	0 (0.00%)
Salivary gland enlargement	1 (2.08%)	0 (0.00%)	0 (0.00%)
Small intestinal obstruction	0 (0.00%)	0 (0.00%)	1 (3.13%)
Varices oesophageal	1 (2.08%)	0 (0.00%)	0 (0.00%)

Vomiting	1 (2.08%)	0 (0.00%)	0 (0.00%)
General disorders and administration site conditions			
Chest pain	0 (0.00%)	0 (0.00%)	1 (3.13%)
Multiple organ dysfunction syndrome	0 (0.00%)	1 (2.13%)	0 (0.00%)
Pyrexia	5 (10.42%)	5 (10.64%)	0 (0.00%)
Hepatobiliary disorders			
Bile duct stenosis	1 (2.08%)	1 (2.13%)	0 (0.00%)
Biliary ischaemia	1 (2.08%)	0 (0.00%)	0 (0.00%)
Biliary obstruction	0 (0.00%)	1 (2.13%)	0 (0.00%)
Biliary tract disorder	0 (0.00%)	1 (2.13%)	0 (0.00%)
Biloma	1 (2.08%)	0 (0.00%)	0 (0.00%)
Cholangitis	2 (4.17%)	1 (2.13%)	0 (0.00%)
Cholangitis acute	1 (2.08%)	1 (2.13%)	0 (0.00%)
Hepatic artery stenosis	0 (0.00%)	2 (4.26%)	0 (0.00%)
Hepatic artery thrombosis	0 (0.00%)	1 (2.13%)	0 (0.00%)
Hepatic function abnormal	1 (2.08%)	0 (0.00%)	0 (0.00%)
Hepatic haematoma	0 (0.00%)	1 (2.13%)	0 (0.00%)
Hepatic haemorrhage	0 (0.00%)	1 (2.13%)	0 (0.00%)
Hepatic mass	0 (0.00%)	1 (2.13%)	0 (0.00%)
Hepatitis cholestatic	1 (2.08%)	0 (0.00%)	0 (0.00%)
Hyperbilirubinaemia	2 (4.17%)	1 (2.13%)	0 (0.00%)

Jaundice	0 (0.00%)	0 (0.00%)	1 (3.13%)
Immune system disorders			
Graft versus host disease	0 (0.00%)	2 (4.26%)	0 (0.00%)
Liver transplant rejection	2 (4.17%)	1 (2.13%)	0 (0.00%)
Transplant rejection	4 (8.33%)	2 (4.26%)	2 (6.25%)
Infections and infestations			
Abscess	0 (0.00%)	1 (2.13%)	0 (0.00%)
Arthritis bacterial	1 (2.08%)	0 (0.00%)	0 (0.00%)
Clostridium difficile colitis	0 (0.00%)	0 (0.00%)	1 (3.13%)
COVID-19	4 (8.33%)	2 (4.26%)	2 (6.25%)
COVID-19 pneumonia	1 (2.08%)	0 (0.00%)	0 (0.00%)
Cytomegalovirus colitis	0 (0.00%)	1 (2.13%)	0 (0.00%)
Cytomegalovirus hepatitis	1 (2.08%)	0 (0.00%)	0 (0.00%)
Cytomegalovirus infection	3 (6.25%)	0 (0.00%)	0 (0.00%)
Cytomegalovirus infection reactivation	1 (2.08%)	1 (2.13%)	0 (0.00%)
Cytomegalovirus viraemia	0 (0.00%)	2 (4.26%)	1 (3.13%)
Endophthalmitis	0 (0.00%)	1 (2.13%)	0 (0.00%)
Enterococcal infection	1 (2.08%)	0 (0.00%)	0 (0.00%)
Escherichia sepsis	1 (2.08%)	0 (0.00%)	0 (0.00%)
Herpes zoster disseminated	0 (0.00%)	1 (2.13%)	0 (0.00%)
Liver abscess	1 (2.08%)	1 (2.13%)	0 (0.00%)
Oral herpes	0 (0.00%)	1 (2.13%)	0 (0.00%)

Peritonitis	2 (4.17%)	0 (0.00%)	1 (3.13%)
Peritonitis bacterial	0 (0.00%)	0 (0.00%)	1 (3.13%)
Pneumocystis jirovecii pneumonia	1 (2.08%)	1 (2.13%)	0 (0.00%)
Pneumonia	2 (4.17%)	0 (0.00%)	1 (3.13%)
Pneumonia cytomegaloviral	1 (2.08%)	0 (0.00%)	0 (0.00%)
Pyelonephritis	1 (2.08%)	0 (0.00%)	0 (0.00%)
Sepsis	1 (2.08%)	0 (0.00%)	0 (0.00%)
Septic shock	0 (0.00%)	0 (0.00%)	1 (3.13%)
Subcutaneous abscess	0 (0.00%)	1 (2.13%)	0 (0.00%)
Toxoplasmosis	1 (2.08%)	0 (0.00%)	0 (0.00%)
Urinary tract infection	0 (0.00%)	2 (4.26%)	0 (0.00%)
Wound infection	0 (0.00%)	1 (2.13%)	0 (0.00%)
Injury, poisoning and procedural complications			
Anastomotic stenosis	0 (0.00%)	0 (0.00%)	1 (3.13%)
Ankle fracture	0 (0.00%)	0 (0.00%)	1 (3.13%)
Biliary anastomosis complication	1 (2.08%)	2 (4.26%)	0 (0.00%)
Complications of transplanted liver	1 (2.08%)	0 (0.00%)	0 (0.00%)
Fall	0 (0.00%)	0 (0.00%)	1 (3.13%)
Femoral neck fracture	2 (4.17%)	0 (0.00%)	0 (0.00%)
Graft loss	0 (0.00%)	2 (4.26%)	1 (3.13%)
Incisional hernia	1 (2.08%)	1 (2.13%)	2 (6.25%)

Liver transplant failure	0 (0.00%)	1 (2.13%)	0 (0.00%)
Peripancreatic fluid collection	1 (2.08%)	0 (0.00%)	0 (0.00%)
Post procedural bile leak	0 (0.00%)	0 (0.00%)	1 (3.13%)
Seroma	0 (0.00%)	1 (2.13%)	0 (0.00%)
Stress fracture	1 (2.08%)	0 (0.00%)	0 (0.00%)
Thoracic vertebral fracture	0 (0.00%)	1 (2.13%)	0 (0.00%)
Toxicity to various agents	1 (2.08%)	0 (0.00%)	1 (3.13%)
Ulna fracture	0 (0.00%)	1 (2.13%)	0 (0.00%)
Vascular pseudoaneurysm	0 (0.00%)	2 (4.26%)	0 (0.00%)
Investigations			
Blood alkaline phosphatase increased	1 (2.08%)	1 (2.13%)	0 (0.00%)
Carbohydrate antigen 19-9 increased	1 (2.08%)	0 (0.00%)	0 (0.00%)
Hepatic enzyme increased	0 (0.00%)	3 (6.38%)	1 (3.13%)
Liver function test abnormal	1 (2.08%)	0 (0.00%)	0 (0.00%)
Liver function test increased	2 (4.17%)	0 (0.00%)	0 (0.00%)
Metabolism and nutrition disorders			
Hyperglycaemia	0 (0.00%)	0 (0.00%)	1 (3.13%)
Hyperkalaemia	0 (0.00%)	1 (2.13%)	1 (3.13%)
Hypervolaemia	0 (0.00%)	0 (0.00%)	1 (3.13%)
Hypokalaemia	1 (2.08%)	0 (0.00%)	0 (0.00%)
Hyponatraemia	0 (0.00%)	0 (0.00%)	1 (3.13%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma	2 (4.17%)	0 (0.00%)	0 (0.00%)
Cholangiocarcinoma	0 (0.00%)	1 (2.13%)	0 (0.00%)
Malignant peritoneal neoplasm	0 (0.00%)	0 (0.00%)	1 (3.13%)
Metastases to lung	0 (0.00%)	1 (2.13%)	0 (0.00%)
Squamous cell carcinoma	1 (2.08%)	1 (2.13%)	0 (0.00%)
Squamous cell carcinoma of skin	1 (2.08%)	0 (0.00%)	0 (0.00%)
Nervous system disorders			
Ischaemic stroke	1 (2.08%)	0 (0.00%)	1 (3.13%)
Lethargy	1 (2.08%)	0 (0.00%)	0 (0.00%)
Tremor	1 (2.08%)	0 (0.00%)	0 (0.00%)
Product issues			
Device dislocation	0 (0.00%)	1 (2.13%)	1 (3.13%)
Psychiatric disorders			
Hallucination	0 (0.00%)	1 (2.13%)	0 (0.00%)
Mental status changes	0 (0.00%)	2 (4.26%)	0 (0.00%)
Suicide attempt	0 (0.00%)	0 (0.00%)	1 (3.13%)
Renal and urinary disorders			
Acute kidney injury	2 (4.17%)	1 (2.13%)	0 (0.00%)
Renal cyst ruptured	1 (2.08%)	0 (0.00%)	0 (0.00%)

Respiratory, thoracic and mediastinal disorders			
Cough	1 (2.08%)	0 (0.00%)	0 (0.00%)
Dyspnoea	2 (4.17%)	0 (0.00%)	0 (0.00%)
Hypoxia	1 (2.08%)	1 (2.13%)	0 (0.00%)
Interstitial lung disease	1 (2.08%)	0 (0.00%)	0 (0.00%)
Pleural effusion	0 (0.00%)	1 (2.13%)	0 (0.00%)
Pneumothorax	1 (2.08%)	0 (0.00%)	0 (0.00%)
Pulmonary mass	1 (2.08%)	0 (0.00%)	0 (0.00%)
Respiratory failure	1 (2.08%)	0 (0.00%)	0 (0.00%)
Skin and subcutaneous tissue disorders			
Petechiae	0 (0.00%)	1 (2.13%)	0 (0.00%)
Rash	0 (0.00%)	1 (2.13%)	0 (0.00%)
Rash maculo-papular	1 (2.08%)	0 (0.00%)	0 (0.00%)
Vascular disorders			
Circulatory collapse	0 (0.00%)	1 (2.13%)	0 (0.00%)
Haematoma	2 (4.17%)	0 (0.00%)	0 (0.00%)
Hypotension	0 (0.00%)	1 (2.13%)	0 (0.00%)

Other (Not Including Serious) Adverse Events

Time Frame	On-treatment adverse events and deaths were reported from first dose of study treatment to 14 weeks after last dose of study medication (CFZ533 participants) and until 12 weeks for TAC participants, up to approx. 184 weeks. Post-treatment deaths were collected in the post treatment period from 15 weeks after last dose of study medication (CFZ533 participants) and from 13 weeks for TAC participants, up to approx. 184 weeks. These are not considered Adverse Events.
Additional Description	Any sign or symptom that occurred during the conduct of the trial and safety follow-up. The safety analysis were done on the safety population, which included all randomized subjects who received at least one dose of study medication.
Source Vocabulary for Table Default	MedDRA (26.0)
Collection Approach for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	CFZ533 300 mg regimen (CFZ533 300 mg + MMF) (On-Treatment) N = 48	**CFZ533 600 mg regimen (CFZ533 600 mg + MMF) (On-Treatment) N = 47**	**TAC Control (TAC + MMF) (On-Treatment) N = 32**	**CFZ533 300 mg regimen (CFZ533 300 mg + MMF) (Post-Treatment) N = 0**	**CFZ533 600 mg regimen (CFZ533 600 mg + MMF) (Post-Treatment) N = 0**	**TAC Control (TAC + MMF) (Post-Treatment) N = 0**
Arm/Group Description	Single loading dose of 30 mg/kg IV on Day 8 (with +/- 2 days window). The subcutaneous (SC) administration of 300 mg (1 injection of 2 mL CFZ533 at 150 mg/mL) every 2	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 started on	Tacrolimus (TAC) + Mycophenolate mofetil (MMF) + Corticosteroids (CS) up to End of Study (EOS). Initial TAC target trough were between 5-15 ng/mL during the run-in period. From	Deaths collected in the post-treatment follow-up period (starting 15 weeks after last dose of study medication (CFZ533 participants, Arms 2 & 3) and until 13 weeks for TAC participants (Arm	Deaths collected in the post-treatment follow-up period (starting 15 weeks after last dose of study medication (CFZ533 participants, Arms 2 & 3) and until 13 weeks for TAC participants (Arm	Deaths collected in the post-treatment follow-up period (starting 15 weeks after last dose of study medication (CFZ533 participants, Arms 2 & 3) and until 13 weeks for TAC participants (Arm

	weeks started on Day 29, in combination with MMF and CS up to EOS.	Day 29, in combination with MMF and CS up to EOS.	randomization onwards, the TAC levels were adjusted as per local label.	1)). No AEs were collected during this period.	1)). No AEs were collected during this period.	1)). No AEs were collected during this period.
Total # Affected by any Other Adverse Event	45	42	30	0	0	0
Total # at Risk by any Other Adverse Event	48	47	32	0	0	0
Blood and lymphatic system disorders						
Anaemia	4 (8.33%)	5 (10.64%)	4 (12.50%)			
Leukopenia	17 (35.42%)	16 (34.04%)	9 (28.13%)			
Lymphopenia	2 (4.17%)	5 (10.64%)	1 (3.13%)			
Neutropenia	14 (29.17%)	10 (21.28%)	4 (12.50%)			
Thrombocytopenia	0 (0.00%)	3 (6.38%)	3 (9.38%)			
Cardiac disorders						
Palpitations	0 (0.00%)	1 (2.13%)	2 (6.25%)			
Tachycardia	2 (4.17%)	4 (8.51%)	0 (0.00%)			
Eye disorders						
Vision blurred	3 (6.25%)	0 (0.00%)	0 (0.00%)			
Gastrointestinal disorders						
Abdominal distension	6 (12.50%)	1 (2.13%)	3 (9.38%)			
Abdominal pain	5 (10.42%)	7 (14.89%)	8 (25.00%)			
Abdominal pain upper	5 (10.42%)	5 (10.64%)	1 (3.13%)			

Ascites	8 (16.67%)	2 (4.26%)	3 (9.38%)
Constipation	6 (12.50%)	4 (8.51%)	4 (12.50%)
Diarrhoea	12 (25.00%)	8 (17.02%)	9 (28.13%)
Intra-abdominal fluid collection	1 (2.08%)	1 (2.13%)	2 (6.25%)
Nausea	8 (16.67%)	4 (8.51%)	5 (15.63%)
Vomiting	7 (14.58%)	3 (6.38%)	4 (12.50%)
General disorders and administration site conditions			
Asthenia	2 (4.17%)	2 (4.26%)	3 (9.38%)
Fatigue	5 (10.42%)	5 (10.64%)	5 (15.63%)
Oedema peripheral	12 (25.00%)	6 (12.77%)	4 (12.50%)
Peripheral swelling	1 (2.08%)	1 (2.13%)	2 (6.25%)
Pyrexia	7 (14.58%)	8 (17.02%)	5 (15.63%)
Hepatobiliary disorders			
Bile duct stenosis	2 (4.17%)	4 (8.51%)	0 (0.00%)
Cholangitis	1 (2.08%)	1 (2.13%)	2 (6.25%)
Portal vein stenosis	1 (2.08%)	0 (0.00%)	2 (6.25%)
Immune system disorders			
Liver transplant rejection	1 (2.08%)	1 (2.13%)	2 (6.25%)
Infections and infestations			
Cellulitis	0 (0.00%)	0 (0.00%)	2 (6.25%)
COVID-19	15 (31.25%)	15 (31.91%)	8 (25.00%)

Cystitis	1 (2.08%)	2 (4.26%)	3 (9.38%)
Cytomegalovirus infection	8 (16.67%)	5 (10.64%)	4 (12.50%)
Cytomegalovirus infection reactivation	2 (4.17%)	5 (10.64%)	2 (6.25%)
Cytomegalovirus viraemia	5 (10.42%)	6 (12.77%)	2 (6.25%)
Nasopharyngitis	1 (2.08%)	3 (6.38%)	0 (0.00%)
Oral herpes	0 (0.00%)	1 (2.13%)	2 (6.25%)
Sinusitis	0 (0.00%)	0 (0.00%)	2 (6.25%)
Upper respiratory tract infection	1 (2.08%)	1 (2.13%)	2 (6.25%)
Urinary tract infection	4 (8.33%)	4 (8.51%)	7 (21.88%)
Injury, poisoning and procedural complications			
Contusion	0 (0.00%)	1 (2.13%)	2 (6.25%)
Overdose	0 (0.00%)	0 (0.00%)	2 (6.25%)
Investigations			
Alanine aminotransferase increased	2 (4.17%)	3 (6.38%)	0 (0.00%)
Blood alkaline phosphatase increased	6 (12.50%)	6 (12.77%)	1 (3.13%)
Blood creatinine increased	1 (2.08%)	0 (0.00%)	4 (12.50%)
Gamma-glutamyltransferase increased	4 (8.33%)	2 (4.26%)	1 (3.13%)
Hepatic enzyme increased	1 (2.08%)	4 (8.51%)	2 (6.25%)
Liver function test increased	8 (16.67%)	4 (8.51%)	2 (6.25%)
Weight increased	1 (2.08%)	3 (6.38%)	0 (0.00%)

Metabolism and nutrition disorders			
Cell death	3 (6.25%)	0 (0.00%)	0 (0.00%)
Decreased appetite	2 (4.17%)	3 (6.38%)	0 (0.00%)
Hyperglycaemia	2 (4.17%)	2 (4.26%)	2 (6.25%)
Hyperkalaemia	2 (4.17%)	2 (4.26%)	4 (12.50%)
Hypertriglyceridaemia	0 (0.00%)	6 (12.77%)	0 (0.00%)
Hypoglycaemia	1 (2.08%)	1 (2.13%)	3 (9.38%)
Hypokalaemia	4 (8.33%)	3 (6.38%)	1 (3.13%)
Hypomagnesaemia	1 (2.08%)	3 (6.38%)	1 (3.13%)
Iron deficiency	3 (6.25%)	0 (0.00%)	1 (3.13%)
Vitamin D deficiency	0 (0.00%)	1 (2.13%)	2 (6.25%)
Musculoskeletal and connective tissue disorders			
Arthralgia	9 (18.75%)	6 (12.77%)	2 (6.25%)
Back pain	8 (16.67%)	5 (10.64%)	4 (12.50%)
Flank pain	0 (0.00%)	3 (6.38%)	1 (3.13%)
Muscle spasms	0 (0.00%)	1 (2.13%)	2 (6.25%)
Pain in extremity	2 (4.17%)	2 (4.26%)	2 (6.25%)
Nervous system disorders			
Headache	5 (10.42%)	10 (21.28%)	7 (21.88%)
Syncope	4 (8.33%)	1 (2.13%)	0 (0.00%)
Tremor	5 (10.42%)	6 (12.77%)	7 (21.88%)

Psychiatric disorders			
Alcoholism	1 (2.08%)	3 (6.38%)	0 (0.00%)
Anxiety	5 (10.42%)	3 (6.38%)	2 (6.25%)
Insomnia	6 (12.50%)	3 (6.38%)	3 (9.38%)
Renal and urinary disorders			
Acute kidney injury	2 (4.17%)	0 (0.00%)	3 (9.38%)
Dysuria	4 (8.33%)	1 (2.13%)	1 (3.13%)
Haematuria	0 (0.00%)	1 (2.13%)	2 (6.25%)
Proteinuria	0 (0.00%)	1 (2.13%)	2 (6.25%)
Urinary incontinence	0 (0.00%)	0 (0.00%)	2 (6.25%)
Respiratory, thoracic and mediastinal disorders			
Cough	7 (14.58%)	5 (10.64%)	0 (0.00%)
Dyspnoea	4 (8.33%)	5 (10.64%)	3 (9.38%)
Pleural effusion	5 (10.42%)	2 (4.26%)	3 (9.38%)
Skin and subcutaneous tissue disorders			
Actinic keratosis	0 (0.00%)	0 (0.00%)	3 (9.38%)
Night sweats	1 (2.08%)	3 (6.38%)	0 (0.00%)
Pruritus	2 (4.17%)	2 (4.26%)	4 (12.50%)
Rash	3 (6.25%)	5 (10.64%)	1 (3.13%)
Vascular disorders			
Hypertension	3 (6.25%)	3 (6.38%)	6 (18.75%)

Hypotension	3 (6.25%)	2 (4.26%)	1 (3.13%)

Other Relevant Findings

None

Conclusion:

This was a multicenter, open-label, active-controlled study to evaluate the efficacy, safety, tolerability, PK and PD of two CFZ533 maintenance doses in de novo liver transplant recipients. The study was designed as a randomized, 36-month clinical trial comprised of a screening period (up to 2 months) including successful liver transplantation (LTx); a run-in treatment period following successful transplantation that ended on the day of randomization or randomization failure; 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; the long-term extension period (Treatment Period 3) starting post Month 24 until the end of the study (EOS); and a minimum 12-week safety follow-up period for all patients after EOS.

Patients were assigned to one of the following three treatment arms in a 2:3:3 ratio: Arm 1 - TAC Control: TAC + MMF + CS up to EOS; Arm 2 - CFZ533 600 mg regimen in combination with MMF and CS up to EOS; Arm 3 - CFZ533 300 mg regimen in combination with MMF and CS up to EOS.

The primary objective was 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. The primary objective would be demonstrated, if the composite efficacy failure rate difference between any of the two CFZ533 arms and the TAC arm is below to the pre-defined margin (0.15) with probability >80%. Hence, the primary endpoint was met for CFZ533 300 mg and was not met for CFZ533 600 mg.

As expected in this high morbid population, almost all patients in the three treatment arms had at least one TEAE. Serious adverse events which were mostly driven by infections were reported in 30 patients (62.5%) in the CFZ533 300 mg arm, 29 patients (61.7%) in the CFZ533 600 mg arm, and 20 patients (62.5%) in the TAC arm.

There were 4 on-treatment deaths (1 death in CFZ533 300 mg arm, 3 deaths in CFZ533 600 mg arm and none in TAC arm) and 1 death not on-treatment in CFZ533 600 mg arm. With the exception of pneumocystis jirovecii pneumonia which was considered as related to study medication in the CFZ533 600 mg arm, all the deaths were not study drug related.

Although 5 deaths occurred in the CFZ533 arms no new safety signals were observed for CFZ533 in the study.

The study CCFZ533A2202 was terminated based on a higher proportion of patients randomized in either of the CFZ533 arms who experienced at Month 12 composite efficacy failure event as compared to TAC: 8/48 (16.7%) in the CFZ533 300 mg arm, 12/48 (25.0%) in CFZ533 600 mg arm, as compared to 3/32 (9.4%) in the TAC arm.

Date of Clinical Trial Report

09-Nov-2023