NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

CFZ533

Trial Indication(s)

de novo renal transplant patients

Protocol Number

CCFZ533X2201

Protocol Title

A 12-month randomized, multiple dose, open-label, study evaluating safety, tolerability, pharmacokinetics/pharmacodynamics (PK/PD) and efficacy of an anti-CD40 monoclonal antibody, CFZ533, in combination with mycophenolate mofetil (MMF) and corticosteroids (CS), with and without tacrolimus (Tac), in de novo renal transplant recipients

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase II

Study Start/End Dates

Study Start Date: February 2015 (Actual)

Primary Completion Date: November 2017 (Actual)
Study Completion Date: November 2017 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

Study CCFZ533X2201 was a randomized, two-part, 6- and 12-month (Part 1 and Part 2, respectively), sequential, adaptive, controlled, open-label, multicenter, and clinical proof-of-concept (POC) study. Study Part 1 focused on measuring the multiple-dose safety, tolerability, PK, and PD of both IV and SC CFZ533 when administered with the SoC treatment regimen. The SoC consisted of concentration-controlled tacrolimus (Tac), a calcineurin inhibitor (CNI), combined with mycophenolate mofetil (MMF), and corticosteroids (CS). Study Part 1 had only Arm 1: CFZ533 (3 mg/kg) + Tac + MMF + CS + CNI. A total of 7 patients who met the inclusion criteria were enrolled within approximately 12 hours pre-transplant. The first dose of 3 mg/kg CFZ533 was administered IV pre-transplant or intra operatively and subsequent 4 doses of 3 mg/kg CFZ533 were administered SC over a period of 3 months (on Days 15, 29, 43 and 71) on top of Tac, MMF and CS. The decision to proceed to Part 2 was made by the Sponsor with the recommendation from the DMC. Study Part 2 investigated efficacy, safety, tolerability, PK and PD of CFZ533 in the absence of Tac starting from transplantation on Day 1. A total of 52 patients who met the inclusion criteria were randomized in a 2:1 fashion within 24 hours pre-transplant to receive the assigned treatment in one of the 2 treatment arms: Arm 2A (34 patients) = Basiliximab + CFZ533 + MMF + CS and Arm 2B Control/SoC (18 patients) = Basiliximab + Tac + MMF + CS. In Part 2 of the study, interim analyses were performed for all safety/tolerability, including tBPAR, AEs, SAEs, laboratory assessments, vital signs and PK/PD data when all patients completed Month 3, 6, and 9 visits. The decision to continue the arms for the entire 12 months period (as planned) was made by the Sponsor with recommendation from the DMC.

Centers

14 centers in 4 countries: United States(6), Germany(4), Netherlands(3), Brazil(1)

Objectives:

Primary Objectives: To assess the safety, tolerability and PK of multiple IV and SC doses of CFZ533 in combination with MMF, CS, and Tac (standard exposure) in *de novo* renal transplant patients over the treatment and follow-up period (Part 1). To assess the potential for CFZ533 to act as the primary immunosuppressant in a CNI-free regimen with MMF in *de novo* renal transplant patients as assessed by tBPAR at Month 3 post-transplantation (Part 2)
Secondary Objectives: Part 1: To quantify the magnitude and duration of peripheral blood CD40 occupancy (free CD40 and total CD40 on B cells). To quantify the change from baseline and recovery of peripheral blood total soluble CD40 and total soluble CD154. To evaluate the immunogenicity of CFZ533 via the quantitative analysis of anti-CFZ533 antibodies. Part 2: To assess the safety and tolerability of CFZ533 administered chronically in combination with MMF and CS against a control of tacrolimus, MMF and CS up to 3 months against a control. To assess the pharmacokinetics of multiple IV doses of CFZ533 during the 12-month treatment period. To quantify the magnitude and duration of peripheral blood CD40 occupancy (free CD40 and total CD40 on B cells) during the treatment period following multiple IV doses of CFZ533. To compare renal function in CFZ533 treatment arm to control over 12 months post transplantation as assessed by estimated eGFR using MDRD. To evaluate the immunogenicity of multiple IV doses of CFZ533 via the quantitative analysis of anti-CFZ533 antibodies. To quantify the change from baseline and recovery of peripheral blood total soluble CD40 during the treatment period following multiple IV doses of CFZ533

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

Part 1: 3 mg/kg CFZ533 was administered IV pre-transplant or intra operatively on Day 1 and subsequently CFZ533 SC was administered on Days 15, 29, 43, and 71 for a period of 3 months. A total of 5 doses were administered. Part 2: 10 mg/kg CFZ533 was administered IV pre-transplant or intra operatively on Day 1 and subsequently CFZ533 IV was administered for 12 months on study Days 3, 7, 15, 29, 43, 57 and thereafter monthly until Month 12 (Days 85, 113, 141, 169, 197, 225, 253, 281, 309, and 337). A total of 17 doses were administered.

Statistical Methods

Primary variable: tBPAR
The posterior mean tBPAR rate was presented together with the 95% credible interval, the number of patients with tBPAR and the posterior probabilities of being above the thresholds, 10%, 15%, 20%, and 25%. A plot of the posterior probability distribution for the tBPAR rate was provided.
The pre-defined success criteria was considered to be a tBPAR rate difference between the CFZ533 arm and the control group of less than 20 percentage points with at least 60% level of proof.

Study Population: Key Inclusion/Exclusion Criteria

Main Inclusion Criteria:
-Written informed consent must be obtained before any assessment is performed.
- Recipients of a kidney transplant from a heart-beating deceased, living unrelated or non-human leukocyte antigen (HLA) identical living related donor.
- Recipients of a kidney with a cold ischemia time (CIT) < 30 hours.

Main Exclusion Criteria:
- Recipients of an organ from a non-heart beating donor.
- ABO incompatible or complement-dependent lymphocytotoxic (CDC) crossmatch positive transplant.
- Subjects receiving a second kidney allograft, unless the first allograft was lost due to surgical complication.
- Subjects at high immunological risk for rejection
- Subjects at risk for tuberculosis (TB)
- Subject with severe systemic infections, current or within the two weeks prior to randomization/enrollment.
- Any additional contraindication to the use of tacrolimus or mycophenolate mofetil according to the national labeling information of these products (see local product label).

Participant Flow Table

Overall Study

	CFZ533 + TAC + MMF (part 1)	CFZ533 + MMF (part 2)	Tac + MMF (part 2)
Started	7	34	18
Completed	6	30	13
Not Completed	1	4	5
Graft Loss	0	0	2
Withdrawal by Subject	0	0	2
Lost to Follow-up	0	0	1

Lack of Efficacy	0	1	0
Physician Decision	1	3	0

Baseline Characteristics

	CFZ533 + TAC + MMF (part 1)	CFZ533 + MMF (part 2)	Tac + MMF (part 2)	Total
Number of Participants [units: participants]	7	34	18	59
Age Continuous (units: years) Mean ± Standard Deviation				
	48.1±9.30	49.0±15.79	53.4±18.01	50.1±15.91
Sex: Female, Male (units: participants) Count of Participants (Not Applicable)				
Female	3	8	6	17
Male	4	26	12	42
Ethnicity (NIH/OMB) (units:) Count of Participants (Not Applicable)				
Hispanic or Latino	0	1	0	1
Not Hispanic or Latino	2	20	9	31
Unknown or Not Reported	5	13	9	27

Summary of Efficacy

Primary Outcome Result(s)

Mean Cmax Pharmacokinetic Parameter- Part I

	CFZ533 + TAC + MMF (part 1)
Number of Participants Analyzed [units: participants]	7
Mean Cmax Pharmacokinetic Parameter- Part I (units: ug/mL) Mean ± Standard Deviation	66.3 ± 12.3

Mean Tmax Pharmacokinetic Parameter - Part I

	CFZ533 + TAC + MMF (part 1)
Number of Participants Analyzed [units: participants]	7
Mean Tmax Pharmacokinetic Parameter - Part I (units: day) Median (Full Range)	0.237 (0 to 1.02)

Mean AUClast Pharmacokinetic Parameter - Part I

	CFZ533 + TAC + MMF (part 1)
Number of Participants Analyzed [units: participants]	7
Mean AUClast Pharmacokinetic Parameter - Part I (units: day*ug/mL) Mean ± Standard Deviation	
	367 ± 52.0

Efficacy as defined by the frequency and severity (Banff classification) of treated biopsy proven acute rejection (tBPAR) adjudicated data - Part II

	CFZ533 + MMF (part 2)	Tac + MMF (part 2)
Number of Participants Analyzed [units: participants]	33	18
Efficacy as defined by the frequency and severity (Banff classification) of treated biopsy proven acute rejection (tBPAR) adjudicated data - Part II (units: events)		
Month 3	6	2
Month 6	7	3
Month 9	7	3
Month 12	7	3

Statistical Analysis

Groups	CFZ533 + MMF (part 2), Tac + MMF (part 2)	
P Value	0.8976	
Method	Other Bayesian posterior probability	Posterior probability that the composite efficacy failure difference between CFZ533 and Tac is < 20%.
Mean Difference (Final Values)	0.095	Month 3
95 % Confidence Interval 2-Sided	-0.067 to 0.263	

Statistical Analysis

Groups	CFZ533 + MMF (part 2), Tac + MMF (part 2)	
P Value	0.8836	
Method	Other Bayesian posterior probability	Posterior probability that the composite efficacy failure difference between CFZ533 and Tac is < 20%.
Mean Difference (Final Values)	0.093	Month 6
95 % Confidence Interval 2-Sided	-0.084 to 0.271	

Statistical Analysis

Groups	CFZ533 + MMF (part 2), Tac + MMF (part 2)
P Value	0.8822

Method	Other Bayesian posterior probability	Posterior probability that the composite efficacy failure difference between CFZ533 and Tac is < 20%.
Mean Difference (Final Values)	0.093	Month 9
95 % Confidence Interval 2-Sided	-0.085 to 0.272	

Statistical Analysis

Groups	CFZ533 + MMF (part 2), Tac + MMF (part 2)	
P Value	0.8821	
Method	Other Bayesian posterior probability	Posterior probability that the composite efficacy failure difference between CFZ533 and Tac is < 20%.
Mean Difference (Final Values)	0.093	Month 12
95 % Confidence Interval 2-Sided	-0.087 to 0.273	

Secondary Outcome Result(s)

Total soluble CD40 and total soluble CD154 concentrations in plasma - Part 1

	sCD40 (part I)	sCD154
Number of Participants Analyzed [units: participants]	7	7

Total soluble CD40 and total soluble CD154 concentrations in plasma - Part 1
(units: ng/ml)
Mean ± Standard Deviation

Baseline	4.03 ± 4.08	0.125 ± 0.007
Day 1	8.86 ± 0.0585	0.0585 ± 0.0711
Day 2	16.7 ± 4.51	0.139 ± 0.193
Day 3	24.8 ± 4.47	0.157 ± 0.235
Day 4	31.3 ± 6.34	0.241 ± 0.418
Day 8	54.0 ± 11.2	0.399 ± 0.636
Day 15	84.1 ± 13.8	0.0879 ± 0.139
Day 22	102 ± 13.9	0.0500 ± 0.132
Day 29	120 ± 15.7	0.225 ± 0.504
Day 36	128 ± 19.2	0.116 ± 0.2
Day 43	145 ± 25.6	0.0193 ± 0.0474
Day 50	156 ± 6.35	0.0478 ± 0.0687
Day 57	161 ± 21.2	0 ± 0
Day 64	163 ± 24.2	0.0316 ± 0.0492
Day 71	156 ± 19.2	0.0148 ± 0.0363
Day 85	168 ± 21.4	0.0139 ± 0.0340
Day 99	155 ± 23.3	0 ± 0
Day 113	85.7 ± 47.9	0.0668 ± 0.164

Day 127	12.2 ± 15.7	0.0488 ± 0.0697
EoS	0.918 ± 0.330	0.0184 ± 0.0411

Free CD40 and total CD40 on B cells - Part II

	Free CD40 on whole blood B ceels	Total CD40 on whole blood B cells
Number of Participants Analyzed [units: participants]	26	29
Free CD40 and total CD40 on B cells - Part II (units: MESF) Mean ± Standard Deviation		
CFZ553 + MMF (Baseline)	30836.00 ± 13648.69	12778.80 ± 7873.76
CFZ553 + MMF (D1 - 6h post dose)	1623.81 ± 1359.85	13806.90 ± 7185.66
CFZ553 + MMF (D15)	799.62 ± 762.38	15160.38 ± 7398.57
CFZ553 + MMF (D 29)	817.63 ± 1540.16	13299.60 ± 6330.89
CFZ553 + MMF (D 57)	597.13 ± 523.55	12234.38 ± 6943.13
CFZ553 + MMF (D 85)	635.47 ± 614.68	9330.86 ± 8484.46
CFZ553 + MMF (D 197)	3699.0 ± 7298.98	2820.72 ± 2347.11
CFZ553 + MMF (253)	2667.38 ± 6146.86	1427.14 ± 740.48
CFZ553 + MMF (EoS)	176.17 ± 266.82	1069.67 ± 809.12

Tac + MMF (Baseline)	31508.33 ± 12759.49	14581.43 ± 9342.79
Tac + MMF (D1 - 6h post dose)	26437.65 ± 11930.50	13715.00 ± 8293.33
Tac + MMF (D15)	24441.67 ± 9125.93	13707.14 ± 6770.14
Tac + MMF (D29)	27840.00 ± 12106.72	12698.75 ± 6002.96
Tac + MMF (D57)	27994.29 ± 12004.57	12583.85 ± 6210.07
Tac + MMF (D85)	25044.00 ± 10896.65	8701.54 ± 4183.00
Tac + MMF (D197)	21360.00 ± 3155.67	2067.60 ± 1617.28
Tac + MMF (D253)	15752.75 ± 7145.32	1750.50 ± 1005.84
Tac + MMF (EoS)	21200.00 ± 4407.95	6276.17 ± 11271.20

Anti-CFZ533 antibodies - Part I

	CFZ533 + TAC + MMF (part 1)
Number of Participants Analyzed [units: participants]	7
Anti-CFZ533 antibodies - Part I (units: anti-CFZ533 antibodies)	
	0

Anti-CFZ533 antibodies - Part II

	CFZ533 + MMF (part 2)	Tac + MMF (part 2)
Number of Participants Analyzed [units: participants]	34	18
Anti-CFZ533 antibodies - Part II (units: anti-CFZ533 antibodies)		
Screening	0	0
Baseline	0	
Day 141	0	0
Day 225	0	0
Day 309	0	0
Study Completion	0	0

eGFR - Part II

	CFZ533 + MMF (part 2)	Tac + MMF (part 2)
Number of Participants Analyzed [units: participants]	32	18
eGFR - Part II (units: ml/min) Mean (90% Confidence Interval)		
Day 1	9.8 (8.3 to 11.3)	9.7 (7.7 to 11.8)
Day 29	55.6 (50.4 to 60.7)	44.3 (37.2 to 51.4)

Day 337	58.2 (52.2 to 64.2)	44.2 (36.1 to 52.3)

CFZ533 plasma PK concentrations - Part II

	CFZ533 + MMF (part 2)
Number of Participants Analyzed [units: participants]	32
CFZ533 plasma PK concentrations - Part II (units: ug/mL) Mean ± Standard Deviation	
Day 84	247 ± 58.2
Day 112	211 ± 51.8
Day 140	178 ± 54.9
Day 168	157 ± 57.4
Day 196	148 ± 53.1
Day 224	147 ± 53.8
Day 252	151 ± 35.2
Day 280	160 ± 87.7
Day 308	132 ± 42.5
Day 336	156 ± 85.2
End of study	133 ± 57.8

Total sCD40 plasma concentrations - Part II

	CFZ533 + MMF (part 2)	Tac + MMF (part 2)

Number of Participants Analyzed [units: participants]	32	17
Total sCD40 plasma concentrations - Part II (units: ng/mL) Mean ± Standard Deviation		
Baseline	3.02 ± 2.44	3.67 ± 2.15
Day 1	6.95 ± 4.29	1.16 ± 1.15
Day 4	24.6 ± 11.0	1.16 ± 1.15
Day 15	69.6 ± 21.5	0.869 ± 1.55
Day 29	101 ± 18.9	0.362 ± 0.0746
Day 57	140 ± 17.4	0.438 ± 0.316
Day 85	189 ± 76.4	0.429 ± 0.324
Day 113	215 ± 75.5	0.391 ± 0.129
Day 141	237 ± 93.1	0.453 ± 0.271
Day 169	238 ± 80.3	0.537 ± 0.215
Day 197	253 ± 81.3	0.423 ± 0.0908
Day 225	258 ± 77.7	0.452 ± 0.119
Day 253	236 ± 36.5	0.457 ± 0.0800
Day 281	273 ± 71.3	0.455 ± 0.0789
Day 309	286 ± 66.0	0.454 ± 0.0957
Day 337	298 ± 57.4	0.411 ± 0.0581
End of Study	303 ± 59.7	0.959 ± 1.88

Summary of Safety

Safety Results

All-Cause Mortality

	CFZ533 + TAC + MMF (part 1) N = 7	CFZ533 + MMF (part 2) N = 34	Tac + MMF (part 2) N = 18	Total N = 59
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse Events (AEs) are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All AEs reported in this record are from date of First Patient First Treatment until Last Patient Last Visit) up to approximately 3 years.
Source Vocabulary for Table Default	MedDRA (20.1)
Assessment Type for Table Default	Systematic Assessment

	CFZ533 + TAC + MMF (part 1) N = 7	CFZ533 + MMF (part 2) N = 34	Tac + MMF (part 2) N = 18	Total N = 59
Total participants affected	4 (57.14%)	21 (61.76%)	12 (66.67%)	37 (62.71%)

Blood and lymphatic system disorders				
Leukopenia	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Pancytopenia	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Cardiac disorders				
Atrial fibrillation	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Tricuspid valve incompetence	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Eye disorders				
Photophobia	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Vision blurred	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Gastrointestinal disorders				
Abdominal pain	1 (14.29%)	1 (2.94%)	0 (0.00%)	2 (3.39%)
Diarrhoea	1 (14.29%)	1 (2.94%)	1 (5.56%)	3 (5.08%)
Diarrhoea haemorrhagic	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Gastrointestinal inflammation	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Inguinal hernia	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Mouth ulceration	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Nausea	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Pancreatitis	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Retroperitoneal haematoma	0 (0.00%)	2 (5.88%)	0 (0.00%)	2 (3.39%)
Vomiting	2 (28.57%)	0 (0.00%)	1 (5.56%)	3 (5.08%)
Immune system disorders				

Kidney transplant rejection	0 (0.00%)	5 (14.71%)	1 (5.56%)	6 (10.17%)
Transplant rejection	0 (0.00%)	2 (5.88%)	0 (0.00%)	2 (3.39%)
Infections and infestations				
Bacteraemia	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Cytomegalovirus infection	0 (0.00%)	3 (8.82%)	2 (11.11%)	5 (8.47%)
Encephalitis	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Enterobacter bacteraemia	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Gastroenteritis	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Gastrointestinal infection	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Hepatitis C	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Pneumocystis jirovecii pneumonia	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Polyomavirus-associated nephropathy	0 (0.00%)	4 (11.76%)	1 (5.56%)	5 (8.47%)
Pyelonephritis	0 (0.00%)	2 (5.88%)	3 (16.67%)	5 (8.47%)
Renal cyst infection	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Urosepsis	0 (0.00%)	0 (0.00%)	2 (11.11%)	2 (3.39%)
Injury, poisoning and procedural complications				
Arteriovenous fistula aneurysm	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Complications of transplanted kidney	1 (14.29%)	1 (2.94%)	2 (11.11%)	4 (6.78%)
Delayed graft function	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Graft loss	0 (0.00%)	0 (0.00%)	2 (11.11%)	2 (3.39%)

Incarcerated incisional hernia	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Incisional hernia	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Transplant dysfunction	0 (0.00%)	1 (2.94%)	1 (5.56%)	2 (3.39%)
Transplant failure	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Investigations				
Amylase increased	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Blood creatinine increased	0 (0.00%)	1 (2.94%)	1 (5.56%)	2 (3.39%)
White blood cell count decreased	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Metabolism and nutrition disorders				
Dehydration	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Hyperglycaemia	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Hyperkalaemia	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Basosquamous carcinoma	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Squamous cell carcinoma	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Nervous system disorders				
Headache	1 (14.29%)	1 (2.94%)	0 (0.00%)	2 (3.39%)
Psychiatric disorders				
Mental status changes	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)

Renal and urinary disorders				
Acute kidney injury	0 (0.00%)	1 (2.94%)	1 (5.56%)	2 (3.39%)
Renal tubular necrosis	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Urinary retention	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Respiratory, thoracic and mediastinal disorders				
Cough	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Pneumothorax	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Pulmonary embolism	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Vascular disorders				
Deep vein thrombosis	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Hypertension	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Hypertensive crisis	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Lymphocele	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Pelvic venous thrombosis	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)

Other Adverse Events by System Organ Class

Time Frame	Adverse Events (AEs) are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All AEs reported in this record are from date of First Patient First Treatment until Last Patient Last Visit) up to approximately 3 years.
Source Vocabulary for Table Default	MedDRA (20.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	2%

	CFZ533 + TAC + MMF (part 1) N = 7	CFZ533 + MMF (part 2) N = 34	Tac + MMF (part 2) N = 18	Total N = 59
Total participants affected	7 (100.00%)	33 (97.06%)	18 (100.00%)	58 (98.31%)
Blood and lymphatic system disorders				
Anaemia	1 (14.29%)	3 (8.82%)	4 (22.22%)	8 (13.56%)
Iron deficiency anaemia	0 (0.00%)	1 (2.94%)	1 (5.56%)	2 (3.39%)
Leukocytosis	1 (14.29%)	3 (8.82%)	2 (11.11%)	6 (10.17%)
Leukopenia	1 (14.29%)	13 (38.24%)	3 (16.67%)	17 (28.81%)
Lymphopenia	0 (0.00%)	2 (5.88%)	0 (0.00%)	2 (3.39%)
Microcytic anaemia	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Nephrogenic anaemia	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Neutropenia	0 (0.00%)	1 (2.94%)	2 (11.11%)	3 (5.08%)
Normocytic anaemia	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Pancytopenia	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Polycythaemia	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Thrombocytopenia	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Thrombocytosis	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Cardiac disorders				
Angina pectoris	0 (0.00%)	1 (2.94%)	1 (5.56%)	2 (3.39%)
Arrhythmia	0 (0.00%)	2 (5.88%)	1 (5.56%)	3 (5.08%)
Atrial fibrillation	0 (0.00%)	2 (5.88%)	1 (5.56%)	3 (5.08%)
Bradycardia	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)

Extrasystoles	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Myocardial infarction	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Palpitations	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Sinus tachycardia	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Tachycardia	2 (28.57%)	4 (11.76%)	1 (5.56%)	7 (11.86%)
Tricuspid valve incompetence	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Congenital, familial and genetic disorders				
Hydrocele	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Ear and labyrinth disorders				
Ear discomfort	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Vertigo	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Endocrine disorders				
Hyperparathyroidism	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Hyperparathyroidism secondary	2 (28.57%)	0 (0.00%)	1 (5.56%)	3 (5.08%)
Eye disorders				
Chalazion	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Dry eye	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Eye movement disorder	2 (28.57%)	0 (0.00%)	0 (0.00%)	2 (3.39%)
Ocular hyperaemia	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Retinal vein occlusion	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Gastrointestinal disorders				
Abdominal discomfort	0 (0.00%)	1 (2.94%)	1 (5.56%)	2 (3.39%)

Abdominal distension	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Abdominal pain	1 (14.29%)	3 (8.82%)	3 (16.67%)	7 (11.86%)
Abdominal pain lower	0 (0.00%)	1 (2.94%)	1 (5.56%)	2 (3.39%)
Abdominal pain upper	0 (0.00%)	5 (14.71%)	0 (0.00%)	5 (8.47%)
Anal fissure	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Aphthous ulcer	1 (14.29%)	1 (2.94%)	0 (0.00%)	2 (3.39%)
Colitis	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Constipation	1 (14.29%)	14 (41.18%)	8 (44.44%)	23 (38.98%)
Diarrhoea	2 (28.57%)	8 (23.53%)	10 (55.56%)	20 (33.90%)
Duodenogastric reflux	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Dyspepsia	2 (28.57%)	1 (2.94%)	1 (5.56%)	4 (6.78%)
Dysphagia	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Flatulence	0 (0.00%)	1 (2.94%)	2 (11.11%)	3 (5.08%)
Gastric polyps	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Gastritis	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Gastritis haemorrhagic	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Gingival pain	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Gingival recession	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Gingival swelling	0 (0.00%)	0 (0.00%)	2 (11.11%)	2 (3.39%)
Haemorrhoids	0 (0.00%)	1 (2.94%)	2 (11.11%)	3 (5.08%)
Ileus	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Inguinal hernia	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Mouth ulceration	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Nausea	4 (57.14%)	10 (29.41%)	9 (50.00%)	23 (38.98%)
Odynophagia	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Oesophagitis	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)

Paraesthesia oral	1 (14.29%)	1 (2.94%)	0 (0.00%)	2 (3.39%)
Stomatitis	0 (0.00%)	0 (0.00%)	2 (11.11%)	2 (3.39%)
Tongue discomfort	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Vomiting	3 (42.86%)	8 (23.53%)	4 (22.22%)	15 (25.42%)
General disorders and administration site conditions				
Asthenia	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Catheter site pain	0 (0.00%)	0 (0.00%)	2 (11.11%)	2 (3.39%)
Chills	0 (0.00%)	3 (8.82%)	0 (0.00%)	3 (5.08%)
Cyst	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Fatigue	1 (14.29%)	5 (14.71%)	5 (27.78%)	11 (18.64%)
Generalised oedema	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Impaired healing	0 (0.00%)	2 (5.88%)	1 (5.56%)	3 (5.08%)
Influenza like illness	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Infusion site swelling	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Malaise	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Oedema peripheral	2 (28.57%)	7 (20.59%)	6 (33.33%)	15 (25.42%)
Pain	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Peripheral swelling	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Pyrexia	0 (0.00%)	1 (2.94%)	1 (5.56%)	2 (3.39%)
Secretion discharge	3 (42.86%)	0 (0.00%)	0 (0.00%)	3 (5.08%)
Swelling	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Hepatobiliary disorders				
Hepatic function abnormal	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Hepatitis	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)

Hepatomegaly	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Immune system disorders				
Drug hypersensitivity	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Kidney transplant rejection	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Infections and infestations				
Acute sinusitis	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
BK virus infection	3 (42.86%)	10 (29.41%)	6 (33.33%)	19 (32.20%)
Bronchitis	0 (0.00%)	4 (11.76%)	0 (0.00%)	4 (6.78%)
Conjunctivitis	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Cytomegalovirus infection	0 (0.00%)	6 (17.65%)	2 (11.11%)	8 (13.56%)
Cytomegalovirus viraemia	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Diarrhoea infectious	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Epstein-Barr virus infection	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Folliculitis	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Fungal skin infection	0 (0.00%)	0 (0.00%)	2 (11.11%)	2 (3.39%)
Gastroenteritis	0 (0.00%)	2 (5.88%)	0 (0.00%)	2 (3.39%)
Gastroenteritis Escherichia coli	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Gastroenteritis norovirus	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Gastroenteritis viral	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Gastrointestinal infection	0 (0.00%)	1 (2.94%)	1 (5.56%)	2 (3.39%)
Herpes zoster	0 (0.00%)	2 (5.88%)	0 (0.00%)	2 (3.39%)

Human polyomavirus infection	0 (0.00%)	2 (5.88%)	0 (0.00%)	2 (3.39%)
Infection	0 (0.00%)	1 (2.94%)	1 (5.56%)	2 (3.39%)
Influenza	0 (0.00%)	2 (5.88%)	1 (5.56%)	3 (5.08%)
Laryngitis	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Latent tuberculosis	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Lung infection	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Mucocutaneous candidiasis	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Nasopharyngitis	1 (14.29%)	10 (29.41%)	4 (22.22%)	15 (25.42%)
Oral candidiasis	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Oral herpes	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Oral infection	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Otitis media	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Pharyngitis streptococcal	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Pneumocystis jirovecii pneumonia	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Pneumonia	0 (0.00%)	2 (5.88%)	0 (0.00%)	2 (3.39%)
Polyomavirus-associated nephropathy	0 (0.00%)	3 (8.82%)	1 (5.56%)	4 (6.78%)
Pyelonephritis	0 (0.00%)	1 (2.94%)	1 (5.56%)	2 (3.39%)
Pyuria	0 (0.00%)	1 (2.94%)	1 (5.56%)	2 (3.39%)
Respiratory tract infection	0 (0.00%)	2 (5.88%)	0 (0.00%)	2 (3.39%)
Rhinitis	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Sinusitis	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Skin infection	0 (0.00%)	1 (2.94%)	1 (5.56%)	2 (3.39%)

Soft tissue infection	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Subcutaneous abscess	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Tinea versicolour	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Tooth infection	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Tracheobronchitis	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Upper respiratory tract infection	0 (0.00%)	2 (5.88%)	0 (0.00%)	2 (3.39%)
Urinary tract infection	1 (14.29%)	8 (23.53%)	7 (38.89%)	16 (27.12%)
Urinary tract infection viral	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Viral infection	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Wound infection bacterial	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Injury, poisoning and procedural complications				
Animal bite	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Arterial injury	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Arteriovenous fistula site complication	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Arthropod bite	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Complications of transplant surgery	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Complications of transplanted kidney	0 (0.00%)	3 (8.82%)	2 (11.11%)	5 (8.47%)
Delayed graft function	0 (0.00%)	3 (8.82%)	3 (16.67%)	6 (10.17%)
Fall	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Graft complication	0 (0.00%)	1 (2.94%)	1 (5.56%)	2 (3.39%)
Incision site complication	0 (0.00%)	1 (2.94%)	1 (5.56%)	2 (3.39%)

Incision site erythema	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Incision site haemorrhage	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Incision site pain	3 (42.86%)	6 (17.65%)	2 (11.11%)	11 (18.64%)
Incisional hernia	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Joint injury	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Ligament sprain	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Lip injury	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Post procedural complication	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Post procedural haemorrhage	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Post procedural swelling	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Postoperative wound complication	0 (0.00%)	5 (14.71%)	1 (5.56%)	6 (10.17%)
Procedural pain	0 (0.00%)	3 (8.82%)	6 (33.33%)	9 (15.25%)
Radius fracture	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Seroma	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Transplant dysfunction	0 (0.00%)	2 (5.88%)	3 (16.67%)	5 (8.47%)
Wound complication	0 (0.00%)	11 (32.35%)	8 (44.44%)	19 (32.20%)
Wound dehiscence	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Wound haematoma	0 (0.00%)	1 (2.94%)	1 (5.56%)	2 (3.39%)
Investigations				
Alanine aminotransferase increased	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Amylase increased	0 (0.00%)	3 (8.82%)	1 (5.56%)	4 (6.78%)

Aspartate aminotransferase increased	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Blood creatine phosphokinase increased	0 (0.00%)	1 (2.94%)	1 (5.56%)	2 (3.39%)
Blood creatinine increased	0 (0.00%)	3 (8.82%)	1 (5.56%)	4 (6.78%)
Blood glucose increased	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Blood lactate dehydrogenase increased	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Blood phosphorus decreased	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Blood phosphorus increased	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Cardiac murmur	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
C-reactive protein increased	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Cytomegalovirus test positive	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Drug level decreased	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Electrocardiogram ST segment abnormal	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Electrocardiogram T wave abnormal	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Gamma-glutamyltransferase increased	0 (0.00%)	2 (5.88%)	1 (5.56%)	3 (5.08%)
Haemoglobin decreased	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Heart rate irregular	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Lipase increased	0 (0.00%)	2 (5.88%)	0 (0.00%)	2 (3.39%)

Polyomavirus test positive	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Vitamin D decreased	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Weight decreased	1 (14.29%)	1 (2.94%)	0 (0.00%)	2 (3.39%)
Weight increased	0 (0.00%)	2 (5.88%)	1 (5.56%)	3 (5.08%)
White blood cell count decreased	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
White blood cell count increased	0 (0.00%)	3 (8.82%)	0 (0.00%)	3 (5.08%)
Metabolism and nutrition disorders				
Decreased appetite	0 (0.00%)	4 (11.76%)	1 (5.56%)	5 (8.47%)
Diabetes mellitus	0 (0.00%)	3 (8.82%)	3 (16.67%)	6 (10.17%)
Dyslipidaemia	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Fluid overload	0 (0.00%)	1 (2.94%)	1 (5.56%)	2 (3.39%)
Folate deficiency	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Hypercalcaemia	0 (0.00%)	2 (5.88%)	1 (5.56%)	3 (5.08%)
Hypercholesterolaemia	0 (0.00%)	1 (2.94%)	2 (11.11%)	3 (5.08%)
Hyperglycaemia	3 (42.86%)	4 (11.76%)	4 (22.22%)	11 (18.64%)
Hyperkalaemia	1 (14.29%)	9 (26.47%)	5 (27.78%)	15 (25.42%)
Hyperlipidaemia	1 (14.29%)	2 (5.88%)	1 (5.56%)	4 (6.78%)
Hyperphosphataemia	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Hypertriglyceridaemia	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Hyperuricaemia	0 (0.00%)	4 (11.76%)	1 (5.56%)	5 (8.47%)
Hypervolaemia	0 (0.00%)	0 (0.00%)	2 (11.11%)	2 (3.39%)
Hypocalcaemia	0 (0.00%)	4 (11.76%)	1 (5.56%)	5 (8.47%)
Hypokalaemia	1 (14.29%)	6 (17.65%)	5 (27.78%)	12 (20.34%)
Hypomagnesaemia	2 (28.57%)	0 (0.00%)	3 (16.67%)	5 (8.47%)

Hyponatraemia	0 (0.00%)	3 (8.82%)	1 (5.56%)	4 (6.78%)
Hypophosphataemia	5 (71.43%)	11 (32.35%)	5 (27.78%)	21 (35.59%)
Increased appetite	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Magnesium deficiency	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Metabolic acidosis	0 (0.00%)	1 (2.94%)	2 (11.11%)	3 (5.08%)
Vitamin D deficiency	2 (28.57%)	2 (5.88%)	1 (5.56%)	5 (8.47%)
Musculoskeletal and connective tissue disorders				
Arthralgia	0 (0.00%)	2 (5.88%)	0 (0.00%)	2 (3.39%)
Back pain	0 (0.00%)	5 (14.71%)	1 (5.56%)	6 (10.17%)
Bursitis	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Flank pain	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Groin pain	1 (14.29%)	3 (8.82%)	1 (5.56%)	5 (8.47%)
Hypercreatinaemia	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Joint effusion	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Muscle spasms	1 (14.29%)	6 (17.65%)	1 (5.56%)	8 (13.56%)
Muscle twitching	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Muscular weakness	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Musculoskeletal discomfort	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Myalgia	0 (0.00%)	4 (11.76%)	0 (0.00%)	4 (6.78%)
Neck pain	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Osteochondrosis	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Pain in extremity	0 (0.00%)	2 (5.88%)	2 (11.11%)	4 (6.78%)
Pain in jaw	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Neoplasms benign, malignant and				

unspecified (incl cysts and polyps)				
Basal cell carcinoma	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Nervous system disorders				
Ataxia	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Burning sensation	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Dizziness	1 (14.29%)	2 (5.88%)	3 (16.67%)	6 (10.17%)
Dizziness postural	1 (14.29%)	0 (0.00%)	1 (5.56%)	2 (3.39%)
Headache	1 (14.29%)	6 (17.65%)	4 (22.22%)	11 (18.64%)
Hypoaesthesia	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Migraine	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Paraesthesia	1 (14.29%)	0 (0.00%)	1 (5.56%)	2 (3.39%)
Peroneal nerve palsy	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Polyneuropathy	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Tremor	2 (28.57%)	3 (8.82%)	6 (33.33%)	11 (18.64%)
Psychiatric disorders				
Anxiety	1 (14.29%)	1 (2.94%)	0 (0.00%)	2 (3.39%)
Delirium	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Insomnia	1 (14.29%)	11 (32.35%)	5 (27.78%)	17 (28.81%)
Mood swings	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Phonophobia	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Restlessness	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Renal and urinary disorders				
Bladder pain	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Bladder spasm	0 (0.00%)	3 (8.82%)	0 (0.00%)	3 (5.08%)

Chronic kidney disease	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Dysuria	1 (14.29%)	1 (2.94%)	0 (0.00%)	2 (3.39%)
Haematuria	0 (0.00%)	1 (2.94%)	2 (11.11%)	3 (5.08%)
Leukocyturia	0 (0.00%)	1 (2.94%)	1 (5.56%)	2 (3.39%)
Micturition urgency	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Nocturia	1 (14.29%)	1 (2.94%)	0 (0.00%)	2 (3.39%)
Perinephric collection	0 (0.00%)	2 (5.88%)	0 (0.00%)	2 (3.39%)
Perinephric oedema	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Polyuria	0 (0.00%)	5 (14.71%)	0 (0.00%)	5 (8.47%)
Proteinuria	0 (0.00%)	2 (5.88%)	1 (5.56%)	3 (5.08%)
Renal impairment	0 (0.00%)	0 (0.00%)	2 (11.11%)	2 (3.39%)
Renal tubular acidosis	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Renal tubular injury	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Renal tubular necrosis	0 (0.00%)	0 (0.00%)	2 (11.11%)	2 (3.39%)
Sterile pyuria	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Tubulointerstitial nephritis	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Urethral pain	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Urinary incontinence	0 (0.00%)	1 (2.94%)	2 (11.11%)	3 (5.08%)
Urinary retention	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Urinary tract disorder	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Urinary tract obstruction	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Reproductive system and breast disorders				
Benign prostatic hyperplasia	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Dysmenorrhoea	0 (0.00%)	0 (0.00%)	2 (11.11%)	2 (3.39%)

Erectile dysfunction	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Menorrhagia	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Penile oedema	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Penile pain	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Prostatomegaly	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Scrotal swelling	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Vulvovaginal pain	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Respiratory, thoracic and mediastinal disorders				
Cough	0 (0.00%)	10 (29.41%)	2 (11.11%)	12 (20.34%)
Dyspnoea	3 (42.86%)	2 (5.88%)	3 (16.67%)	8 (13.56%)
Dyspnoea exertional	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Lung infiltration	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Nasal congestion	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Oropharyngeal pain	0 (0.00%)	3 (8.82%)	0 (0.00%)	3 (5.08%)
Pleural effusion	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Productive cough	1 (14.29%)	1 (2.94%)	0 (0.00%)	2 (3.39%)
Respiratory distress	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Rhinorrhoea	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Sleep apnoea syndrome	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Wheezing	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Skin and subcutaneous tissue disorders				
Acne	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Alopecia	1 (14.29%)	2 (5.88%)	2 (11.11%)	5 (8.47%)
Decubitus ulcer	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)

Dermatitis	0 (0.00%)	2 (5.88%)	0 (0.00%)	2 (3.39%)
Hyperhidrosis	0 (0.00%)	3 (8.82%)	0 (0.00%)	3 (5.08%)
Lipohypertrophy	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Night sweats	0 (0.00%)	2 (5.88%)	1 (5.56%)	3 (5.08%)
Pityriasis	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Pruritus	0 (0.00%)	1 (2.94%)	2 (11.11%)	3 (5.08%)
Rash	0 (0.00%)	0 (0.00%)	3 (16.67%)	3 (5.08%)
Skin lesion	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Urticaria	0 (0.00%)	1 (2.94%)	0 (0.00%)	1 (1.69%)
Vascular disorders				
Deep vein thrombosis	0 (0.00%)	0 (0.00%)	1 (5.56%)	1 (1.69%)
Haematoma	0 (0.00%)	2 (5.88%)	0 (0.00%)	2 (3.39%)
Hot flush	0 (0.00%)	2 (5.88%)	0 (0.00%)	2 (3.39%)
Hypertension	1 (14.29%)	13 (38.24%)	6 (33.33%)	20 (33.90%)
Hypotension	0 (0.00%)	2 (5.88%)	3 (16.67%)	5 (8.47%)
Lymphocele	0 (0.00%)	1 (2.94%)	1 (5.56%)	2 (3.39%)
Orthostatic hypotension	1 (14.29%)	0 (0.00%)	0 (0.00%)	1 (1.69%)
Poor venous access	0 (0.00%)	2 (5.88%)	0 (0.00%)	2 (3.39%)

Other Relevant Findings

Not applicable

Conclusion:

Patients in the CFZ533 arm had significantly better renal function throughout the study; the difference in eGFR being approximately 10 mL/min and the risk for acute rejection was similar to that of patients treated with Tac.

The rate of reported BPAR was rather high in both treatment arms most likely due to extra investigator vigilance after the recently failed competitor trial. Thus, the independent, blinded AC was crucial for the success of the trial providing important learnings for future transplant studies.
The risk for NODAT seems much lower with CFZ533 and if anything there was a tendency to fewer complications with CFZ533 than with Tac. Thus, CFZ533 was well tolerated and the safety profile, PK and efficacy results support further development into Phase II/III trials.

Date of Clinical Trial Report

25 OCT 2018