

Novartis Institutes for BioMedical Research

**CFZ533**

Clinical Trial Protocol CCFZ533X2201

**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**

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## Notification of serious adverse events

A serious adverse event (SAE) is any event which is fatal or life-threatening, which requires or prolongs hospitalization, which is significantly or permanently disabling or incapacitating, which constitutes a congenital anomaly or a birth defect, or which is medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Any SAE occurring in a subject from consent until 3 months after his/her last dose of CFZ533 or 2 months after the end of study visit for patients on standard of care treatment must be reported either on the paper SAE report form or via the electronic SAE form within the clinical data capture system (where available).

For SAEs reported using the paper SAE report form, the Investigator will ensure that the form is completed and faxed by the Investigator to the local Novartis Drug Safety and Epidemiology Department within 24 hours of learning of the occurrence of the SAE even if the SAE does not appear to be drug-related. The original SAE form, together with the fax confirmation sheet, must be kept with the case report forms at the study site.

For SAEs recorded *electronically* in the Novartis clinical data capture system, information should be entered, saved and e-signed within 24 hours of awareness of the SAE. These data will automatically be submitted to Novartis Chief Medical Office and Patient Safety Department.

More details in [Section 7](#) of this protocol.

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## List of abbreviations

AC	Adjudication Committee
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
APC	antigen presenting cell
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	American Transplant Congress
b.i.d.	twice a day
BMI	Body Mass Index
BPAP	biopsy-proven acute rejection
BUN	blood urea nitrogen
CDC	complement-dependent lymphocytotoxic
CD-ROM	compact disc – read only memory
CFR	Code of Federal Regulation
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Equation
CI	confidence interval
CIT	cold ischemic time
CK	creatinine kinase
CMO&PS	Chief Medical Office & Patient Safety
CMV	cytomegalovirus
CNI	calcineurin inhibitor
CO <sub>2</sub>	carbon dioxide
CPO	Country Pharma Organization
CRF	Case Report/Record Form
CRO	Contract Research Organization

CV	coefficient of variation
CYP3A4	cytochrome P450 3A4
DBL	database lock
DGF	delayed graft function
DMC	Data Monitoring Committee
DS&E	Drug Safety & Epidemiology
DSA	Donor specific antibodies
EBV	Epstein-Barr virus
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	estimated GFR
ELISA	Enzyme-linked immunosorbent assay
EOS	end of study
EOT	end of treatment
FAS	full analysis set
FDA	Food and Drug Administration
GC	Germinal center
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
$\gamma$ -GT	Gamma-glutamyl transferase
h	hour
HbA1c	glycosylated hemoglobin
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIGM	Hyper-Immunoglobulin M Syndrome
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
NHP	non human primates
HR	heart rate

HUVEC	Human umbilical vein endothelial cells
IA	Interim Analysis
IB	Investigator Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INN	International Nonproprietary Name
IRB	Institutional Review Board
IRT	Interactive Response Technology
IS	immunosuppressant
ITT	intent-to-treat
IV	intravenous
KLH	keyhole limpet hemocyanin
LDH	lactate dehydrogenase
LLQ	lower limit of quantification
LLN	lower limit of normal
MABEL	minimal anticipated biological effect level
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
ml	milliliter(s)
MMF	mycophenolate mofetil
MPA	mycophenolic acid
NHP	Non human primate
NI	non-inferiority
NOAEL	no observed adverse effect level
NODAT	new onset diabetes mellitus after transplantation
o.d.	once a day
PA	posteroanterior
PAD	pharmacologically active dose
PBMC	peripheral blood mononuclear cells
PCP	Pneumocystis jiroveci pneumonia

PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PI	package insert
PK	pharmacokinetic(s)
p.o.	oral
PoC	Proof of Concept
PP	per-protocol
PRA	panel reactive antibodies
PTLD	post-transplant lymphoproliferative disease
RA	Rheumatoide Arthritis
RBC	red blood cell(s)
RDC	remote data capture
REB	Research Ethics Board
RO	receptor occupancy
SA	surface area (1.73 square meters)
SAE	serious adverse event
SC	subcutaneous
SCD	standard criteria donor
SD	single-dose
sCD40	soluble CD40
sCD40L	soluble CD40 ligand (or soluble CD154)
SD	standard deviation
SMQ	standardized MedDRA query
SoC	standard of care
SOC	system organ class
Tac	tacrolimus
TBL	total bilirubin
TDAR	T cell dependent antibody response
tBPAR	treated biopsy-proven acute rejections
TPDI	Therapeutic Protein Drug Interactions
UCL	upper confidence limit
ULN	upper limit of normal

ULQ                    upper limit of quantification

WBC                   white blood cell(s)

## Pharmacokinetic definitions and symbols

AUC <sub>0-t</sub>	The area under the plasma concentration-time curve from time zero to time 't' where t is a defined time point after administration [ $\mu\text{g}\cdot\text{day}/\text{mL}$ ]
AUC <sub>inf</sub>	The area under the plasma concentration-time curve from time zero to infinity [ $\mu\text{g}\cdot\text{day}/\text{mL}$ ]
AUC <sub>last</sub>	The area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration [ $\mu\text{g}\cdot\text{day}/\text{mL}$ ]
AUC <sub>tau</sub>	The area under the plasma concentration-time curve from time zero to the end of the dosing interval tau [ $\mu\text{g}\cdot\text{day}/\text{mL}$ ]
AUC <sub>tau,ss</sub>	The area under the plasma concentration-time curve from time zero to the end of the dosing interval tau at steady state [ $\mu\text{g}\cdot\text{day}/\text{mL}$ ]
C <sub>av,ss</sub>	The average steady state plasma concentration during multiple dosing
C <sub>max</sub>	The observed maximum plasma concentration following drug administration [ $\mu\text{g}/\text{mL}$ ]
C <sub>max,ss</sub>	The observed maximum plasma concentration following drug administration at steady state [ $\mu\text{g}/\text{mL}$ ]
C <sub>min,ss</sub>	The lowest plasma concentration observed during a dosing interval at steady state [ $\mu\text{g}/\text{mL}$ ]
CL	The systemic clearance from plasma following intravenous administration [ $\text{mL}/\text{day}$ ]
CL/F	The apparent systemic clearance from plasma (or serum or blood) following extravascular administration [ $\text{mL}/\text{day}$ ]
F	Bioavailability of a compound. F <sub>abs</sub> is the absolute bioavailability, i.e., the fraction (or percentage) of the administered extravascular dose systemically available.
T <sub>1/2</sub>	The terminal elimination half-life [day]
T <sub>max</sub>	The time to reach the maximum concentration after drug administration [day]
V <sub>z</sub>	The volume of distribution during the terminal elimination phase following intravenous administration [mL]
V <sub>z/F</sub>	The apparent volume of distribution during the terminal elimination phase following extravascular administration [mL]
V <sub>ss</sub>	The volume of distribution at steady state following intravenous administration [mL]

## Glossary of terms

Assessment	A procedure used to generate data required by the study.
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Enrollment	Point/time of subject entry into the study; the point at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol).
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product”.
Investigational treatment	<p>All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls.</p> <p>This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination.</p> <p>Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.</p>
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Subject number	A number assigned to each subject who enrolls in the study. When combined with the center number, a unique identifier is created for each subject in the study.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study assessments.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment.
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation

	visit.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy: CFZ533 + tacrolimus and CFZ533 + mycophenolate mofetil
Study drug discontinuation	Point/time when subject permanently stops taking study drug (any component of the regimen) for any reason.
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time-points.

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## Protocol synopsis

<b>Protocol number</b>	CCFZ533X2201
<b>Title</b>	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 <i>de novo</i> renal transplant recipients
<b>Brief title</b>	Efficacy and safety study of CFZ533 in kidney transplant patients
<b>Sponsor and Clinical Phase</b>	Novartis Phase II
<b>Investigation type</b>	Drug (biologic)
<b>Study type</b>	Interventional
<b>Purpose and rationale</b>	<p>The purpose of this adaptive, two-part study is to investigate the potential for CFZ533 to replace calcineurin inhibitors (CNI), while providing a similar rate of acute rejection prophylaxis and better renal function in a <i>de novo</i> renal transplant population receiving an allograft from standard criteria donors..</p> <p>Part 1 of this trial will focus on profiling the multiple dose pharmacokinetics (PK), pharmacodynamics (PD) and tolerability for both IV and SC CFZ533 administration in the setting of standard-of-care, CNI-based immunosuppression.</p> <p>Part 2 will evaluate the safety and efficacy of CFZ533 in the absence of a CNI in combination with adjunct MMF and basiliximab induction therapy for up to 12 months.</p> <p>Overall, results of this study will be used to inform the CFZ533 dose and regimen selection for investigation in the next phase of clinical development.</p>
<b>Primary Objectives</b>	<ul style="list-style-type: none"> <li>Part 1: PK, PD and Safety <ul style="list-style-type: none"> <li>To assess the safety, tolerability and pharmacokinetics of multiple IV and SC doses of CFZ533 in combination with MMF, CS, and Tac (standard exposure) in <i>de novo</i> renal transplant patients over the treatment and follow-up period</li> </ul> </li> <li>Part 2: CNI-free Proof-of-Concept <ul style="list-style-type: none"> <li>To assess the potential for CFZ533 to act as the primary immunosuppressant in a CNI-free regimen with MMF in <i>de novo</i> renal transplant patients as assessed by tBPAR at Month 3 post-transplantation</li> </ul> </li> </ul>
<b>Secondary Objectives</b>	<ul style="list-style-type: none"> <li>Part 1: PK, PD and Safety <ul style="list-style-type: none"> <li>To quantify the magnitude and duration of peripheral blood CD40 occupancy (free CD40 and total CD40 on B cells)</li> <li>To quantify the change from baseline and recovery of peripheral blood total soluble CD40 and total soluble CD154</li> <li>To evaluate the immunogenicity of CFZ533 via the quantitative analysis of anti-CFZ533 antibodies</li> </ul> </li> <li>Part 2: CNI-free Proof-of-Concept <ul style="list-style-type: none"> <li>To assess the safety and tolerability of CFZ533 administered chronically in combination with MMF and CS up to 3 months against</li> </ul> </li> </ul>

	<p>a control</p> <ul style="list-style-type: none"> <li>To assess the pharmacokinetics of multiple IV doses of CFZ533 during the 12-month treatment period</li> <li>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</li> <li>To compare renal function in CFZ533 treatment arms to control at Month 3 post-transplantation as assessed by: <ul style="list-style-type: none"> <li>Estimated GFR using MDRD</li> <li>Proportion of patients with eGFR &lt;60 mL/min/1.73m<sup>2</sup></li> <li>Proportion of patients with negative eGFR slope</li> </ul> </li> <li>To evaluate the immunogenicity of multiple IV doses of CFZ533 via the quantitative analysis of anti-CFZ533 antibodies</li> <li>To quantify the change from baseline and recovery of peripheral blood total soluble CD40 during the treatment period following multiple IV doses of CFZ533</li> </ul>
<b>Study design</b>	<p>A randomized, two-part, 6- or 12-month, sequential, adaptive, controlled, open-label, multicenter, clinical proof-of-concept study to evaluate the efficacy, safety, tolerability, PK and PD of CFZ533 + MMF + CS, with standard exposure (Part 1) or no tacrolimus (Part 2), for initial and maintenance prophylaxis of organ rejection in adult <i>de novo</i> renal transplant recipients as compared to standard of care.</p> <p><u>Part 1 (PK, PD and Safety):</u> For Arm 1, 6 patients total will be enrolled to receive IV induction (Day 1) and SC administration on Days 15, 29, 43 and 71 of 3 mg/kg CFZ533 with standard-exposure tacrolimus (whole blood trough concentration 4-11 ng/mL), MMF and CS. Corporate Confidential Information</p> <p>All patients enrolled into Part 1 will remain on SoC until Month 6 (EOS). Corporate Confidential Information</p> <p><u>Part 2 (CNI-free PoC):</u> Following 2:1 randomization, 45 patients will be enrolled in Arms 2A and 2B in a parallel manner. Arm 2A will receive multiple intravenous CFZ533 10 mg/kg doses with basiliximab induction, MMF and CS; Arm 2B (control) will receive standard-exposure tacrolimus (whole blood trough concentration 4-11 ng/mL) with basiliximab induction, MMF and CS. Corporate Confidential Information</p>
<b>Population</b>	<i>de novo</i> adult renal transplant patients
<b>Inclusion criteria (key)</b>	<ul style="list-style-type: none"> <li>Written informed consent</li> <li>Male or female patients ≥ 18 years old</li> <li>Recipients of a transplant from a heart-beating deceased, living unrelated or non-human leukocyte antigen (HLA) identical living related donor</li> <li>Recipients of a kidney with a cold ischemia time (CIT) &lt; 30 hours</li> </ul>

<b>Exclusion criteria (key)</b>	<ul style="list-style-type: none"> <li>• Multi-organ transplant recipients</li> <li>• Recipient of an organ from a non-heart beating donor</li> <li>• ABO incompatible allograft or complement-dependent lymphocytotoxic (CDC) cross-match positive transplant</li> <li>• Receipt of a second kidney allograft, unless the first allograft was lost due to surgical complication</li> <li>• High immunological risk for rejection as determined by local practice for assessment of anti-donor reactivity (e.g., high panel reactive antibodies (PRA) &gt; 20%, presence of pre-existing donor-specific antibodies (DSA))</li> <li>• At risk for tuberculosis (TB)</li> <li>• Anti-HIV positive, HBsAg-positive or anti-HCV positive</li> <li>• EBV negative (in Part 1 only)</li> <li>• History of coagulopathy or medical condition requiring long-term anticoagulation which would preclude renal biopsy after transplantation</li> <li>• Active infection</li> <li>• Pregnant or nursing (lactating) women</li> <li>• Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 12 weeks after the study medications have been stopped</li> </ul>
<b>Investigational and reference therapy</b>	<p><b>Part 1</b></p> <ul style="list-style-type: none"> <li>• <b>Arm 1</b>, n=6: CFZ533 at 3.0 mg/kg SC (5 doses; first dose is IV, SC on Days 15, 29, 43 and 71) + tacrolimus (4-11 ng/mL) + MMF 1.0 g BID + CS</li> </ul> <p><b>Part 2</b></p> <ul style="list-style-type: none"> <li>• <b>Arm 2A</b>, n=30: Basiliximab 20 mg (Days 1, 4) + CFZ533 at 10 mg/kg IV (17 doses) + MMF 1.0 g BID + CS</li> <li>• <b>Arm 2B Control/Standard of Care</b>, n=15: Basiliximab 20 mg (Days 1, 4) + tacrolimus (4-11 ng/mL) + MMF 1.0 g BID + CS</li> </ul> <p><b>Concomitant treatments</b></p> <ul style="list-style-type: none"> <li>• CMV, PCP, HBV &amp; BK virus prophylaxis</li> <li>• Oral Candida treatment</li> </ul>
<b>Efficacy assessments</b>	Treated biopsy proven acute rejection (tBPAR), graft loss, death, estimated GFR

<b>Safety assessments</b>	<ul style="list-style-type: none"> <li>• Renal function</li> <li>• Adverse and serious adverse events</li> <li>• Infections</li> <li>• Cytokines</li> <li>• Donor specific antibodies</li> <li>• NODAT</li> <li>• EBV, CMV and BK virus and tuberculosis surveillance</li> <li>• Viral serology</li> <li>• Immunogenicity</li> <li>• ECG</li> <li>• Vital signs</li> <li>• Clinical labs</li> </ul>
<b>Other assessments</b>	<ul style="list-style-type: none"> <li>• Pharmacokinetics: <ul style="list-style-type: none"> <li>• Free CFZ533 in plasma</li> <li>• Tac trough levels</li> <li>• MPA trough levels</li> </ul> </li> </ul> <p>Corporate Confidential Information</p> <ul style="list-style-type: none"> <li>• Soluble CD40 and soluble CD154 in plasma</li> <li>• Graft survival</li> <li>• Patient survival</li> <li>• Lymph node / tissue biopsy</li> </ul> <p>Corporate Confidential Information</p>
<b>Data analysis</b>	<p><b>Part 1</b></p> <p>Posterior probabilities of the tBPAR rates for the treatment regimen above various thresholds such as 10%, 15%, 20%, 25% will be presented as:</p> <p><math>\Pr(\theta_{CFZ533} \geq T \mid \text{data})</math> for <math>T=0.1, 0.15, 0.2, 0.25</math>.</p> <p>assuming a non-informative neutral prior of <math>\text{Beta}(1/3, 1/3)</math>.</p> <p><b>Part 2</b></p> <p>The efficacy analysis for the first 3 months of Part 2 considers whether the CFZ533 treatment arm meets the pre-defined criteria for PoC declaration: <math>\Pr(\theta_{CFZ533} - \theta_{SoC} &lt; 0.20 \mid \text{data}) &gt; 60\%</math></p> <p>The required posterior probabilities will be estimated from simulations of the posterior distributions of <math>\theta_{CFZ533} - \theta_{SoC}</math> and compared to the thresholds for the levels of proof.</p>
<b>Key words</b>	<p>Safety, efficacy, pharmacokinetics, pharmacodynamics, CFZ533, <i>de novo</i> renal transplant patients CNI-free immunosuppression, CD40, B cells</p>

## Assessment schedule – Part 1

Part 1	Study phase	Screening (3)	Baseline (4)	Treatment																	Follow- Up	Study Com- pletion <sup>(17)</sup>	
Visit Numbers	1	99		101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	199
Month				1											2		3			4		5	
Week				1											2		3			4		5	
Day	D-28 to 1	D-1 to 1		D 1	2	3	4	8	10	15	22	29	36	43	50	57	64	71	85	99	113	127	155
Hour (h)			Pre	0	EOI <sup>(15)</sup>	6 <sup>(15)</sup>	24 <sup>(15)</sup>	48 <sup>(15)</sup>	72 <sup>(15)</sup>		Pre	0		Pre	0		Pre	0		Pre	0		
Window						±30m	± 1h	± 2h	± 2h						± 3 days								
Demography	X																						
Inclusion / Exclusion criteria	X <sup>#</sup>	X <sup>#</sup>																					
Informed consent <sup>(1)</sup>	X																						
Kidney transplant background recipient/donor		X																					
Kidney transplant procedure		X																					
Medical history	X																						
Physical examination	S <sup>#</sup>	S <sup>#</sup>					S																S
Pregnancy test <sup>(2)</sup>	X <sup>#</sup>	X <sup>#</sup>							X							X							X
Screening phase disposition <sup>(3)</sup>		X																					
Enrollment	S <sup>#</sup>	S <sup>#</sup>																					
Viral serology <sup>(6)</sup> recipient/donor record <sup>(8)</sup>		X		X							A		A		A			A					
Donor specific antibodies (DSA)	X <sup>#</sup>	X <sup>#</sup>																					A
ECG evaluation	X <sup>#</sup>	X <sup>#</sup>						A									A						X
Local laboratory <sup>(5)</sup>	X <sup>#</sup>	X <sup>#</sup>	X <sup>#</sup>		A	A	A	A		A		A				X			X	X			X
Systemic cytokines (central lab)	X <sup>#</sup>	X <sup>#</sup>	X <sup>#</sup>		A	A	A	A		A		A				A			A	A			A
Vital signs																							
Height	X																						
Weight	X <sup>#</sup>	X <sup>#</sup>					A	A	A		A		A		A		A		A	A	A	A	X
Temperature <sup>(9)</sup>	X <sup>#</sup>	X <sup>#</sup>	X <sup>(9)</sup>			A	A	A		A		A		A		A		A	A	A	A	A	X
Blood pressure/pulse <sup>(9)</sup>	X <sup>#</sup>	X <sup>#</sup>	X <sup>(9)</sup>			A	A	A		A		A		A		A		A	A	A	A	A	X
EBV, CMV & BK virus											X					X							X
Tuberculosis surveillance <sup>(10)</sup>		X														X							X
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MPA trough levels <sup>(12)</sup>							X	X		X		X	X		X	X	X	X		X	X	X	X
Tacrolimus trough levels <sup>(12)</sup>							X	X		X		X	X		X	X	X	X		X	X	X	X
CD40 receptor occupancy <sup>(11)</sup>		X	X	X	X	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
sCD40, sCD154 <sup>(11)</sup>		X	X	X	X	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Immunogenicity <sup>(11)</sup>			X									A				A		A		A	A	A	A

AE, SAE (14)		Ongoing
Comments		As required
Concomitant medications (16)		Ongoing
Death		As required
Prophylaxis (18)		As required
Surgical & medical procedures		As required
Withdrawal of informed consent		As required
Kidney allograft biopsy		As required
Kidney allograft rejection		As required
Dialysis		As required
Graft loss		As required
Hospitalizations		As required
Study completion (17)		As required
		X

## Assessment schedule – Part 2

Part 2	Study phase	Screening (3)	Baseline (4)	Treatment																				EOT	Study Com- pletion (17)						
	Visit Numbers	1	98	101		102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	199						
	Study Month			1										2		3	4	5	6	7	8	9	10	11	12	13					
	Study Week			1										2		3	4	5	6	7	8	9	10	11	12						
	Study Day	D-28 to 1	D-1 to 1	D 1		2	3	4	7	10	15	29	43	57	85	113	141	169	197	225	253	281	309	337	364						
	Hour (h)			Pre	0	EOI <sup>(18)</sup>	6 <sup>(18)</sup>	24 <sup>(18)</sup>	48 <sup>(18)</sup>	72 <sup>(18)</sup>																					
	Window						±30m	±1h	±2h	±2h	±1d	±1d					±3d													±7d	
Demography		X															±3d														
Inclusion / Exclusion criteria		X <sup>a</sup>	X <sup>d</sup>																												
Informed consent <sup>(1)</sup>		X																													
Kidney transplant background recipient/donor			X																												
Kidney transplant procedure			X																												
Medical history		X																													
Physical examination		S <sup>a</sup>	S <sup>d</sup>						S																	S					
Pregnancy test <sup>(2)</sup>		X <sup>a</sup>	X <sup>d</sup>							X					X			X			X			X		X					
Screening phase disposition <sup>(3)</sup>			X											X											X						
Randomization		S <sup>a</sup>	S <sup>d</sup>																												
Viral serology <sup>(6)</sup> recipient/donor			X																												
Drug administration record					X				A		A		A	A	A	A	A	A	A	A	A	A	A	A							
Study medication <sup>(8)</sup>					X																										
Basiliximab induction <sup>(7)</sup>					X				X																						
Donor specific antibodies (DSA)		X <sup>a</sup>	X <sup>d</sup>						X											A				A		A					
ECG evaluation		X <sup>a</sup>	X <sup>d</sup>												A			A		A						X					
Local laboratory <sup>(5)</sup>		X <sup>a</sup>	X <sup>d</sup>	X <sup>a</sup>			A	A	A	A		X	X		X	X	X	X	X	X	X	X	X	X	X	X					
Central lab (eGFR/ cytokines)		X <sup>a</sup>	X <sup>d</sup>	X <sup>a</sup>			A	A	A	A			A	A		A	A	A	A	A	A	A	A	A	A	X					
Vital signs																															
Height		X																													
Weight		X <sup>a</sup>	X <sup>d</sup>											A		A	A	A	A	A	A	A	A	A	A	X					
Temperature <sup>(9)</sup>		X <sup>a</sup>	X <sup>d</sup>		X <sup>(9)</sup>		A	A	A	A		A	A	A	A	A	A	A	A	A	A	A	A	A	A	X					
Blood pressure/pulse <sup>(9)</sup>		X <sup>a</sup>	X <sup>d</sup>		X <sup>(9)</sup>		A	A	A	A		A	A	A	A	A	A	A	A	A	A	A	A	A	A	X					
EBV, CMV & BK virus surveillance												X	X		X	X	X	X	X	X	X	X	X	X	X	X					
Totals (n=101, n=98, n=101, n=101)																										X					

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AE, SAE <sup>(14)</sup>			Ongoing	
Comments			As required	
Concomitant medications <sup>(16)</sup>			Ongoing	
Death			As required	
Prophylaxis <sup>(16)</sup>			As required	
Surgical & medical procedures			As required	
Withdrawal of informed consent			As required	
Kidney allograft biopsy			As required	
Kidney allograft rejection			As required	
Dialysis			As required	
Graft loss			As required	
Hospitalizations			As required	
Study completion <sup>(17)</sup>			As required	X

## Assessment schedule – Footnotes and Legend

X = assessment for all subjects in study regardless of on- or off- randomized study regimen, to be recorded in clinical database.

A = assessment ONLY for subjects maintaining their randomized study regimen, to be recorded in clinical database.

S = assessment to be recorded on source documentation.

m= minute; h = hour; d = day; EOT = End of Treatment; Study Month = 28 days;

# = only need to be performed once in a 12-hour period if Screening, Baseline and Day 1 occur in close proximity.

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

(2) Only for females of child-bearing potential. Pregnancy tests should be carried out according to local practice. Local result must be available and negative prior to randomization/enrollment.

(3) Screening may extend up to 4 weeks prior to transplant (e.g., for scheduled living donor transplants) and ends when the subject is either randomized or becomes a screening failure. For every consented subject, the Screening Period Disposition CRF page must be completed to indicate whether the subject was randomized or considered a screening failure.

(4) Baseline covers the transplant period from up to 24 hours prior to surgery until randomization/enrollment or its failure. Randomization/Enrollment should occur within 24 hours of the start of the transplant surgery.

(5) Viral serology includes HCV, HIV, HBV surface antigen, CMV, EBV and BK virus. For the initial assessment, measurements made within the last 6 months will be accepted. Otherwise, the initial tests should be performed within one week of randomization/enrollment.

(6) First dose of CFZ533 will be administered intravenously pre- or intra-operatively and must be completed by the time of unclamping or up to 6 hours prior to the time of unclamping. Other study drugs (e.g., Tac, MMF, CS) should be started within 24 hours post-transplantation or according to local practice.

(7) First dose of basiliximab induction should be given within 2 hours prior to transplant surgery, or according to local practice. The second dose should be given on Day 4, or according to local practice.

(8) Local laboratory tests include: hematology, urinalysis, serum chemistries, renal function, and coagulation parameters.

(9) Obtained every 15 mins for 2 hrs after the start of the first CFZ533 IV infusion or time of SC injection.

(10) Negative test result must be available prior to randomization/enrollment.

(11) Blood collections and safety assessments should be taken pre-dose if the sampling falls on a dosing day.

(12) Blood draws for trough concentrations should be performed before the next dose is given. In addition, they should be performed locally as shown and additionally 5±2 days following each clinic visit in which doses are changed.

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(14) All serious adverse events, serious infections and pregnancies must be reported from informed consent until 3 months after his/her last dose of CFZ533 or 2 months

after EoS visit for patients on SoC treatment.

(15) Induction therapy (e.g., basiliximab) and pre-transplant immunosuppression (if used) should be recorded on the Concomitant Medications CRF page under the Immunosuppressive category.

(16) Prophylaxis for CMV, PCP, HBV, BK and oral candida to be considered per protocol [Section 5.5.8](#), and recorded on the Concomitant Medications CRF page if administered.

(17) All patients are expected to continue in the study to Month 6 or 12 and complete the Month 6 or 12 Completion page, regardless of whether they are on or off study medication. If subjects discontinue study treatment, he/she should continue in the study on SOC per local practice and attend study visits to Month 6 or 12. Any permanent discontinuation of the randomized study regimen should be recorded on the appropriate DAR CRF pages. After discontinuation of study regimen, the immunosuppressive regimen prescribed should be recorded on the Concomitant Medications CRF under the Immunosuppressive category.

(18) EOI = End of Infusion (IV) or End of Injection (SC). Blood samples obtained immediately after infusion for IV-administered CFZ533 or immediately after injection for SC-administered CFZ533.

(19) Timepoint calculated from start of infusion for patients on CFZ533 treatment and from Start of Transplant surgery for TAC treatment

## 1 Introduction

### 1.1 Background

Over the past decades, organ allotransplantation has become a common medical procedure with considerable impact on extending and improving the quality of life of patients with end stage renal, cardiac, hepatic or pulmonary failure. To maximize efficacy and minimize adverse effects, current immunosuppressant (IS) regimens use combinations of IS drugs. Care is taken to achieve synergy or additive immunosuppressive effects via the administration of submaximal doses of individual agents with different mechanism of actions while avoiding overlapping toxicities. Most treatment regimens today include two or more primary and adjunct immunosuppressants with or without an induction agent. Induction agents are administered during the first hours to days post transplantation to suppress the recipient's immune system and priming of an immune response to the allograft while the other IS agents are reaching effective concentrations. Induction agents include the anti-CD25 mAb basiliximab (Simulect<sup>®</sup>, Novartis) or polyclonal anti-T cell globulin (Thymoglobulin<sup>®</sup>, rabbit ATG, rATG, Genzyme). In highly sensitized patients, induction with an anti-CD52 mAb, alemtuzumab (Campath<sup>®</sup>, Sanofi-Aventis SA) which leads to long-term lymphocyte depletion has been used. Within 1-2 days following transplant, the maintenance treatment regimen is initiated with two or more of the following agents: a calcineurin inhibitor (CNI) such as cyclosporine (CsA, Neoral<sup>®</sup>, Novartis) or tacrolimus (Tac, FK506, Prograf<sup>®</sup>, Astellas), together with a lymphocyte proliferation inhibitor such as mycophenolic acid (MPA; Myfortic<sup>®</sup>, Novartis) or mycophenolate mofetil (MMF; CellCept<sup>®</sup>, Roche) or proliferation signal inhibitor such as everolimus (Zortress<sup>®</sup>, Certican<sup>®</sup>, Novartis) or sirolimus (Rapamune<sup>®</sup>, Pfizer). More recently, the T cell co-stimulation blocker belatacept (Nulojix<sup>®</sup>, BMS), a fusion protein, demonstrated the potential of a biologic agent to replace CNIs in a calcineurin-free treatment regimen with MPA.

Although the current standard-of-care regimens provide excellent short-term efficacy with very low acute rejection rates, there is still an opportunity to increase long-term graft and patient survival. The current rate of renal allograft graft survival in the first year and 5 years post-transplant is 95% and 68% ([Matas et al 2013](#)), respectively, with a rapid decline thereafter. The estimated glomerular filtration rate at 12 months has been strongly associated with subsequent graft failure ([Kasiske et al 2011](#)). As such, kidney allograft function is also an important predictor of graft survival. Other factors, such as donor age, acute rejection and vascular remodeling may also play a role in overall graft survival, but the nephrotoxic effects of calcineurin inhibitors are directly associated with irreversible renal function deterioration ([Naesens et al 2009](#)). By eliminating CNIs from the treatment regimen, mechanism-based side effects, such as nephrotoxicity, hypertension, dyslipidemia, neurotoxicity, gastrointestinal and hematological toxicity, and/or diabetogenic effects may be minimized or eliminated. In the search for novel therapeutics, there has been an increasing interest in the role B cells, plasma cells and antibodies play in the immune response to an allograft, specifically acute cellular rejection and chronic humoral or antibody mediated rejection ([Clatworthy 2011](#)). By developing a specific treatment that decreases the priming of T and B cells and subsequent production of donor specific antibodies and eliminating CNIs, it is hypothesized that chronic

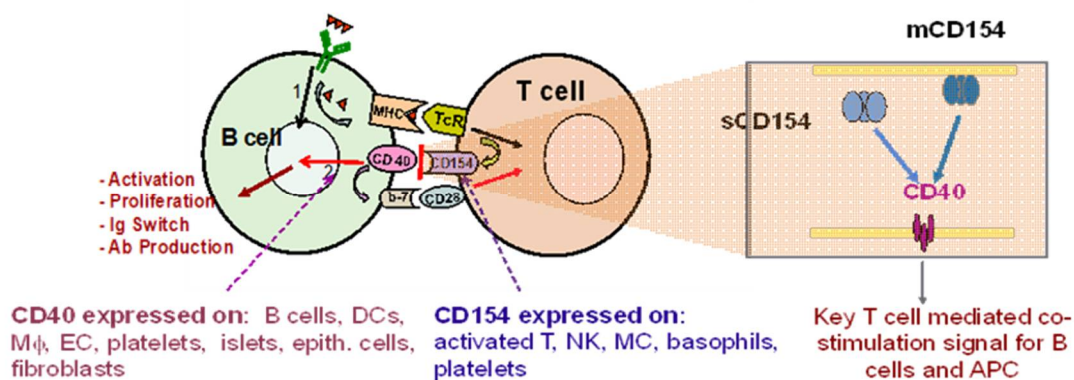
rejection can be minimized and long-term graft survival may be increased. Hence, there is a significant need for new immunosuppressant agents.

### 1.1.1 CD40/CD40L co-stimulation: a target for transplantation

CD40 is a transmembrane glycoprotein constitutively expressed on B cells and antigen-presenting cells (APCs) such as monocytes, macrophages, and dendritic cells (DC). CD40 is also expressed on platelets, and under specific conditions can be expressed on eosinophils and activated parenchymal cells. Ligation of CD40 on B cells results in downstream signaling leading to enhanced B cell survival and important effector functions, including clonal expansion, cytokine secretion, differentiation, germinal center formation, development of memory B cells, affinity maturation, immunoglobulin (Ig) isotype switching, antibody production and prolongation of antigen presentation. CD154-mediated activation of the antigen-presenting cell (APC) also leads to induction of cytokine secretion and expression of surface activation molecules including CD69, CD54, CD80, and CD86 that are involved in the regulation of CD4<sup>+</sup> T helper cell and CD8<sup>+</sup> T cell cross-priming and activation.

CD154 exists in two forms – membrane-bound and soluble. Membrane-bound CD154 is a transmembrane glycoprotein expressed on activated CD4<sup>+</sup>, CD8<sup>+</sup>, and  $\gamma\delta$ T-lymphocytes, mast cells, monocytes, basophils, eosinophils, natural killer (NK) cells, activated platelets and has been reported on B cells. It may also be expressed at low levels on vascular endothelial cells and up-regulated during local inflammation. Soluble CD154 (sCD154) is formed after proteolysis of membrane-bound CD154 and is shed from lymphocytes and platelets following cell activation. Once shed, sCD154 remains functional and retains its ability to bind to the CD40 receptor.

**Figure 1-1 Roles of CD40-CD154 signaling in the T and B cell**



Targeting CD40-154 interactions in transplantation and autoimmune disease. CD40-CD154 interactions are essential for APC activation, T cell priming in the context of APC-T cell interactions and T cell dependent humoral responses.

NOTE: mCD154=membrane bound CD154; sCD154=soluble CD154

The critical role of CD40/CD154 interactions *in vivo* are best illustrated by patients suffering from Hyper-Immunoglobulin M (HIGM) as a result of loss of function mutations in CD40 or its ligand. Patients with HIGM present with a severe impairment of T cell dependent antibody responses, lack of B cell memory, and little to no circulating IgG, IgA or IgE. In patients with mutations in CD40 signaling, a similar phenotype and disease presentation has been described ([van Kooten and Banchereau 2000](#)).

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Using monoclonal antibodies to target CD154 has been hampered by the occurrence of thromboembolic complications ([Kawai et al 2000](#)) so an alternative approach is to target the receptor, CD40.

### 1.1.2 CFZ533: mechanism of action

CFZ533 is a fully human, Fc-silent, blocking IgG1 anti-CD40 antibody that binds to the CD154 binding site on CD40, preventing CD154 binding and the activation of CD40 pathway signaling and downstream effector functions on multiple cell types expressing the receptor. CFZ533 harbours a mutation rendering it unable to bind Fcγ receptors or mediate antibody-dependent cell-mediated cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC).

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### **CFZ533: Patients with rheumatoid arthritis (10 and 30 mg/kg IV)**

Single doses of CFZ533 at 10 mg/kg in RA patients have been well-tolerated. There have been no deaths, suspected SAEs or discontinuations due to AEs.

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### **Data from ASKP1240 clinical trials (FIH and kidney transplantation)**

ASKP1240 is a monoclonal antibody blocking CD40 ([Okimura et al 2014](#)) with PK properties similar to those of CFZ533 based on data from NHP ([Ma et al 2014](#)) and healthy volunteers ([Goldwater et al 2013](#)). At ATC 2015, the preliminary data of a Ph II clinical trial was presented ([Harland et al 2015](#)). The study failed in the CNI-free arm, i.e. there were more rejections with ASKP1240 than with SoC.

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In fact, many individuals lost target saturation in peripheral blood, i.e. ASKP1240 concentration <15 µg/mL ([Goldwater et al 2013](#)). The clearance of ASKP1240 was markedly higher during the first month after transplantation reflecting an

enhanced expression of CD40 receptors post-transplantation. The anti-CD40 mAb levels required for full RO in target tissues during the first two months are likely to be 60-80 µg/mL, which is in accordance with observations in NHP studies (Ma et al 2014).

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## Comparator and background medication

In adult *de novo* kidney transplant recipients, the use of Tac, MMF, and CS is an approved regimen (e.g. Prograf® PI 2013) and is the current standard of care used in more than 80% of kidney transplants globally. When Tac is combined with an MPA-based regimen and with induction using an IL-2 antagonist, the labeled trough concentration range for Tac is 4-11 ng/mL (e.g. Prograf® PI 2013), and this range will be employed in this clinical study.

CFZ533 will be tested in Part 1 on top of Tac, MMF and CS, and in Part 2 in a Tac/CNI-free regimen with MMF and induction therapy. All concomitant medication will be used according to label.

### Tacrolimus (Tac)

Tac is a calcineurin inhibitor that blocks T cell activation and IL-2 transcription. Tac (e.g. Prograf®) is indicated for the prophylaxis of organ rejection in patients receiving allogeneic kidney transplants. It is recommended that Tac be used concomitantly with azathioprine or mycophenolate mofetil (MMF) and adrenal corticosteroids. Therapeutic drug monitoring is recommended for all patients receiving Tac. In kidney transplant patients, the initial dose of Tac (e.g. Prograf®) may be administered within 24 hours of transplantation, but should be delayed until renal function has recovered. In combination with MMF/IL-2 receptor antagonist a starting dose of 0.1 mg/kg/day and a target trough concentration during the first 12 months of 4-11 ng/mL is recommended. The most common adverse reactions (≥ 30%) in kidney transplant patients were infection, tremor, hypertension, abnormal renal function, constipation, diarrhea, headache, abdominal pain, insomnia, nausea, hypomagnesemia, urinary tract infection, hypophosphatemia, peripheral edema, asthenia, pain, hyperlipidemia, hyperkalemia, anemia. For more information on Tac, please refer to the local package insert (e.g. Prograf® PI 2013)

### Mycophenolate mofetil (MMF)

MMF (e.g. CellCept®) is a prodrug of mycophenolic acid (MPA), a reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH) in purine (guanine) biosynthesis which is necessary for the growth of T cells and B cells. Other cells are able to recover purines via a separate salvage pathway and are thus able to escape the effect thus MMF has potent cytostatic effects on lymphocytes. MMF is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. MMF should be used concomitantly with cyclosporine and corticosteroids. A dose of 1 g administered orally twice a day (daily dose of 2 g) is recommended for use in renal transplant patients. MMF (e.g. CellCept®) carries a warning for female patients who may become pregnant. Some manufacturers of MMF recommend male contraception (condom). Use during pregnancy is associated with

increased risks of first trimester pregnancy loss and congenital malformations. Females of reproductive potential (FRP) must be counseled regarding pregnancy prevention and planning. Due to the risks related to the drug's use during pregnancy, a Risk Evaluation and Mitigation Strategy (REMS) program has been established in the United States for products containing mycophenolate and details pertaining to this program are provided in [Appendix 2](#). Other common side effects of MMF include diarrhea, vomiting, pain, stomach area pain, swelling of the lower legs, ankles and feet, high blood pressure. For more information please refer to the local package insert (e.g. [CellCept® PI 2013](#)).

### **Basiliximab**

Basiliximab (e.g. Simulect®) is a chimeric CD25 monoclonal antibody of the IgG1 isotype. It acts as an antagonist at the interleukin-2 (IL-2) binding site of the p55 subunit (Tac antigen) of the high affinity IL-2 receptor (CD25) on the surface of the activated T lymphocytes. Basiliximab is indicated for the prophylaxis of acute organ rejection in patients receiving renal transplantation when used as part of an immunosuppressive regimen that contains cyclosporine and corticosteroids. Basiliximab is for central or peripheral IV administration only. Reconstituted basiliximab should be given either as a bolus injection or diluted to a volume of 25 mL (10 mg vial) or 50 mL (20 mg/vial) with normal saline or dextrose 5% and administered as an IV infusion over 20-30 minutes. The recommended regimen for adult patients is two 20 mg doses; the first dose is suggested to be given within 2 hours prior to transplantation and the second dose is suggested to be given 4 days after transplantation. Bolus administration may be associated with nausea, vomiting and local reactions including pain.

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## **1.2 Study purpose**

The purpose of this adaptive, two-part study is to investigate the potential for CFZ533 to replace calcineurin inhibitors (CNI), while providing a similar rate of acute rejection prophylaxis and better renal function in a *de novo* renal transplant population receiving an allograft from standard criteria donors. Part 1 of this trial will focus on profiling the multiple-dose PK, PD and tolerability for both IV and SC CFZ533 administration in the

setting of standard-of-care, CNI-based immunosuppression. Part 2 will evaluate the safety and efficacy of CFZ533 in the absence of a CNI in combination with adjunct MMF and basiliximab induction therapy for up to 12 months.

Overall, results of this study will be used to inform the CFZ533 dose and regimen selection for investigation in the next phase of clinical development.

## **2 Study objectives**

### **2.1 Study Part 1: PK, PD and Safety**

#### **2.1.1 Primary objective**

- 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

#### **2.1.2 Secondary objectives**

- 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

### **2.2 Study Part 2: CNI-free Proof-of-Concept**

#### **2.2.1 Primary objective**

- 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

#### **2.2.2 Secondary objectives**

- To assess the safety and tolerability of CFZ533 administered chronically in combination with 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 GFR using MDRD
  - Proportion of patients with eGFR <60 mL/min/1.73m<sup>2</sup>
  - Proportion of patients with negative eGFR slope

- 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

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### **3 Investigational plan**

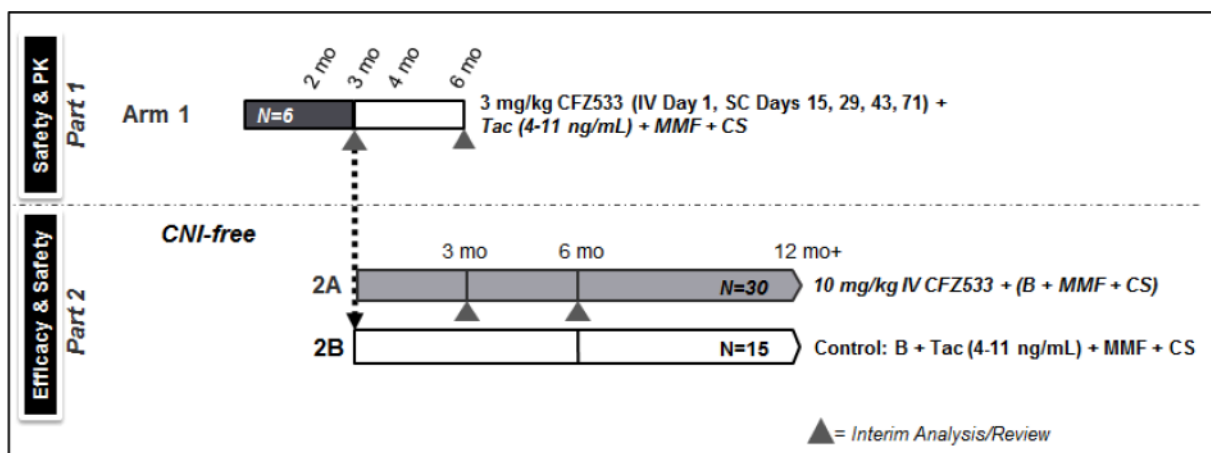
#### **3.1 Study design**

##### **3.1.1 General overview**

Study CCFZ533X2201 is a randomized, two-part, 6- or 12-month, sequential, adaptive, controlled, open-label, multicenter, clinical proof-of-concept study to evaluate the efficacy, safety, tolerability, PK and PD of CFZ533 + MMF + CS, with standard exposure (Part 1) or no Tac (Part 2), for initial and maintenance prophylaxis of organ rejection in adult *de novo* renal transplant recipients as compared to standard of care.

As illustrated in [Figure 3-1](#), each study part will evaluate a set of CFZ533 doses or treatment regimens in a parallel arm manner.

**Figure 3-1 CFZ533X2201 Study design**



Study Part 1 of this trial will focus on measuring the multiple-dose safety, tolerability PK and PD of CFZ533 when administered with the contemporary standard of care (SoC) treatment regimen. The SoC consists of concentration-controlled Tac, a calcineurin inhibitor (CNI), combined with mycophenolate mofetil (MMF) and corticosteroids (CS). Arm 1 will investigate CFZ533 3 mg/kg administered IV on Day 1, followed by subcutaneous (SC) administration on Days 15, 29, 43 and 71. <sup>Corporate Confidential Information</sup> will be measured on an ongoing basis during this portion of the trial to confirm the exposure-PD response <sup>Corporate Confidential Information</sup>.

. After the last dose, patients enrolled in Part 1 will remain on their background SoC treatment regimen, to be managed per local practice. Patients in Part 1 will not be carried over to Part 2.

Study Part 2 will continue the investigation of efficacy, safety, tolerability, PK and PD with the addition of induction therapy and avoidance of Tac. <sup>Corporate Confidential Information</sup>

Any significant deviations in PK or PD effects which may require a revision in the dosing scheme (dose, frequency or route of administration) will be addressed via an amendment prior to initiating the affected dose(s) in Part 2. <sup>Corporate Confidential Information</sup>

### 3.1.2 All cohorts

Before any study-related evaluations are performed, the patient must give written informed consent. Once consent is obtained, pre-transplant screening and baseline assessments will occur to determine the patient's eligibility to participate in the study starting up to 28 days prior to transplantation. If the screening, baseline and study Day 1 visits occur in close proximity of each other (i.e., within a 12 hour timespan), certain repeated assessments may be omitted, as noted in the [Assessment schedule](#). Data collection from assessments performed at the clinical site as part of medical standard of care but prior ICF sign-off is acceptable in order to confirm patient eligibility for patients receiving an organ from a deceased donor, if assessed shortly before transplantation (i.e within 24h– matching the baseline window of Day -1 to Day 1) and in-line with inclusion and exclusion criteria.

Day 1 is defined as the day of randomization/enrollment and transplantation. This protocol defines 7 days to a week and 4 weeks (or 28 days) to a Study Month. For example, Week 2 is considered to start on Day 8 and Study Month 2 is considered to start on Week 5/Day 29. Randomization/enrollment should occur within 24 hours pre-transplant and drug administration will begin after randomization/enrollment. If CFZ533 is to be administered, the first dose of CFZ533 will be administered IV pre-transplant or intra-operatively, and must be completed by the time of unclamping. Other study drugs must be started within 24 hours post-transplant or according to local practice.

Patients who are randomized/enrolled but not transplanted will be replaced. All randomized/enrolled subjects are expected to continue in the study up to Month 6 (Part 1) or Month 12 (Part 2) regardless of being on or off randomized/assigned treatment. All subjects will be followed-up for safety (e.g., SAEs) for approximately three months after their last dose of CFZ533 or 2 months after the EoS visit for patients on SoC treatment.

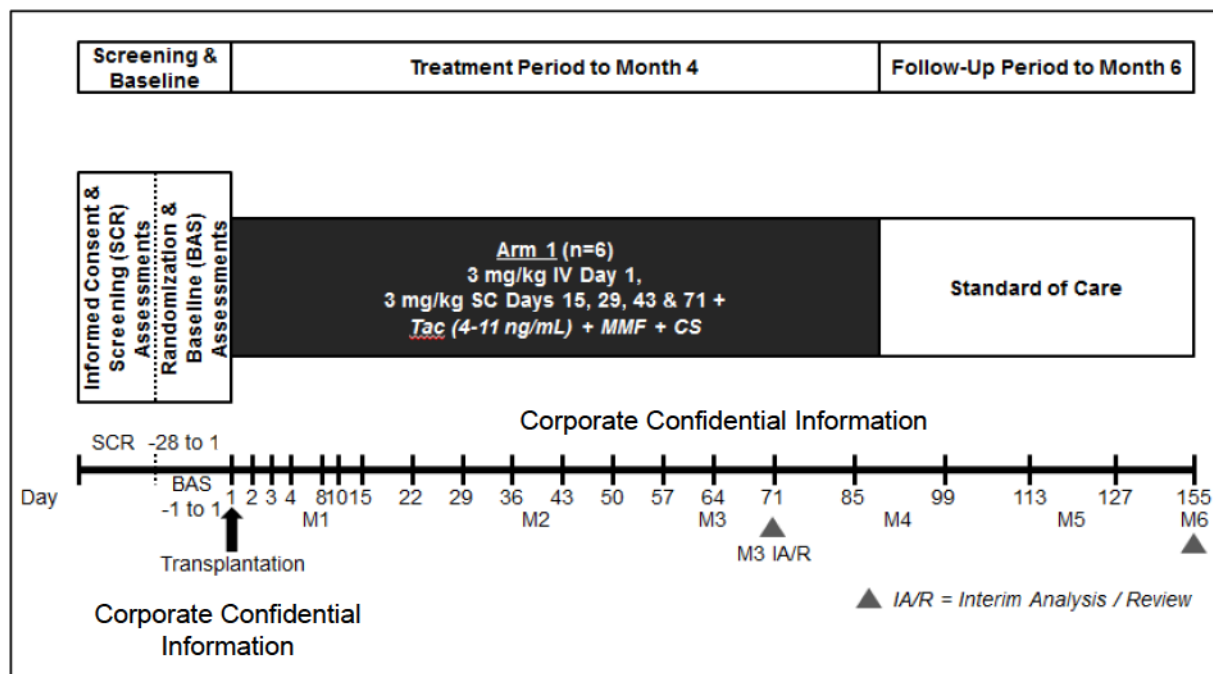
Any treatment arm in which the rejection rate fulfills the *a priori* defined stopping rules (see [Section 5.5.10](#)) will be immediately discontinued at any time during the study.

The transition from one arm to the next including Parts 1 to 2 will be based on *a priori* defined rules as described in [Section 9.4](#). Any changes in dosing or clinical conduct of the study will be implemented via an amendment, approved by the ethics committee responsible for approval of this study, and by the local health authority when mandated by local regulations.

Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, urinalysis) AE and SAE monitoring as well as special assessments as outlined in [Section 6.5](#).

### 3.1.3 Part 1 – Arm 1

Figure 3-2 Part 1 Design



Approximately 6 patients who meet the inclusion criteria will be enrolled within approx. 12 hours pre-transplant to receive IV and SC CFZ533 at 3 mg/kg on Days 1 (IV), 15, 29, 43 and 71) with standard-exposure Tac (whole blood trough concentration 4-11 ng/mL), mycophenolate mofetil 1.0g BID and CS (Figure 3-2).

**The first dose of CFZ533** will be administered IV pre-transplant or intra-operatively. Drug administration will begin after enrollment and must be completed by the time of unclamping. Subsequent doses of CFZ533 will be administered SC for a period of approximately 3 months.

**Other study drugs** must be started within 24 hours post-transplant.

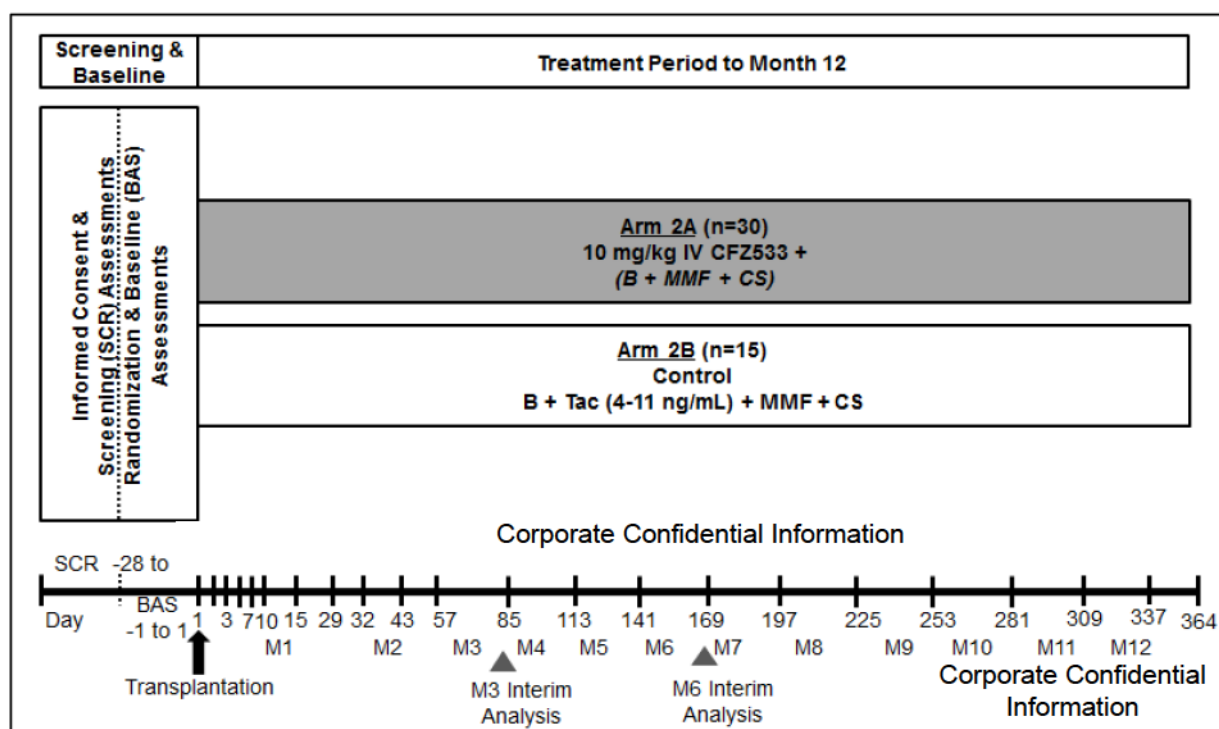
The day of enrollment and transplant will be considered to be study Day 1. Thereafter, post-transplant hospitalization will occur and then patients will make weekly study visits during Months 1-3 (up to approximately Day 71), then approximately every other week for Months 4-6 (up to approximately Day 155).

Cumulative efficacy and safety data will be collected on an ongoing basis during the conduct of the study.

PK, PD and tBPARs will be reviewed on an ongoing basis by the clinical trial team. If at any time the observed number of tBPARs exceeds the *a priori*-defined stopping criteria (see Section 5.5.10) the study will be stopped.

### 3.1.4 Part 2 – Arms 2A-2B

Figure 3-3 Part 2 Design



Approximately 45 patients who meet the inclusion criteria will be randomized in a 2:1 fashion within 24 hours pre-transplant to receive one of the 2 treatment arms (Figure 3-3):

1. **Arm 2A**, n=30: Basiliximab 20 mg (Days 1, 4) + **CFZ533 at 10 mg/kg IV** (17 doses) + MMF 1.0g BID + CS
2. **Arm 2B Control/SoC**, n=15: Basiliximab 20 mg (Days 1, 4) + Tac (4-11 ng/mL) + MMF 1.0 g BID + CS

**Induction therapy** must be started within 2 hours prior to transplantation, or according to local practice.

**The first dose of CFZ533** will be administered IV pre-transplant or intra-operatively. Drug administration will begin after randomization and must be completed by the time of unclamping. Subsequent doses of CFZ533 will be administered IV (Arm 2A), over a period of 12 months.

**Other study drugs** (apart from Basiliximab) should be started within 24 hours post-transplant. The second dose of basiliximab will be administered on Day 4, or according to local practice.

The day of randomization and transplant will be considered to be study Day 1. Further treatment will be given on study Days 3, 7, 15, 29, 43, 57 and then monthly thereafter until Months 12 (up to approximately Day 337). Subjects will then undergo Study Completion evaluations.

The primary endpoint of Part 2 will be assessed to determine whether the success criteria (safety and tBPAR) have been met

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If notable AEs or safety concerns meeting the *a priori*-defined stopping criteria (see [Section 5.5.10](#)) one of the planned dose levels may be changed or discontinued via amendment.

Subjects will undergo Study Completion evaluations at the end of the trial.

### 3.2 Rationale for study design

The open-label, adaptive design selected for Part 1 of this prospective, multicenter study will allow for a cautious comparison and evaluation of the multiple dose CFZ533 safety, tolerability, PK and PD as added to MMF + Tac and CS for 3 months. Part 2 expands upon the knowledge gained in Part 1 to assess the clinical activity and exposure-response of CFZ533 in a well powered CNI-free treatment regimen with basiliximab induction + MMF and CS for initial and maintenance prophylaxis of organ rejection in adult *de novo* renal transplant recipients.

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Although the ideal study would employ a double-blind, double-dummy methodology to minimize bias, in consideration of the inherent complexity of this adaptive study (multiple arms, frequent visits, interim analysis and extensive investigations), it has been decided to utilize an open-label design. This open-label design will not only minimize the risks for patients during the initial investigation of CFZ533 should the need for rapid intervention arise, such as emergent SAEs, but it also avoids the additional difficulties and

errors associated with sham-dose adjustments for a Tac placebo in CFZ533 arms and placebo injections/infusions in the control group. It is recognized that Investigator bias can affect the management of patients receiving investigational treatment; especially in an open-label study setting. In general, such scrutiny biases the study in favor of the control arm. As such, efforts to minimize bias for or against the CFZ533 treatment arms will be managed through the use of a limited number of high-quality transplant centers with a similar standard of care and patient management. In order to overcome any bias introduced by the open-label design, in Part 2, a blinded external independent adjudication committee (AC) has been formed to centrally evaluate all biopsies taken for suspected rejection reactions and other kidney disease related events in an unbiased, standardized and blinded manner. Adjudication outcome will be entered into the eCRF and additional outputs provided.

This first-in-transplant study will enroll a *de novo* patient population who receive a kidney from donors per the inclusion and exclusion criteria outlined in the clinical study protocol (see [Section 4](#)). This population was selected since they typically present the lowest risk of post-transplant complications, including delayed graft function and provide a fair assessment of clinical activity while not requiring the highest level of immunosuppression. Safety risks will be reviewed on a regular basis by an external DMC (see [Section 8.4](#)), with particular attention given to serious infections and malignancies associated to those (e.g., PTLT), as well as thromboembolic events.

### **Appropriateness of efficacy assessments**

The efficacy endpoints of treated BPAR and GFR are consistent with recent HA guidance ([CHMP/EWP/263148/06 2009](#)) and discussions ([FDA Workshop 2012](#)) on including an assessment of graft function as well as the traditional efficacy endpoints (e.g., tBPAR, BPAR) with or without clinical outcomes (i.e., Death and Graft loss).

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

Overall, this design is consistent with well-established precedents by global health authorities for clinical development of immunosuppressive regimens in kidney transplantation.

### **3.3 Rationale for dose/regimen, duration of treatment**

The initial CFZ533 dose to be administered to *de novo* renal transplant patients via both IV and SC route is 3 mg/kg CFZ533 (Part 1). For all CFZ533 treatment regimens, the first dose of CFZ533 will be administered IV prior to or during transplant surgery to ensure full CD40 target occupancy on B cells in the periphery at the time of unclamping and revascularization of the transplanted organ; the timing avoids initiation of an immune reaction in the initial presence of the foreign antigens. The SC route is preferred for patient convenience and ease of administration while the IV route is reserved for high doses and administration of the initial dose during surgery.

The following section discusses the overall CFZ533 dose rationale and specifics for Parts 1 and 2 in turn:

**Dose selection for Part 1:** In healthy volunteers, 3 mg/kg IV or SC led to full (>90%) CD40 saturation on B cells for about 4 weeks. Nevertheless, it is recognized that differences in expression level and/or turnover of membrane bound ([Lowe et al 2010](#)) and soluble targets ([Schwabe et al 1999](#), [Contin et al 2003](#), [Komura et al 2007](#)) may have an impact on the PK/PD profile of therapeutic antibodies. To profile the multiple-dose CFZ533 PK and PD in *de novo* renal transplant patients, both IV and SC doses of 3 mg/kg CFZ533 will be investigated over about 2 1/2 months in Part 1 of this study. In addition, to better control for inter-patient variability and minimize the number of patients exposed to quadruple immunosuppression, it is planned to evaluate both IV and biweekly and monthly SC administration within the same 6 patients. A simulation of the expected CFZ533 PK and CD40 receptor occupancy planned for Part 1 is presented in [Figure 3-4](#).

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This CFZ533 regimen is expected to result in complete CD40 suppression in peripheral whole blood over the treatment interval.

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Results from Part 1 will provide PK and PD data that will be used to better inform modeling and selection of IV and SC dosing regimens to be investigated in Part 2 of this trial.

To further minimize the risk for over immunosuppression, no basiliximab induction therapy will be administered to patients participating in this part of the trial. Patients will also receive prophylaxis for CMV and PCP and recipients with negative EBV serology will be excluded. Upon completion of the final CFZ533 dose administration, patients will remain on SoC to be managed based on defined local practices and will be monitored through Month 6 per the study protocol.

**Dose selection for Part 2:** In Part 2 of this trial, CFZ533 will be investigated at 10 mg/kg IV (a loading regimen consisting of 7 doses is being used in the first 2 months, then monthly (q4w) dosing starting on study Day 57).

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PK and PD data of ASKP1240 has been published for NHP ([Ma et al 2014](#)) and for healthy volunteers ([Goldwater et al 2013](#)) and some data have been revealed for a Phase 2 clinical trial in kidney transplant ([Harland et al 2015](#)).

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**Data from ASKP1240, a monoclonal antibody blocking CD40:** At the American Transplant Congress 2015, preliminary data from a Ph II trial in kidney transplantation (Harland et al Abstract ATC 2015), suggested efficient target mediated clearance of ASKP1240 during the first two months post-transplantation, Corporate Confidential Information

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Part 1 PK/PD data in transplanted patients will be analyzed prior to start Part 2. Any relevant deviations in the CFZ533 PK or CD40 occupancy profile for 3 mg/kg IV/SC measured in Part 1 of this trial Corporate Confidential Information will be modeled to further support the 10 mg/kg IV regimen prior to the initiation of Part 2. Any further dose or regimen adjustments will be implemented via amendment.

### 3.4 Rationale for choice of comparator

In adult *de novo* kidney transplant recipients, the use of Tac, MMF, and CS is an approved regimen (e.g. [Prograf® PI 2013](#)) and is the current standard of care used in more than 80% of kidney transplants globally. When Tac is combined with an MPA-based regimen and with induction using an IL-2 antagonist, the labeled trough concentration range for Tac is 4-11 ng/mL (e.g. [Prograf® PI 2013](#)), and this range will be employed in this clinical study. Over the past decade, the clinical use of calcineurin inhibitors, including Tac, has focused on minimization of the CNI to mitigate many of the associated adverse effects. Current clinical use of Tac with an MPA-based regimen results in excellent graft and patient survival as well as low rates of acute rejection.

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### 3.6 Risks and benefits

In this two part trial, there is no benefit expected for patients participating in Part 1 of this study. The risk (particularly of increased infections) to patients in Part 1 will be minimized by adherence to the inclusion/exclusion criteria, close clinical monitoring and minimization of the overall exposure to CFZ533 <sup>Corporate Confidential Information</sup> during treatment period. In Part 2, the benefit of a CNI-free regimen carries the expectation of improved renal function and vascular/metabolic profile ([Vincenti et al 2010](#)). The risks of insufficient efficacy (higher rate of acute rejection-tBPAR than standard of care) will be minimized by frequent monitoring of clinical labs and signs and symptoms suggesting tBPAR and the early discontinuation of any treatment arm that is ineffective according to the Stopping Rules (see details in [Section 5.5.10](#)).

The below sections list the risks related to CFZ533 treatment. For further details please see

Section 7 of the current Investigator's Brochure. Information and guidance for the standard of care treatment used in this study is provided in the local labelling information and should be strictly followed.

### **3.6.1 CFZ533**

Risks of CFZ533 administration include those generally associated with administration of a monoclonal antibody in humans. These include the possibility of a hypersensitivity reaction characterized by acute or delayed allergic reaction, anaphylaxis, urticaria, rash, dyspnea, hypotension, fever, chills and immunogenicity. A serious infusion reaction that results in anaphylaxis is a rare event in monoclonal antibody therapy. CFZ533 is a fully humanized monoclonal antibody of the IgG1 class. This class of antibody is normally abundant in humans. Therefore, the antibody itself is expected to be less immunogenic in humans compared to chimeric or other humanized antibodies. Assays to detect a putative antibody response to CFZ533 are included in the study design.

In consideration of the Phase 1 study results and non-clinical toxicology study results for CFZ533 as well as clinical studies with antibodies that target CD40 and CD154 (CD40L), the potential risks of CFZ533 in humans may include:

1. Infusion reactions, systemic inflammation and cytokine release
2. Immunosuppression and infections
3. Lymphoproliferative disorders
4. Other hypothetical risks

These risks and an overall risk mitigation strategy are discussed in turn below.

#### **3.6.1.1 Infusion reactions, systemic inflammation and cytokine release**

##### **Infusion reactions and cytokine release**

CFZ533 is a human, non-agonistic, Fc silent, IgG<sub>1</sub> antibody.

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clinical results with CFZ533 have not demonstrated signs or symptoms of cytokine release syndrome or elevation of cytokines as determined by multiplex cytokine assays.

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### 3.6.1.2 Immunosuppression and infections

CFZ533 is being developed for its expected immunosuppressive activity. CD40 ligation is linked to the functional activity of antigen presentation, as well as T cell priming, B cell differentiation, antibody production and immune memory. Administration of CFZ533 is expected to result in general immunosuppression with a decreased capacity to mount a response to novel immunogens, including those of bacterial, viral, fungal and parasitic origin. Corporate Confidential Information has been achieved. Patients receiving CFZ533 may be immune suppressed from weeks to months depending on the dose. During this time of immunosuppression subjects may be at a higher risk for infection.

It has been shown that patients with an X-linked genetic dysfunction in CD40-CD154 signaling, hyper-IgM (HIGM) syndrome, are at an increased risk for recurrent bacterial infections and infection with intracellular pathogens such as *Cryptosporidium* and *Pneumocystis jiroveci* pneumonia (PCP) (van Kooten and Banchereau 2000).  
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Considering the pharmacology of CFZ533, induction of a transient HIGM-like phenotype in patients receiving CFZ533 is possible, limiting their ability to mount an immune response to new infectious pathogens and induction of long-lasting immune memory to new immunogens.

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Although the ability to mount a primary immune response will be affected by CFZ533, the memory B cell repertoire and immune recall response should remain intact and protective. In addition, subjects will have adequate preformed antibody to maintain protective humoral response for extended periods of time (months).

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Similarly, cytotoxic T lymphocyte (CTL) response to viral infections may be reduced due to impairment of antigen presentation, but are expected to remain intact.  
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In patients receiving weekly to bi-monthly administration of the parent antibody lucatumumab, the rate of infection was very low and similar to control, supporting these above hypotheses.

### 3.6.1.3 Lymphoproliferative disorders

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It has been shown pre-clinically that the Epstein-Barr virus utilizes the CD40 signaling pathway to infect B cells and induce long term survival (Lougariis et al 2005). Therefore EBV reactivation is not expected. To minimize the risk in Part 1 of this trial, patients who are EBV-negative will be excluded. For patients in Part 2, the immunosuppressive burden is lower in the context of a

CNI-free treatment regimen, and recipients with a negative or positive EBV status will be eligible. During the trial all patients will be monitored with regular assessments of hematology, EBV-status as per local practice and clinical signs and symptoms (see [Assessment schedule](#)).

#### **3.6.1.4 Thrombosis**

There is a hypothetical risk for thromboembolic complications when targeting the CD40-CD154 co-stimulatory pathway. This risk is based on clinical results from previous compounds which have targeted CD154 and resulted in a fatal hypercoagulable phenotype.

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During the Phase 1 program, a focus on coagulation was included in the trial, including regular hematology, PT, aPTT and thromboelastography (TEG). In addition, there have been no reports of thromboembolic complications with the non-Fc silent competitor anti-CD40 antibody ASKP1240 (Astellas Pharma; [Goldwater et al 2013](#); [Yang et al 2012](#)).

In Part 1 of this study, one patient suffered from deep vein thrombosis (DVT), pulmonary embolism (PE) and dyspnea. Venous thrombotic events are known to occur in patients after renal transplantation with published literature suggesting a risk of up to 8.3% ([Andrassy et al 2004](#)). In addition, the medical history of this patient included kidney disease, smoking, diabetes, obesity, a sedentary lifestyle, and tacrolimus use and are all likely to be contributory factors to the thromboembolic events observed. Therefore, given the available information, the causal relationship between CFZ533 administration and these thromboembolic events remains unclear, however, cannot be definitively excluded, and therefore the incident was classified as SUSAR.

#### **3.6.2 Adjunct immunosuppression**

The combination of CFZ533 and adjunct immunosuppression with Tac (e.g. [Prograf® PI 2013](#)), MMF (e.g. [CellCept® PI 2013](#)), basiliximab (e.g. [Simulect® PI 2011](#)) and CS is not known. Please refer to the local labeling for the other agents for full disclosure of the expected risks associated with use in the setting of *de novo* renal transplantation for the investigational arms as well as control.

#### **3.6.3 Risk mitigation strategy**

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With initial administration of a biologic, the first 4 hours of exposure are most critical with most infusion reactions (including hypersensitivity, cytokine release, anaphylaxis) occurring within the first 2 hours of exposure ([Tabrizi and Roskos 2007](#)).

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release or anaphylaxis has not been reported with similar compounds targeting the CD40 receptor. Patients will receive their first dose of CFZ533 in the pre- to inter-operative time period, a time where patients are under the close supervision of clinical staff in a hospital environment. Any infusion related reactions can be managed at that time in accordance with local protocols.

Considering the expected immunosuppressive nature of the compound alone and in combination with induction and adjunct immunosuppressive agents, patients will be screened for a history of TB. A negative test result for TB (PPD, QuantiFeron test or chest X-ray) that has been performed within 6 month of randomization will be required prior to enrollment. Tests will be performed periodically during the trial. If there is suspicion of TB, a chest x-ray may be performed in accordance with local guidelines; subjects with a positive test will be excluded from participation. Patients will be screened for Epstein-Barr virus and if sero-negative, excluded from participation in Part 1 due to the high immunosuppressive burden expected in this cohort. Prophylaxis for CMV and PCP will be administered to all patients during the trial according to local practice.

Patients will be hospitalized for the first few days post-transplant and will return to the clinic frequently during the first month with a progressively increasing visit window as the study progresses to monthly visits at Month 6 through 12. During these visits safety, efficacy and PK/PD assessments will be collected. Standard safety assessments will include vital signs, physical examinations, ECGs, clinical laboratory evaluations (hematology, blood chemistry and urinalysis), AEs and SAEs monitoring as outlined in the [Assessment schedule](#). In addition to standard clinical laboratory assessments, subjects will be monitored regularly for signs and symptoms of infectious, inflammatory, hematologic or renal toxicity as outlined below.

Patients will be regularly evaluated while domiciled and upon return to the clinic for signs and symptoms which might indicate a severe infection, i.e., fever, nausea, myalgia, headache, arthralgia, chills, diarrhea, stiff neck, and malaise, and treated as appropriate per local practice depending on the infectious agent. Patients will be informed to report any of the aforementioned symptoms to the clinical staff to assure proper assessment and care can be administered in a timely manner.

Viral reactivation will be assessed for EBV, CMV and BK according to local practice on a regular basis.

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In agreement with the secondary objectives, changes in renal function will be assessed via serum creatinine and calculated creatinine clearance (MDRD).  
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Hypercoagulability and coagulopathy will be assessed using standard coagulation studies, including prothrombin time (PT) and activated partial thromboplastin time (aPTT) according to local practice.

Finally, key safety data will be reviewed by the Sponsor in a blinded manner in an ongoing basis. A DMC will review un-blinded study data regularly and on an *ad hoc* basis to assess whether the benefit/risk of each treatment arm remains acceptable. *A priori* defined stopping criteria and guidelines (Section 5.5.10) in addition to the clinical opinion of the Investigator and biopsy results managed per local practice will be used to protect individual patient safety during the trial.

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Cases of serious infections  
or neoplasms will also be monitored and reviewed on an ongoing basis.

Based on the information outlined above, the risk of administering CFZ533 in combination with MMF, corticosteroids, and basiliximab as well as add on to a Tac-based standard of care regimen appears manageable and reasonable to investigating the clinical activity of CFZ533 in the intended patient population.

## 4 Population

Parts 1 and 2 (initial PoC phase) of this multicenter study will be conducted in approximately 20 centers worldwide. The study population of Parts 1 and 2 will consist of approximately 51 male and female *de novo* adult renal transplant patients.

The Investigator must ensure that all subjects being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the Investigator, in order that the study population will be representative of all eligible subjects.

Subject selection is to be established by checking through all inclusion/exclusion criteria at screening/baseline. A relevant record (e.g., checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from **any** entry criterion excludes a subject from enrollment into the study.

#### 4.1 Inclusion criteria

Subjects eligible for inclusion in this study have to fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male or female patients  $\geq 18$  years old.
3. Recipients of a kidney transplant from a heart-beating deceased, living unrelated or non-human leukocyte antigen (HLA) identical living related donor.
4. Recipients of a kidney with a cold ischemia time (CIT)  $< 30$  hours.
5. Able to communicate well with the Investigator, to understand and comply with the requirements of the study.

#### 4.2 Exclusion criteria

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

1. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer.
2. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.  
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4. Recipients of an organ from a non-heart beating donor.
5. ABO incompatible or complement-dependent lymphocytotoxic (CDC) crossmatch positive transplant (isolated positive B cell crossmatches are not an exclusion criterion).
6. Subjects receiving a second kidney allograft, unless the first allograft was lost due to surgical complication.
7. Subjects at high immunological risk for rejection as determined by local practice for assessment of anti-donor reactivity (e.g., high PRA  $> 20\%$ , presence of pre-existing

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10. Subjects at risk for tuberculosis (TB), specifically subjects who:
  - Have current clinical, radiographic or laboratory evidence of active or latent TB
  - Have a history of active TB
    - a. Within the last 2 years even if it was treated
    - b. Greater than 2 years ago, unless there is documentation of adequate treatment according to locally-accepted clinical practice
  - In the opinion of the Investigator and based upon an appropriate evaluation, have a

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13. Subject with severe systemic infections, current or within the two weeks prior to randomization/enrollment.

- C
16. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.

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18. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 12 weeks after the study medications have been stopped. Highly effective contraception methods include:
- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
  - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
  - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
  - Combination of any two of the following (a+b or a+c, or b+c):
    - a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example, hormone vaginal ring or transdermal hormone contraception.
    - b. Placement of an intrauterine device (IUD) or intrauterine system (IUS).
    - c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

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

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

follow up hormone level assessment is she considered not of child bearing potential.

20. Any additional contraindication to the use of Tac or mycophenolate mofetil according to the national labeling information of these products (see local product label).

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

## **5 Treatment**

### **5.1 Protocol requested treatment**

#### **5.1.1 Investigational treatment**

The following drugs will be used in this study and will be administered in accordance with this protocol and where applicable, current local labeling. Not all dosage forms listed are available in each country, dependent on local approval status and regulations. The treatment regimen to which subjects are randomized comprises of up to four components: MMF (all study parts), CS (all study parts), CFZ533 and/or Tac (both in Part 1; either one in Part 2 ) and basiliximab (Parts 2 only).

- CFZ533 is provided as 150 mg/mL lyophilized open-label bulk medication requiring reconstitution. CFZ533 150 mg/mL concentrate for solution for infusion/ solution for injection (liquid in vial) will be introduced. Instructions for preparation and administration to be described in a separate pharmacy manual.

#### **5.1.2 Control and concomitant drugs**

Concomitant medication will be used according to label.

- Tac (e.g. Prograf® or Generics) as 0.5 mg, 1.0 mg or 5.0 mg capsules or tablets
- Mycophenolate mofetil ( e.g. CellCept® or Generics) 250 mg or 500 mg film-coated tablets, or 250 mg capsules, or 500 mg vial for IV administration
- Basiliximab as 20 mg lyophilized vial for IV administration following reconstitution with sterile water.

CS for oral and IV administration, MMF, Tac and basiliximab will be supplied locally.

#### **5.1.3 Additional study treatment**

No additional immunosuppressive agents may be used other than what is defined as per protocol. Concomitant therapies are as described below in [Section 5.5.8](#).

## **5.2 Treatment arms**

In Part 1, subjects will be enrolled into Arm 1. In Part 2, subjects will be randomized to one of the Arms 2A-2B. Study treatments are defined as:

### **Part 1**

- **Arm 1**, n=6: CFZ533 at 3.0 mg/kg SC (5 doses; first dose IV) + Tac (4-11 ng/mL) + MMF 1.0 g BID + CS

### **Part 2**

- **Arm 2A**, n=30: Basiliximab 20 mg (Days 1, 4) + CFZ533 at 10 mg/kg IV (17 doses) + MMF 1.0 g BID + CS
- **Arm 2B Control/Standard of Care**, n=15: Basiliximab 20 mg (Days 1, 4) + Tac (4-11 ng/mL) + MMF 1.0 g BID + CS

### 5.3 Treatment assignment

Randomization/Treatment numbers will be assigned to eligible subjects in Part 2 (see [Section 5.5.1](#) for details) prior to surgery. If provided, the Investigator will enter the randomization/treatment number onto the Electronic Case report Form (eCRF).

Patients in Part 1 will be enrolled sequentially across centers and will keep their screening/subject number throughout the trial. Patients in Part 2 will be randomized 2:1 to Arms 2A:2B.

The randomization/treatment numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and Investigator staff, as applicable:

- For Part 1, the Investigator or his/her designee will contact the Sponsor at screening or baseline and confirm the subject fulfills the population criteria.
- For Part 2, IRT will be used. IRT is a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. The Investigator or his/her designee will log into the IRT system at screening or baseline and confirm that the subject fulfills the population criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm. Detailed instructions on the use of the IRT can be found in the separate IRT manual.

### 5.4 Treatment blinding

This is an open-label, exploratory study and it is not planned to blind patients or site staff to treatment. In Part 1 since there is just one treatment arm, it will be known to the whole Clinical Trial Team that the subjects all received 3mg/kg CFZ533. In Part 2, core Clinical Trial Team members will be unblinded to continuously review safety and clinical data and evaluate the stopping rules.

### 5.5 Treating the subject

#### 5.5.1 Subject numbering

##### Subject number

Each subject is uniquely identified by a subject number assigned by Novartis or IRT system which is composed of a site number and a sequential number at each site. Once assigned, the Subject Number will not be re-used and will be the primary identifier for the subject in the study.

For Part 1, upon signing the informed consent form, the subject is assigned the next sequential subject number as given by the Investigator using the next blank eCRF book available from the EDC system.

If the subject fails to be randomized or treated for any reason, the reason will be entered into

the Screening Disposition eCRF.

For Part 2, upon signing the informed consent form, the subject is assigned the next sequential subject number by the Investigator via Interactive Response Technology (IRT). The Investigator or his/her staff will log into the IRT system and provide the requested identifying information for the subject to register them into the IRT. The site should select the eCRF book with a matching Randomization Number from the EDC system to enter data.

If the subject fails to be treated for any reason, the IRT should be updated within 2 days that the subject was not treated, the reason will be entered into the Screening Disposition eCRF.

### **Randomization/treatment number**

In addition to the subject number primary identifier, subjects in randomized studies will also be assigned a randomization/treatment number linked to treatment. Once the subject is deemed eligible for randomization/enrollment, the randomization/treatment number will be assigned. Once assigned to a subject, the randomization/treatment number will not be reused.

Patients will keep the subject number throughout the trial.

## **5.5.2 Dispensing the study treatment**

The investigational drug, CFZ533 will be prepared by Novartis and supplied to the Investigators as open-labeled bulk medication.

For preparation of the study medication in Part 2, the unblinded pharmacist or designee at the Investigator's site will need to log into the IRT system to receive the treatment code. In addition, the unblinded pharmacist or designee at the Investigator's site will prepare the medication for administration to subjects based on a separate pharmacy manual.

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

Bulk medication labels will be in the local language, will comply with the legal requirements of each country, and will include storage conditions for the drug but no information about the subject.

Each patient will be supplied by the study site with commercial drugs. Commercial Novartis drugs and/or 3<sup>rd</sup> party drugs used for this trial will be locally purchased and supplied either by the local CPO or by the clinical site per local regulations. In exceptional cases, central supply may be carried out.

## **5.5.3 Handling of study treatment**

### **5.5.3.1 Handling of investigational treatment**

Investigational treatment must be received at the study site by a designated person, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated staff have access. Upon receipt, the study drugs should be stored according to the instructions specified on the labels.

Storage conditions must be adequately monitored and appropriate temperature logs maintained as Source data.

The Investigator must maintain an accurate record of the shipment and dispensing of study

drug in a drug accountability ledger. Drug accountability will be noted by the Monitor during site visits and/or at the completion of the trial.

All drug supplies are to be used only for this protocol and not for any other purpose. Unless specifically instructed by Novartis, the Investigator must not destroy any drug labels, or any partly used or unused drug supply.

At the conclusion of the study, and, if allowed during the course of the study (e.g., an open-label study or an unblinded monitor), the Investigator will provide a copy of the drug accountability ledger to the monitor.

Only after receiving a written authorization by Novartis, the Investigator/designee will send all the unused and partly used drug supplies as well as the empty containers to the address provided at the time of authorization for destruction, or have the unused and partly used drug supplies as well as the empty containers destroyed by the site's pharmacist, providing a drug destruction certificate.

#### **5.5.4 Instructions for prescribing and taking study treatment**

The Investigator will dispense the appropriate amount of study drugs to cover each visit and additional drug in case of loss, breakage, or scheduling problems. Drug accountability will be performed to assess compliance. The Investigator should promote compliance by instructing the patient to take the study drug exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the Investigator if he/she is unable for any reason to take the study drugs as prescribed.

If MMF, Tac and/or CS are part of the assigned regimen, they will be taken concomitantly as per standard of local practice. The study drugs may be taken with or without food, but in a consistent fashion. Special attention must be taken to avoid concomitant administration of drugs, food or beverages which are known to be a strong inducer or inhibitor of CYP3A4 (see [Appendix 5](#)).

All drug trough levels assessed in this study (CFZ533, Tac, MPA) will be measured per the [Assessment schedule](#) or as per local practice (Tac/ MPA). For all samples sent for central analysis, the exact time and the date of sampling, together with the exact time and date of the last study medication dose prior to the sampling must be recorded on the central laboratory request form (refer to the separate Laboratory Manual). CFZ533 and MPA will be measured in plasma and Tac will be measured in whole blood samples. The patient will be instructed not to take his/her morning dose of immunosuppressant medications the day of a scheduled sampling, to record the medication dosage and time of last dose on the day prior to the blood sampling, and to bring all study drugs to the visit so that a dose may be administered upon completion of blood sampling.

All dosages of CFZ533 (all parts), MMF and Tac and all dose changes during the study must be recorded, with reason for administration, on the corresponding Dosage Administration Record eCRF.

All immunosuppressive drugs used and dosages administered must be recorded during the study. All changes to the immunosuppressive medication dosing regimen should be recorded

in the appropriate eCRF, along with the reason for change and dates.

### **Induction therapy, pre and post-transplant immunosuppression**

For patients randomized to the control arm or where Tac, MMF and/or steroids are to be administered per protocol, they may be administered prior to transplant according to center practice but such practice must be applied consistently to all subjects at a given center. At randomization/enrollment, all subjects must follow the assigned regimen. Pre-transplant immunosuppression, including induction therapy and any Tac or MMF should be recorded on the Concomitant medication eCRF under the Immunosuppressive category.

### **Basiliximab induction therapy**

Subjects randomized to receive induction therapy will receive 2 x 20 mg doses of basiliximab administered IV. The first dose should be given within 2 hours prior to transplant surgery, and the second dose should be administered on Day 4 post-transplant, or according to local practice.

The 20 mg vial should be reconstituted with 5 mL sterile water. The resultant solution is isotonic and may be injected as an IV bolus. Alternatively, the solution may be diluted to a volume of 50 mL with sterile saline and 5% dextrose and administered as an infusion over 30 minutes. If venous irritation occurs following bolus administration, the next dose (if appropriate) should be administered as a 30 minute infusion. There is no maintenance dose, and no other antibodies are permitted for induction therapy. All basiliximab doses and changes must be recorded in the Concomitant Medications eCRF under the Immunosuppressive category.

### **CFZ533 therapy**

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

The first dose of CFZ533 will be administered IV pre-transplant or intra-operatively. Drug administration will begin after randomization/enrollment and must be completed up to 6 hours prior to or at the time of unclamping.

The study medication preparation and administration guidelines are described in a separate pharmacy manual. The subject will be weighed at the Baseline visit and this weight value will be used for the initial study medication preparation and the calculation of the dose. Most actual weight will serve as basis for further dose calculations.

All dosages prescribed and dispensed to the subject and all dose changes during the study must be recorded on the CFZ533 Dose Administration Record eCRF. Patients can be released after each treatment if deemed appropriate by the Investigator.

### **MMF administration**

Mycophenolate mofetil will be 2 tablets of 500 mg or 4 capsules of 250 mg b.i.d. (2 g/day). For patients who remain intubated >24 hours post-transplant and/or whom are otherwise unable to swallow oral medication, IV MMF may be substituted until oral conversion is

possible.

The first dose of MMF will be administered immediately after randomization/enrollment and no later than 24 hours after graft reperfusion of the allograft or according to local practice.

Dose adjustment/interruption guidance for MMF is provided in [Appendix 4](#). All MMF doses and changes must be recorded on the MMF Dose Administration Record eCRF (Part 1) and Concomitant Medications eCRF under the Immunosuppressive category (Part 2).

### **Tacrolimus administration**

Tac will be administered as PO capsules b.i.d. and adjusted to maintain within the target ranges of 4-11 ng/mL. Tac should be initiated as soon as possible and no later than 24 hours after reperfusion of the graft. The lowest permitted dosing of Tac in this study is 0.5 mg b.i.d. If Tac is discontinued for more than 21 consecutive days, and the study regimen cannot be maintained, the patient must be discontinued from the randomized treatment and managed per local practice. Subjects who discontinue their study regimen are expected to remain in the study on standard of care to Month 6 in Part 1 or Month 12 in Part 2.

Tac dosing will be modified by Investigators as needed and recorded on the Tacrolimus Dosage Administration Record (Part 1) and Concomitant Medication (Part 2) eCRF at each visit. In the event of Tac intolerance (e.g., nephrotoxicity, neurotoxicity) dose reduction of Tac may be necessary. If it occurs that the Tac trough level is outside the required target level, then the Investigator will be asked to confirm the intended Tac trough level, to record the start date and reason for dose reduction on the Tacrolimus Dosage Administration Record (Part 1) and Concomitant Medication (Part 2 ) eCRF.

The co-administration of drugs known to interfere with Tac metabolism (see [Appendix 5](#)) should be avoided if possible. If these drugs are required, the Investigator should carefully monitor Tac trough levels.

The patient will be instructed to record the time of the last dose on the day prior to the blood draw and to bring the morning dose to the visit so it may be administered after the blood sampling is completed.

### **Corticosteroids**

CS will be administered according to local standard practice in a way that is consistent in all patients enrolled at each site. Dosing of CS should be recorded in the Concomitant Medications eCRF under the Immunosuppressive category.

### **5.5.5 Permitted dose adjustments and interruptions of study treatment**

In general, symptomatic treatment should be considered first to treat patients who have difficulties to tolerate their immunosuppressive regimen. However, for patients who are still unable to tolerate the protocol-specified study treatment, dose adjustments and interruptions of study drugs are permitted in order to keep the patient on study treatment as follows below.

#### **MMF/ MPA**

Dose adjustment/interruption guidance for MMF is provided in [Appendix 4](#). All MMF doses and changes should be recorded on the MMF Dose Administration Record eCRF (Part 1) and Concomitant Medications eCRF under the Immunosuppressive category (Part 2).

MMF (e.g. Cellcept) is known to cause significant gastrointestinal side effects in some patients. In case of acute intolerance of MMF, other medications (e.g. Myfortic) can be given to reach target mycophenolate trough levels when used according to drug label and as per local practice at the clinical sites. Each case should be discussed individually with the Sponsor. At clinical sites where mycophenolates other than MMF (e.g. Myfortic) are being used as SoC, these drugs can be considered instead of MMF after discussion with the Sponsor.

#### **Tacrolimus**

Tac dosing will be modified by Investigators as needed and recorded on the Tacrolimus Dosage Administration (Part 1) and Tacrolimus Concomitant Medication (Part 2) eCRF at each visit.

#### **CFZ533**

No dose adjustments beyond changes based on the patient's weight are permitted to the CFZ533 dose during the study.

In case of notable AEs, SAEs including loss of efficacy and/or associated PK/PD data collected during the study, changes to the next planned dose level may be considered and implemented via an amendment.

### **Treatment of Acute Rejection Episodes**

In all suspected acute rejection episodes, regardless of initiation of anti-rejection treatment, an allograft biopsy must be performed within 48 hours. Handling of biopsies is addressed in [Section 6.5.1](#).

All episodes of acute rejection must be entered on the corresponding eCRF (e.g., Acute Rejection eCRF, Kidney Allograft Biopsy eCRF) preferably within 24 hours. Sites should complete a SAE form for all confirmed acute rejection events in Part 1 and 2 and inform Sponsor within 24h.

Acute rejections should be treated with bolus methylprednisolone (other CS are acceptable at an equivalent dose) according to local practice. Recommended treatment is with at least 3 boluses of IV methylprednisolone with a minimal dose of 250 mg/bolus or at least 2 boluses of IV methylprednisolone with a minimal total dose of 750 mg.

Patients who experience steroid-resistant rejections, vascular rejections or rejections with a Banff grade  $\geq$  2B ([Appendix 8](#)) should be discontinued from study treatment, converted to local SoC and may be treated with other anti-rejection therapies (i.e., antibody therapy).

All medications used for the treatment of suspected or confirmed acute rejections must be recorded on the Concomitant Medications eCRF under the Immunosuppressive category.

### **Management of signs of over-immunosuppression**

CFZ533 was highly effective in preventing renal transplant rejection in NHP when used as monotherapy. Combining CFZ533 with MPA and CS after basiliximab induction may increase the risk for over-immunosuppression (e.g. BK viremia). For CFZ533 to be effective, full inhibition of CD40 signaling is required. Reducing the CFZ533 dose is not advisable, since under-dosing of CFZ533 may trigger loss of immunosuppression. In case of suspected over-immunosuppression clinical sites should first consider reducing the MPA level by 50 % or more (if MPA is completely stopped, CS may be slightly increased) with a follow up within the next weeks as per local practice. If there still are signs of over-immunosuppression, they should consider removing MPA and/ or reduce CS. If there still are signs of over-immunosuppression, or if the symptoms are severe, patient should be discontinued from CFZ533 and be switched to SoC.

### **Management of BK viremia**

In case of diagnosed BK virus in urine, MPA levels should be reduced as a first measure as described in the Section above “Management of signs of over-immunosuppression”. Patients are considered to have significant BK viremia when their plasma PCR results report  $\geq$ 10,000 copies/mL of BK virus ([Sood et al 2012](#)).

If a patient is found to have BK viremia that reaches  $\geq$ 10,000 copies/mL in plasma, reducing/ stopping of MPA should be considered as a first measure. If patients have biopsy-proven BK nephropathy they should be discontinued from their randomized treatment and be switched to standard-of-care treatment as per local center practice.

### **Management of Patients with Delayed Graft Function (DGF)**

DGF for this trial is defined as:

- A dialysis performed within 7 days of transplant
- **excluding** up to two dialysis sessions to correct electrolyte abnormalities (e.g., hyperkalemia) in the post-transplant time period

In case a patient experiences DGF, the DGF is by definition starting at reperfusion after the transplantation procedure. If the graft dysfunction is starting later according to the Investigator, then this condition is considered secondary graft dysfunction.

DGF must be reported as an AE for patients who experience DGF without requiring dialysis. In case DGF is reported as an AE and dialysis is also reported, the end of DGF is considered the day the last dialysis session ends.

In case of DGF, treatment will be according to local practice. DGF treatments must maintain

sufficient immunological coverage for the graft and may include maintaining, interrupting or reducing the dose of study drug and the use of anti-thymocyte globulin. If a polyclonal antibody or anti-thymocyte globulin is used, the study treatment must be discontinued and the subject will be placed on standard of care per local practice.

Primary graft non-function (PGNF) is defined as dialysis started 7 days after transplantation with a continuous record of post-transplant dialysis until either transplantectomy or death. PGNF should be reported on the Graft Loss eCRF.

If a subject is placed on permanent dialysis (or retransplanted), study treatment must be discontinued, the Graft Loss and Adverse Event eCRFs should be completed, and an SAE report of graft loss submitted. Dialysis treatments should be recorded on the Dialysis eCRF. Retransplantation should be recorded on the Surgical and Medical Procedures eCRF.

#### **5.5.6 Recommended treatment of adverse events**

Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies eCRF.

#### **5.5.7 Rescue medication**

Not applicable.

#### **5.5.8 Concomitant treatment**

The Investigator should instruct the subject to notify the study site about any new medications he/she takes after the subject was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study will be recorded on the Concomitant Medications eCRF or the Surgical and Medical Procedures eCRF respectively.

#### **CMV prophylaxis**

Cytomegalovirus (CMV) prophylaxis, with i.v. ganciclovir or oral valganciclovir, will be used in patients (CMV positive and CMV negative) as per local medical practice. Prophylaxis should be recorded on the Concomitant Medications eCRF.

#### ***Pneumocystis jirovecii* (*Pneumocystis carinii*) pneumonia (PCP) prophylaxis**

All patients will be started on trimethoprim-sulfamethoxazole, starting when oral medication can be tolerated and continued throughout the study. The same regimen should be administered to all patients at a given study center. Aerosolized pentamidine or dapsone may be administered to patients unable to tolerate trimethoprim-sulfamethoxazole. Prophylaxis should be recorded on the Concomitant Medications eCRF.

#### **Hepatitis B (HBV) prophylaxis**

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

## **BK virus**

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

## **Oral Candida treatment**

For oral thrush (Candida), Nystatin may be used in a swish and swallow regimen; alternatively, clotrimazole (Mycelex<sup>®</sup>) lozenges/troches may be used. Routine use of systemic agents, e.g., itraconazole, voriconazole and fluconazole, will not be allowed in study Part 1 unless patients are systemically infected since azoles may increase blood concentrations of Tac. Systemic therapy in Part 2 is to be based on center practice and at the Investigator's discretion. Treatment should be recorded on the Concomitant Medications eCRF.

### **5.5.9 Prohibited treatment**

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

The exception is for the treatment of acute rejection not responding to corticosteroids.

### **5.5.10 Discontinuation of study treatment and premature subject withdrawal**

#### **Study “Stopping rules”**

The following stopping rules based on potential toxicities will serve as the basis for placing the study on hold. Although the stopping criteria do not incorporate an absolute requirement for causality, the potential relationship between an AE and CFZ533 will be evaluated carefully on a case-by-case basis between the Sponsor and the Investigator. Following a review of the AE(s), a decision to permanently discontinue enrollment or re-initiate dosing will be made by the DMC.

- Two (2) or more patients presenting with PTLD or PML

In addition, specific stopping rules for the incidence of tBPAR will be applied. These rules are designed to ensure that a CFZ533 treatment arm will be stopped if there is high probability (>90%) that the true tBPAR rate is greater than 20%. Corporate Confidential Information

Corporate Confidential Information

In addition to the automatic hold criteria and tBPAR criteria presented above, the DMC will review safety data regularly as outlined in their charter (see [Section 8.4](#)) during quarterly and *ad hoc* meetings. The DMC can recommend stopping a specific study arm(s) or the entire trial if significant changes or effects that, in their collective opinion, are deemed unsafe or unethical to continue administering CFZ533.

### **Discontinuation of study regimen**

The Dosage Administration Records for CFZ533 (all parts), MMF and Tac (Part 1 only) and Concomitant Medication eCRF for MMF and Tac (Part 2) will be used to record if a subject has permanently discontinued study treatment and why.

Possible reasons for study treatment discontinuation are:

- Adverse Event
- Lack of Efficacy
- Technical problem during transplant surgery
- Subject/Guardian Decision
- Lost to follow-up
- Death
- Graft Loss

The Investigator should discontinue a subject from their randomized treatment regimen if, on balance, he/she believes that continuation would be detrimental to the subject's well-being.

Subjects who become pregnant while taking study medication must be discontinued from study medication and from the study, such pregnancies should be reported as SAEs to Novartis DSE and entered as AEs in the eCRF, the reason for discontinuation of study medication should be recorded as AE and reason for discontinuation from study is pregnancy (see next section below).

Subjects who discontinue study medication (CFZ533 or Tac) should remain in the study, if possible, and receive standard of care immunosuppression, according to local practice, until completing the study at Month 6 (Part 1) or Month 12 (Part 2). Visits and assessments for such subjects are described in the [Assessment schedule](#). All immunosuppressants after discontinuation of study regimen must be recorded on the Concomitant Medication eCRF under the Immunosuppressive category.

Subjects who discontinue their study treatment regimen should NOT be considered withdrawn from the study UNLESS they withdraw their consent to participating in all the elements of the study (see [Section 5.5.11](#)). Information on treatment discontinuation needs to be captured on the end of treatment eCRF page. Such subjects should remain in the study, if possible, and receive standard of care immunosuppression, according to local practice, until completing the study at Month 6 (Part 1) or Month 12 (Part 2). See the [Assessment schedule](#) for the required assessments of these subjects after discontinuation of study regimen. If they fail to return for these assessments for unknown reasons, every effort should be made to contact them as specified in [Section 5.5.12](#).

#### **5.5.11 Withdrawal of consent**

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a subject does not want to participate in the study anymore and does not want any further visits or assessments and does not want any further study related contacts and does not allow analysis of already obtained biologic material.

If a subject withdraws consent, the Investigator must make every effort to determine the primary reason for this decision and record this information in the eCRF. Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

#### **5.5.12 Loss to follow-up**

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject (e.g., dates of telephone calls, registered letters). A subject should not be considered lost to follow-up until his/her scheduled end of study visit would have occurred.

#### **5.5.13 Replacement of early withdrawals or discontinuations**

The sponsor allows for over-recruitment of 2 patients in Part 1 and additional 10% in Part 2, to compensate for potential early withdrawals or discontinuations from the study.

#### **5.5.14 Emergency unblinding of treatment assignment**

Not applicable.

#### **5.5.15 Study completion and post-study treatment**

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them (as applicable based on local regulations). Subjects who are prematurely withdrawn from the study should be treated according to local standard of care per Investigator's judgment. The study will complete when the last subject completes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator.

For Part 2: patients who completed the study on treatment with CFZ533 should be switched to

tacrolimus (or other SoC treatment) not earlier than 28 days after having received their last CFZ533 dose in order to not cause over-immunosuppression. From Days 28 to 35 after last dose, the concentration of tacrolimus should be at the lower recommended level before increasing it to the dose considered appropriate for the individual patient. Doses of MMF and CS may remain unchanged or be adapted accordingly.

### **5.5.16 Early study termination**

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the subject should be seen as soon as possible and treated as a prematurely withdrawn subject. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The Investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

## **6 Visit assessments**

The full [Assessment schedule](#) is presented at the end of the synoptic section, above. "X" indicates assessments that are to be performed for all subjects. "A" indicates assessments only to be performed for subjects maintaining the study regimen.

All randomized subjects are expected to continue in the study up to Month 6 (Part 1) or Month 12 (Part 2) regardless of being on or off randomized treatment. Subjects who discontinue their randomized study treatment regimen should be treated according to standard of care immunosuppression and return for the assessments indicated by "X" in the [Assessment schedule](#). If they refuse to return for these assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the subject and graft status.

Subjects should be seen for all visits on the designated day with an allowed visit window as specified in the [Assessment schedule](#).

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

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

At a minimum, subjects will be contacted for safety evaluations (e.g., SAEs) up to 3 months after his/her last dose of CFZ533, and 2 months after End of Study visit (EoS) for patients in the control arm for Part 2. Documentation of attempts to contact the subject should be recorded in the source documentation.

### **6.1 Dietary, fluid and other restrictions**

Not applicable.

## 6.2 Information to be collected on screening failures

All subjects who have signed informed consent but do not enter the next period (i.e., Randomized treatment to Month 6 or Month 12) will have the Study Completion eCRF for the screening period, demographics (giving reason for screen failure), inclusion/exclusion and SAE data collected. AEs that are not SAEs will be followed by the Investigator and collected only in the source data. All consented subjects must be entered in the IRT system at screening for Part 2. For subjects who are not randomized, the Screening Disposition eCRF must both be updated to indicate screen failure.

Rescreening is only allowed for subjects who were screen failures on the initial Screening visit (e.g., due to lab values out of range). Rescreened subjects should be recorded as screen failures under their original Subject ID number and assigned a new Subject ID number in the database when consented for rescreening.

All subjects who have signed informed consent and received study treatment will have all AEs **occurring after informed consent is signed** recorded on the Adverse Event eCRF until they completed the study.

Investigators will have the discretion to record abnormal test findings on the Medical History eCRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

## 6.3 Subject demographics/other baseline characteristics

After informed consent has been signed and the subject's eligibility to participate in the study has been determined, baseline subject information will be obtained in accordance with local regulations, including date of birth, age, sex (with child bearing status for females), race and ethnicity. In addition, relevant medical history (including CKD and ESRD history) and current medical conditions at screening, a full physical examination, vital signs and a pregnancy test (for females of child-bearing potential) will also be performed.

At Baseline/Transplantation, information on the renal transplant procedure, recipient and donor transplant background, recipient and donor viral serology and recipient/donor HLA testing results will be recorded. For randomization/enrollment of subjects in Part 1, the sponsor must be contacted and the sponsor will assign the treatment number. For randomization of subjects in Part 2, the IRT must be contacted and the IRT will assign the randomization number. For all subjects regardless of randomization/enrollment status, the Enrollment (Part 1) or IRT (Part 2) and Screening Disposition eCRF must be completed to document all consented subjects as either randomized or as screen failures and the reason for screen failure recorded in the eCRF.

## 6.4 Treatment exposure and compliance

CFZ533 concentrations and PK parameters (measures of treatment exposure) will be determined in all subjects treated with study treatment, as detailed in [Section 6.7](#).

All pre-transplant immunosuppression administered pre-randomization/enrollment, such as basiliximab, Tac, MMF and/or CS, will be recorded on the Concomitant Medications eCRF under the Immunosuppressive category.

All post-randomization/enrollment doses of CFZ533 (all parts), Tac and MMF (Part 1 only) will be recorded on their respective Dose Administration Record eCRFs. For Part 2, Tac will be recorded on the Tac Concomitant Medications eCRF. Basiliximab (all parts), MMF (Part 2) and/or CS will be recorded on the Concomitant Medications eCRF under the Immunosuppressive category.

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

Tac and MPA trough levels will be determined locally and recorded on the relevant trough level eCRF. The local trough values will be used to adjust the Tac and MPA dosing as needed. Post-discontinuation of study regimen, for patients remaining in study to Month 6 (Part 1) or Month 12 (Part 2), the trough levels should be recorded on the appropriate trough level eCRF.

Other drugs administered prior to and continuing at start of study medication will be entered on the Concomitant Medications eCRF.

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

## **6.5 Efficacy / Pharmacodynamic assessments**

### **6.5.1 Efficacy assessments**

#### **Treated Biopsy Proven Acute Rejection (tBPAR)**

A treated BPAR is any condition where the subject received anti-rejection treatment and was histologically diagnosed as acute rejection (according to the Banff 2009 criteria, [Appendix 8](#) or the Banff 2013 criteria. Borderline histological findings are interpreted according to local medical practice and fulfill the criteria of tBPAR if anti-rejection treatment is given). Renal biopsies will be collected for all cases of suspected acute rejection.

#### **Kidney allograft biopsy**

For all suspected rejection episodes, regardless of initiation of anti-rejection treatment, an allograft biopsy must be performed according to local practice preferably within 48 hrs. Biopsies will be read by the local pathologist according to the updated Banff 2009 criteria ([Appendix 8](#), or the Banff 2013 criteria depending on the local practice). The results of the biopsy read by the local pathologist will be listed on the Kidney Allograft Biopsy eCRF. The results will be used for subject management for acute rejection. The local pathologist will remain blinded to treatment. Any biopsies performed according to local practice (e.g., not for cause) should also be recorded. In Part 2, biopsies performed for suspected rejection and other kidney disease related events will also be evaluated centrally by an independent Adjudication Committee.

## **Graft loss**

The allograft will be presumed to be lost on the day the subject starts dialysis and is not able to subsequently be removed from dialysis. If the subject undergoes allograft nephrectomy prior to starting permanent dialysis, then the day of nephrectomy is the day of graft loss. The reason for graft loss will be recorded on the Graft Loss eCRF. This will be reported on the Study Completion eCRF and Treatment Phase Disposition eCRF with Graft Loss as the reason for study discontinuation and on the appropriate Dosage Administration Record eCRF(s) if death occurs while on randomized treatment. Graft loss is considered a SAE and should be reported on the Adverse Event eCRF (as serious) and the SAE reported to the local Novartis Drug Safety and Epidemiology Department local Novartis Drug Safety and Epidemiology (DS&E) Department within 24 hrs.

## **Death**

In the event of subject death, the SAE leading to death should be reported to Novartis DS&E within 24 hrs. The events leading to the death should be entered on the Adverse Event eCRF and the death should be indicated on the appropriate Dosage Administration Record eCRF(s) (if death occurs while on randomized treatment), on the Study Completion eCRF and on the Treatment Phase Disposition eCRF.

### **6.5.2 Pharmacodynamic assessments**

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## **Soluble CD40 and soluble CD154**

Peripheral blood total soluble CD40 and total soluble CD154 concentrations will be determined in Part 1, before, during and after administration of CFZ533. Only total soluble CD40 levels will be determined in Part 2.

### **6.5.2.1 Pharmacodynamic sample collection and processing**

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. All samples will be given a unique sample number (as listed in [Appendix 1](#)). The details of sample processing, handling, storage, and shipment will be described in a separate laboratory manual.

### **6.5.2.2 Pharmacodynamic analytical methods**

Analytical methods will be described in a separate laboratory manual.

### **6.5.2.3 Pharmacodynamic parameters**

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## **Total soluble CD40 and total soluble CD154**

Peripheral blood total soluble CD40 and total soluble CD154 (concentrations before, during or after treatment, as applicable) will be analyzed, as applicable.

## **6.6 Safety assessments**

### **6.6.1 Physical examination**

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

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

### **6.6.2 Vital signs**

Vital signs (radial pulse rate, blood pressure and body temperature) will be recorded as indicated in the [Assessment schedule](#). Blood pressure and pulse rate will be assessed at the same arm each time of determination and after the subject has rested in the sitting position (may be supine if during hospitalization) for at least five minutes. Systolic and diastolic blood pressure will be measured three times using an automated validated device (e.g., OMRON) with an appropriately sized cuff. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

The repeat sitting measurements will be made at up to 5 minute intervals and measurements will be recorded on the Vital Signs eCRF. Clinically notable vital signs are defined in [Appendix 7](#).

Body temperature should be measured as per local practice – the same method to be used consistently for all patients at each site.

### 6.6.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured.

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

- $BMI = \text{Body weight (kg)} / [\text{Height (m)}]^2$

Results will be recorded in the Vital Signs eCRF.

### 6.6.4 Laboratory evaluations

In the case where a laboratory assessment that is listed in the inclusion/exclusion criteria is outside of a **protocol-specified range** at screening and/or at the initial baseline, the assessment may be repeated once prior to randomization/enrollment. If the repeat value remains outside of protocol-specified ranges, the subject is excluded from the study.

Results from routine blood laboratory evaluation - directly assessed before Transplantation (i.e. within 24h prior to Tx) - can be used instead of further baseline laboratory evaluation. No second assessment implying second drawing of venous blood needs to be done.

In the case where a laboratory range is **not specified by the protocol**, but is outside the reference range for the laboratory at screening and/or initial baseline, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once prior to randomization/enrollment.

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

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

Clinically notable laboratory findings are defined in [Appendix 7](#).

#### 6.6.4.1 Hematology

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

#### 6.6.4.2 Clinical chemistry

Albumin, alkaline phosphatase, total bilirubin, bicarbonate/CO<sub>2</sub>, calcium, cholesterol, chloride, creatinine, CK, gamma-GT, glucose, HbA1c, LDH, inorganic phosphorus, lipase, amylase, magnesium, potassium, total protein, AST, ALT, sodium, triglycerides, BUN and uric acid will be measured. At timepoints on 6h, 24h, 48h and 72h samples have to be taken only for Mg, K, creatinine, Ca and glucose.

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

#### 6.6.4.3 Urinalysis

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

If the dipstick result is positive for protein, nitrite, leucocytes and/or blood the sample will be sent for microscopic analysis of WBC, RBC and casts according to local practice.

Local practice for transplant patients is that **no** microscopic analysis of the urine is done **for the first two weeks** after transplantation.

- Within the first two weeks after transplantation additional microscopic analysis will only need to be performed if the dipstick result is 3+ (or more) positive for leucocytes and/or blood (no WBC, RBC cast is expected to be seen with only proteinuria).
- From visit 108 (Study Day 29) onwards a microscopic analysis should be performed, except if the dipstick is completely negative.

#### 6.6.4.4 Special clinical laboratory evaluations

The details of sample processing, handling, storage, shipment and analysis for the following assays will be described in a separate laboratory manual, as required.

#### 6.6.4.5 Renal Function

Renal function will be assessed by calculated eGFR using the MDRD formula.

#### 6.6.4.6 Coagulation studies

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

#### 6.6.4.7 Cytokine assessment

Blood samples will be collected during the study (see [Assessment schedule](#)) for cytokine assessment via multiplex cytokine (or similar) platform (e.g., IL-2, IL-12, IFN-gamma, IL-4, IL-5, IL-10, IL-13, IL-1b, IL-6, IL-8, TNF-alpha, IL2R) and analyzed centrally, triggered by safety signals such as for example:

- hyper acute rejection or tBPAR associated with CFZ533 administration or in close proximity to the administration of CFZ533

- a febrile response around the time of CFZ533 administration as an indicator of an inflammation

#### **6.6.4.8 Donor specific antibodies (DSA)**

Blood samples for donor specific antibodies (antibodies directed against antigens expressed on donor organs) will be collected and evaluated locally.

#### **6.6.4.9 Immunogenicity**

The presence of anti-CFZ533 antibodies will be determined using a bridging ELISA-based assay.

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#### **6.6.4.11 Viral tests and EBV/CMV/BK virus surveillance**

All subjects will be screened/monitored for hepatitis B, hepatitis C, HIV, Epstein-Barr Virus (EBV), cytomegalovirus (CMV) and BK virus per local center practice. For centers where no protocol exists, details on the assessment requirements will be provided in the laboratory manual. Results of these assessments are to be transcribed into the appropriate eCRF pages.

#### **6.6.5 Electrocardiogram (ECG)**

The Fridericia QT correction formula (QTcF) will be used for clinical decisions.

Single 12 lead ECGs are collected. The original ECGs on non-heat-sensitive paper, appropriately signed, should be collected and archived at the study site.

Each ECG tracing should be labeled with study number, subject initials, subject number, date and time, be appropriately signed and dated to confirm review and filed in the study site source documents. For any ECGs with subject safety concerns, two additional ECGs should be performed to confirm the safety finding. Clinically significant ECG findings prior to dosing with investigational treatment must be discussed with the sponsor.

Clinically significant abnormalities should be recorded on the relevant section of the Medical History/Current Medical Conditions/AE eCRF page as appropriate.

### **6.6.6 Pregnancy**

Pregnancy tests will be required for all females of child-bearing potential at timepoints as designated in the Assessment Schedule, and defined below.

Serum or urine pregnancy tests should be carried out according to local practice. Local result must be available and negative prior to randomization/enrollment.

### **6.6.7 Tuberculosis surveillance**

Patients should have no history of active tuberculosis (per their pre-transplant assessments). A tuberculosis (TB) test (e.g. QuantiFeron, PPD or chest X-ray) will be conducted during screening whenever local procedures will allow (e.g. for living donors). For patients enrolled in areas where TB is endemic or who are at higher risk of active or latent TB disease, local screening result should be available and negative prior to randomization/enrollment for recipients of transplants from living donors. For deceased donor transplants a TB test showing negative results performed within 6 months prior to enrollment/ randomization is acceptable. Samples for a TB test will be collected at baseline and at various time points throughout the conduct of the study as defined in the [Assessment schedule](#). Chest X-ray to verify or monitor TB status of the patients is acceptable depending on local regulations. Whenever during the course of the study a positive test for TB is being confirmed, the patient will be discontinued from study treatment and returned to SoC.

## **6.7 Pharmacokinetic assessments**

See Sample log tables ([Appendix 1](#)).

### **6.7.1 PK Blood collection and processing**

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. Details of sample processing, handling, storage and shipment will be described in a separate laboratory manual. All samples will be given a unique sample number and a collection number (as listed in the blood log, [Appendix 1](#)). The actual sample collection date and time will be entered on the PK blood collection page of the eCRF. Sampling problems will be commented in the eCRFs.

### **6.7.2 Pharmacokinetic analytical methods**

Analytical methods will be described in a separate laboratory manual.

### **6.7.3 Pharmacokinetic parameters**

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

If data permit, typical exposure metrics and parameters could be determined using the actual recorded sampling times and non-compartmental method(s) with WinNonlin Pro or Phoenix, including (but not limited to): C<sub>max</sub>, C<sub>min</sub>, C<sub>trough</sub>, T<sub>max</sub>, , AUC<sub>t</sub>, from the plasma concentration-time data.

Concentrations below the LLQ will not be considered for PK parameter calculations.

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Defining bioavailability using the ratio of dose-normalized AUC approach, or the ratio of doses that provide equal AUCs approach, could be misleading (even if identical doses are administered IV and SC). Indeed, a non-compartmental approach, requires linear kinetics even if the same IV and SC doses are used. For mAbs, subject to target mediated disposition, clearance and distribution are dose/concentrations-dependent. A dose-independent, model-based analysis of IV and SC data would be the best way to determine bioavailability in this study. Such analysis may be reported in a separate standalone report.

## **6.8 Other assessments**

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## **7 Safety monitoring**

### **7.1 Adverse events**

An AE is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

For all subjects who have signed informed consent and are entered into the study will have all adverse events occurring after informed consent is signed recorded on the Adverse Event eCRF.

Pre-existing medical conditions/diseases (i.e., Medical History(ies)) are considered AEs if they worsen after providing written informed consent. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, or are considered clinically significant, or they require therapy.

The occurrence of AEs should be sought by non-directive questioning of the subject at each visit during the study. AEs also may be detected when they are volunteered by the subject during or between visits or through physical examination, laboratory test, or other assessments.

AEs must be recorded on the Adverse Event eCRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
2. its relationship to the investigational treatment (no/yes), or other study treatment (non-investigational) (no/yes), or both or indistinguishable,
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved should be reported.
4. whether it constitutes a serious adverse event (SAE)
5. action taken regarding investigational/other study treatment
6. whether other medication or therapies have been taken (concomitant medication/non-drug therapy)
7. its outcome

An SAE is defined as any AE which meets any one of the following criteria:

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

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

**Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see [Section 7.2](#).**

All AEs should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e., further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this AE; concomitant medication given; non-drug therapy given. The action taken to treat the AE should be recorded on the Adverse Event eCRF.

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

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the informed consent and should be discussed with the subject during the study as needed.

## **7.2 Serious adverse event reporting**

To ensure subject safety, every SAE, regardless of causality, occurring from after the subject has provided informed consent and until 3 months after his/her last dose of CFZ533 or 2 months after the EoS visit for patients on SoC treatment must be reported to Novartis within 24 hours of learning of its occurrence.

A SAE form for each confirmed acute rejection event should be completed since these are considered to be “medically significant events” for this clinical trial requiring timely and detailed reporting. The SAE form should be completed as soon as the PI at the site confirms the event based on the histological report from the local pathologist together with a clinical assessment of the event.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the Investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (*either initial or follow up information*) is collected and recorded on the paper Serious Adverse Event Report Form. The Investigator must assess the relationship to *each specific component of study treatment (if study treatment consists of several drugs)* complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the Investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

Follow-up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

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

### **7.3 Pregnancy reporting**

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the Investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment to pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Any SAE experienced during pregnancy must be reported on the SAE Report Form. If a patient of a US study center becomes pregnant, please also refer to the country-specific instructions in [Appendix 2](#).

### **7.4 Early phase safety monitoring**

The Investigator will monitor AEs in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

## **8 Data review and database management**

### **8.1 Site monitoring**

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Novartis representative will review the protocol and eCRFs with the Investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

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

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

### **8.2 Data collection**

Designated Investigator staff will enter the data required by the protocol into the eCRFs using fully validated software that conforms to 21 CFR Part 11 requirements. Designated Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to Novartis or the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the eCRFs are complete and accurate. After database lock, the Investigator will receive a CD-ROM or paper copies of the subject data for archiving at the investigational site.

All data captured for this study will have an external originating source (either written or electronic); the eCRF is not considered as source.

### **8.3 Database management and quality control**

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

Novartis staff or the CRO working on behalf of Novartis will review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated Investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be sent (e.g., fax, e-mail) to the site. Site personnel will complete and sign the copy, then send it (with original signature) back to Novartis staff or CRO working on behalf of Novartis, who will make the correction to the database.

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

Certain laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes in Part 2 will be tracked using an Interactive Response Technology (IRT). An internal Novartis IRT (NIRT) system will be used in Part 2. The data will be sent electronically to Novartis (or a designated CRO).

The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Global Head of Clinical Information Sciences and the Clinical Franchise Head.

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### **8.4 Data Monitoring Committee**

A DMC will be constituted. The mission of the DMC will be to ensure the ethical conduct of the study and to protect the safety interests of patients in this study. The DMC will be responsible for reviewing the safety and efficacy results from the interim and final analyses, as well as overseeing the data accruing in the trial at regular intervals. It is expected that the DMC may consist of a nephrologist, transplant surgeon, statistician, and infectious disease specialist.

Details on the working procedures of the DMC are described in the DMC Charter.

## **8.5 Adjudication Committee**

Not required for Part 1.

Since the study is open-label for investigators, for Part 2 an independent and blinded Adjudication Committee (AC) has been appointed in order to centrally evaluate all events reported as acute rejection, delayed graft function or other kidney dysfunction in an unbiased manner.

Details on the working procedures of the AC are described in a separate AC charter. An additional supportive PD analysis will be performed for BPAR and tBPAR based on adjudicated results.

## **9 Data analysis**

Data from Part 1 and Part 2 will be presented separately.

### **9.1 Analysis sets**

#### **Part 1 and Part 2:**

The Full Analysis Set will include all subjects that received at least one dose of study drug and who were transplanted.

The Safety Analysis Set will include all subjects that received at least one dose of study drug.

The PK Analysis Set will include all subjects with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received any study drug and experienced no protocol deviations with relevant impact on PK data.

The PD Analysis Set will include all subjects in the Full Analysis set with available PD data and no protocol deviations with relevant impact on PD data.

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

### **9.2 Subject demographics and other baseline characteristics**

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group.

Subject demographics will include age, sex, race, ethnicity, height, weight and BMI. Other baseline disease characteristics include relevant medical history, current medical conditions, results of laboratory screens, transplant history, donor characteristics (e.g., age, sex, race, type, CIT) and any other relevant information.

Summary statistics will be presented for the subjects in the Full Analysis Set.

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

### **9.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)**

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment group and subject.

#### **9.3.1 Study medication**

The duration (days) of study medication administration will be summarized. This will be calculated by subtracting the date of the last administration of study medication from the date of first administration and then adding the dosing interval for CFZ533 or Tac (i.e., 28 days for treatment administered once every 4 weeks). In calculating the duration of treatment, days of temporary interruption of study medication for any reason will be included. Further, the frequency of dose changes (including temporary dose interruption) will be presented by reason for the change.

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

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

#### **9.3.2 Concomitant immunosuppressants**

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

The dose of antibodies used for the treatment of acute rejection episodes will be recorded as well.

#### **9.3.3 Other co-medications**

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

### **9.4 Analysis of the primary variable(s)**

#### **9.4.1 Variable(s)**

##### **Parts 1 and 2:**

The primary variable is tBPAR after 3 months of treatment. For the analysis in Part 2, the total “on treatment time” in each treatment group is required.

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## 9.4.2 Statistical model, hypothesis, and method of analysis

### Handling of missing values/censoring/discontinuations

The primary analysis only considers the events “on treatment” (apply the window defined in [Section 9.4.1](#)), thus accounting for discontinuations from the randomized treatment arm or study.

#### Part 1

The number of patients with tBPAR is assumed to follow a binomial distribution, i.e.,

$r_i \sim \text{Binomial}(n_i, \theta_i)$ , where  $r_i$  is the number of patients with tBPAR in treatment group  $i$ ,  $n_i$  is the number of patients in treatment group  $i$  and  $\theta_i$  is the probability of tBPAR.

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The posterior mean tBPAR rate will be presented together with the 95% credible interval.

#### Part 2

The number of patients with tBPAR is assumed to follow a binomial distribution, i.e.,

$r_i \sim \text{Binomial}(n_i, \theta_i)$ , where  $r_i$  is the number of patients with tBPAR in treatment group  $i$ ,  $n_i$  is the number of patients in treatment group  $i$  and  $\theta_i$  is the probability of tBPAR.

The primary efficacy analysis for the first 3 months of Part 2 evaluates whether a CFZ533 treatment arm meets the pre-defined success criteria

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$\Pr(\theta_{\text{CFZ533}} - \theta_{\text{SoC}} < 0.20 \mid \text{data}) > 60\%$ .

The required posterior probabilities will be estimated from simulations of the posterior distributions of  $\theta_{\text{CFZ533}} - \theta_{\text{SoC}}$  and compared to the thresholds for the levels of proof.

The prior distributions will be assumed to be a non-informative Beta(1/3, 1/3) for CFZ533 and an informative prior of Beta(1, 13) for placebo. This informative prior corresponds to an approximate mean response rate of 7% with a 95% confidence interval of (0.2%, 24%) and was determined via a meta-analysis of control therapies (see [Section 9.6](#)).

The posterior mean tBPAR rates for each treatment group and for the difference in mean response rates between treatments will be presented together with 95% credible intervals.

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### **9.4.3 Supportive analyses**

#### **Part 2**

The tBPAR (or BPAR) rate will be analyzed at 6 months and 12 months post transplantation using the same method as described for the month 3 analysis in [Section 9.4.2](#).

## **9.5 Analysis of secondary and exploratory variables**

### **9.5.1 Efficacy**

Other efficacy variables will be analyzed similarly to the primary efficacy endpoint, although without the non-inferiority test:

- tBPAR at Months 3, 6 and 12
- BPAR at Months 3, 6 and 12
- Graft loss at Months 6 and 12
- Death at Months 6 and 12
- Graft loss or death at Months 6 and 12
- Antibody mediated tBPAR at Month 12

For each of the efficacy endpoints (primary and secondary), simple event rate estimates (proportion of events) will be obtained and each CFZ533 treatment arm event rate will be compared with the control arm event rates using Z-statistics based on two-sided 95% confidence intervals for differences in event rates.

As supportive analyses, BPAR and tBPAR will also be analyzed using the adjudicated results.

### **9.5.2 Pharmacodynamics**

## Total soluble CD40 and total soluble CD154

These data will be summarized by treatment and subject. Descriptive statistics will also be provided such as mean, median, standard deviation, minimum and maximum, by time point and treatment.

### 9.5.3 Safety

Unless otherwise specified, safety analyses include all data collected, including after discontinuation of randomized treatment.

#### 9.5.3.1 Main safety endpoint: estimated GFR using the MDRD formula

The key secondary and safety variable is renal function as assessed by eGFR (MDRD formula). This will be evaluated at Month 12 by comparing the mean eGFR values between groups.

The MDRD formula is defined as follows ([Levey et al 2003](#)):

$$\text{GFR [mL/min/1.73m}^2\text{]} = 186.3 * (\text{C}^{-1.154}) * (\text{A}^{-0.203}) * \text{G} * \text{R}$$

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

A is age [years]

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

R=1.21 when race is **black**, otherwise R=1.

Local laboratory serum creatinine values will be used for all renal function data analysis. Serum creatinine results are in units of umol/L, so the following formula should be used to convert to the required unit of mg/dL:

$$\text{C [mg/dL]} = \text{serum concentration of creatinine [umol/L]} / 88.4.$$

Estimated GFR will be determined and summarized in each part of the study.

#### Handling of missing values/censoring/discontinuations

The analysis will be made on the FAS population. The following imputation method will be applied for patients with missing eGFR values:

- Patients that lose their graft will be assigned a value of zero for their missing GFR value.
- Patients that die or are lost to follow-up with a functioning graft will have an imputed value using the last-observation-carried-forward (LOCF) method.
- For patients that discontinue randomized treatment the eGFR will be considered missing after applying the windows defined in [Section 9.4.1](#).

Graft loss patients do not have a functioning graft; hence the lowest possible GFR value (zero) will be assigned to such patients. In contrast, patients that die with a functioning graft, die for different reasons (e.g., suicide, car accident, cancer). Similarly, patients who are lost to follow-up have renal function, but missing values for various reasons (e.g., moving from the area or not being able to make the site visit during the Month 6 or Month 12 visit window). Patients who have a functioning graft at the time of death or are Lost to Follow-up with a functioning graft will be analyzed via an imputation method that employs LOCF.

### **9.5.3.2 Other safety endpoints**

#### **Vital signs**

All vital signs data will be listed by treatment, subject, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

#### **ECG evaluations**

All ECG data will be listed by treatment, subject and visit/time; abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

#### **Clinical laboratory evaluations**

All laboratory data will be listed by treatment, subject, and visit/time and if normal ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

#### **Adverse events**

All information obtained on AEs will be displayed by treatment and subject.

AEs and infections collected are to be coded with the MedDRA dictionary that gives preferred term and primary system organ class information. AEs and infection preferred terms are to be analyzed as a whole under the heading of AEs for each treatment arm. The incidence of AEs will be summarized by body system, severity and relationship to study drug by the following:

- AEs by primary SOC and PT
- AEs rated to have relationship to study drug by SOC and PT
- AEs by primary SOC, PT, and maximum severity
- SAEs by SOC and PT
- SAEs rated to have relationship to study drug by SOC and PT
- Deaths by SOC and PT
- AEs leading to discontinuation of a study drug by SOC and PT
- AEs leading to dose adjustment or interruptions of a study drug by SOC and PT
- infections by type of infection (viral, bacterial, fungal, and others) and microorganism of infection
- serious infections by type of infection and micro-organism of infection
- new onset diabetes mellitus (as defined in [Section 6.6.4.4](#))

- AEs by standardized MedDRA query (SMQ) levels (broad and narrow search)
- AEs by standardized MedDRA query (SMQ) and preferred term (broad and narrow search)

#### Multiple Occurrences for Tables:

In all tables about incidence rates of AEs / Infections, if a patient has multiple occurrences of an AE, this patient will be counted only once in the corresponding AE category. If a patient has multiple AEs within a system organ class, s/he will be counted only once for that class. If a patient has multiple severity ratings for an AE while on treatment, s/he is only counted under the maximum rating.

Information pertaining to AEs noted during the study will be listed by patient, including the verbatim term given by the Investigator, the PT and SOC given by the MedDRA dictionary, start and end date, causality, severity, and relationship to study drug as assessed by the Investigator.

### **BK-polyoma viremia and nephropathy**

The following variables will be analyzed descriptively:

- occurrence of BK-polyoma viremia any time post-transplantation “on treatment”
- occurrence of BK-polyoma viremia any time after switching a patient to SoC treatment
- occurrence of BK-polyoma virus nephropathy any time post-transplantation “on treatment”
- occurrence of BK-polyoma viremia any time after switching a patient to SoC treatment.

The difference of the investigational regimens to the control regimen will be summarized by risk ratios and appropriate CIs.

### **EBV, CMV and TB**

All EBV, CMV and TB surveillance data will be listed by treatment, subject, and visit/time and if normal ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

### **Laboratory data**

Abnormalities according to clinically notable criteria will be identified. A by-subject listing of individual subject laboratory data will be generated. Values outside of the clinically notable limits will be flagged. Shift tables describing changes from randomization/enrollment based on the clinical notable criteria will be presented.

Descriptive statistics (mean, standard deviation, minimum, median and maximum) of quantitative laboratory variables, including change from randomization/enrollment, will be generated by visit.

## **New onset diabetes mellitus (NODAT)**

The incidence of subjects developing new onset diabetes mellitus after transplantation (NODAT) will be summarized by treatment group. The probabilities of developing NODAT will be compared between treatment groups at 6 and 12 months post-transplant using logistic regression models with HbA1c levels at randomization/enrollment as predictive variables. Death, graft loss, or loss to follow up without NODAT before Month 12 will not be counted as developing NODAT. This analysis will be performed using subjects in the FAS population who do not have DM at randomization/enrollment.

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### **9.5.4 Model based dose-exposure response analysis**

Not applicable.

### **9.5.5 Pharmacokinetics**

CFZ533 plasma concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ, which will be reported as zero. Summary statistics will include mean (arithmetic and geometric), SD, 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.

If data permit, PK parameters will be calculated as described in [Section 6.7.3](#) and will be listed by treatment and subject. Concentrations below the limit of quantification will not be considered for the calculation of PK parameters. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented.

A dose-independent, model-based analysis of IV and SC dosing may be used to determine the bioavailability of the SC administration in this study (see [Section 6.7.3](#) for more details). Also, any dose(concentration)-exposure relationship should be derived using same the approach. Such analysis will be reported in a separate standalone report.

### **9.5.6 Pharmacokinetic / pharmacodynamic interactions**

The relationship between CFZ533 concentration (PK) and PD variables will be explored graphically. Modeling of PK/PD data using a population approach may be performed as appropriate and will be reported in a separate standalone report. The broad principles outlined in the FDA Guidance for Industry: Population Pharmacokinetics will be followed.

## Drug-drug interactions

This study is also collecting data to document potential Therapeutic Protein Drug Interactions (TPDI) when CFZ533 is given in combination with mycophenolate mofetil and Tac in *de novo* kidney transplant patients.

To evaluate the potential for CFZ533 to cause TPDI via indirect (target binding) mechanisms, an exploratory population pharmacokinetic (PPK) approach may be conducted, aiming to identify unexpected TPDI with planned co-therapies (monitoring trough concentrations of Tac and MPA), and to provide a first risk assessment in *de novo* transplant patients. This approach is aiming to evaluate CFZ533 (i) as a perpetrator, with potential interactions with drugs specific to the target indication (mycophenolate mofetil and Tac), or (ii) as a victim drug, treating concomitant medications as covariates, by assessing a drug interaction effect on clearance. This exploratory approach should be generating hypothesis, with findings to be confirmed through a prospective pooled PPK approach based on data collected in Phase III and Phase II, to ensure unbiased and conclusive analysis results.

Such exploratory analysis applying a population pharmacokinetic approach may be reported in a separate standalone modeling report.

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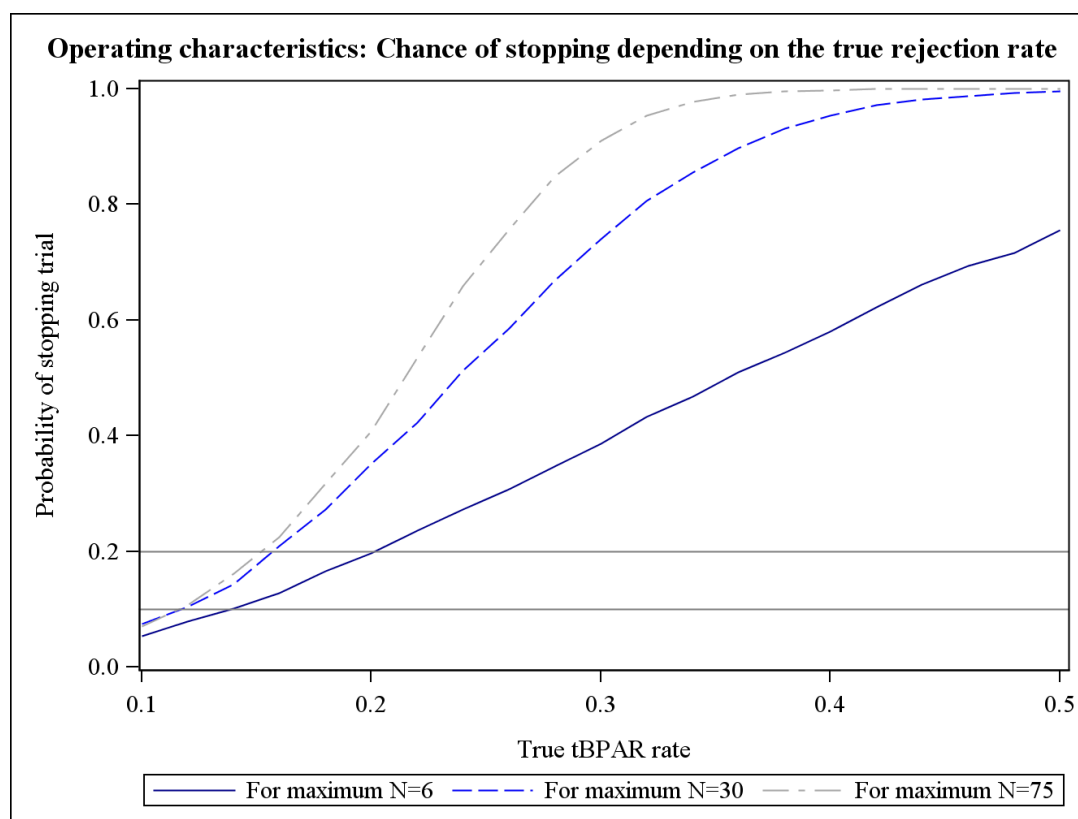
## 9.6 Sample size calculation

### All Parts:

The stopping rules as defined in [Section 5.5.10](#) are designed to ensure that a CFZ533 treatment arm will be stopped if there is a high probability (>90%) that the true tBPAR rate is greater than 20%.

[Figure 9-1](#) indicates the probability of stopping for an arm for various true tBPAR rates and shows that the stopping rules ensure that the chance of stopping an arm are sufficiently high for true high tBPAR rates while remaining appropriately low when the true rates are low.

**Figure 9-1 Probability of stopping a cohort for various true tBPAR rates**



### Part 2

#### Operating characteristics

The sample size justification for Part 2 considers the probability of progressing further development or not progressing based on the planned safety stopping rules and the success criteria for the planned sample size.

The safety stopping rules (see [Section 5.5.10](#)) ensure that the study will not continue if:

$$\Pr(\theta_{CFZ533} > 0.20 \mid \text{data}) > 90\%$$

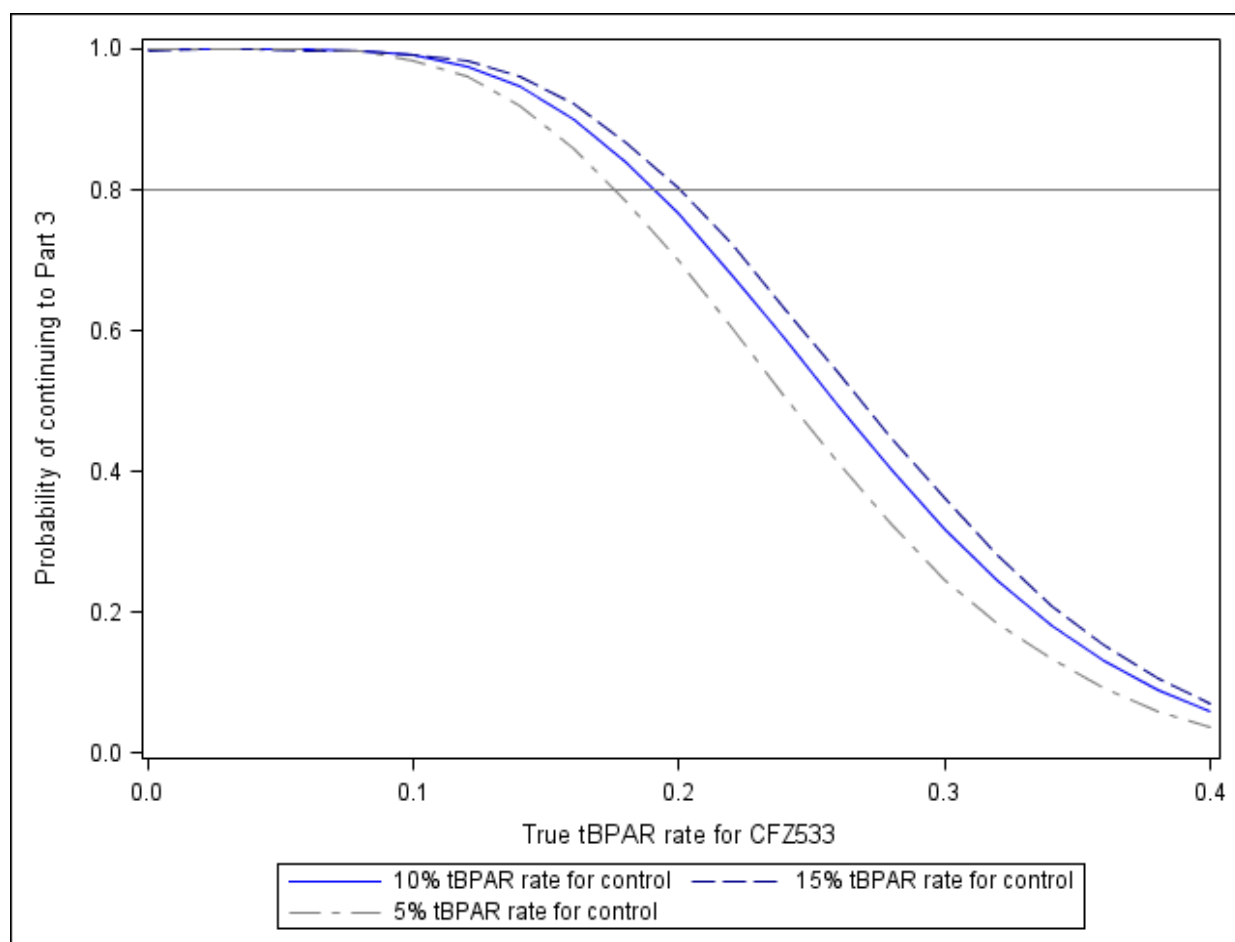
The success criteria (see [Section 9.4.2](#)) are met if:

$$\Pr(\theta_{\text{CFZ533}} - \theta_{\text{SoC}} < 0.20 \mid \text{data}) > 60\%.$$

[Figure 9-2](#) shows the chances of continuing development (i.e., of not meeting the safety stopping rules and meeting the success criteria) on the y-axis for a range of true values of the tBPAR rate for CFZ533 (x-axis) and for three possible control rates (blue and grey curves). The probability of moving is high when CFZ533 has a low true tBPAR rate and is comparable to control. For example, if the true CFZ533 rate is less than 20% and the true control rate is around 10%, there is a greater than 80% probability of progressing to Part 3.

Conversely, when the true tBPAR rate for CFZ533 is high, the probability of not continuing is high. For example, there is an approximately 80% probability of not progressing when the true CFZ533 rate is more than 25% greater than the true control rate.

**Figure 9-2** Probability of progressing for different true values of tBPAR for CFZ533 and control



These calculations assume that the primary efficacy variable, rate of tBPAR, follows a binomial distribution. The prior distribution for the control tBPAR rate, Beta(1, 13), is estimated from a Bayesian meta-analysis of tBPAR rates from four previous studies using a control treatment similar to the one used in this study. The four studies were selected from the studies used in a previous Novartis generated meta-analysis studies and are summarized in Table 9-1.

**Table 9-1 Summary of historical control data**

Study	Treatment	Number of patients with tBPAR	Total number of patients	tBPAR rate
1 - <a href="#">Vincenti et al 2007</a>	B+Tac+MMF+CS	24	346	0.069
2 - <a href="#">Silva et al 2007</a>	B+Tac XL+MMF+CS	17	214	0.079
3 - <a href="#">Silva et al 2007</a>	B+Tac+MMF+CS	8	212	0.038
4 - <a href="#">Scholten et al 2006</a>	B+Tac+ MMF(0.5g)+CS	4	63	0.063

B=basiliximab

Prediction of the control rate for a future trial resulting from the Bayesian meta-analysis is shown in Figure 9-3.

**Figure 9-3 Results of Bayesian meta-analysis prediction**

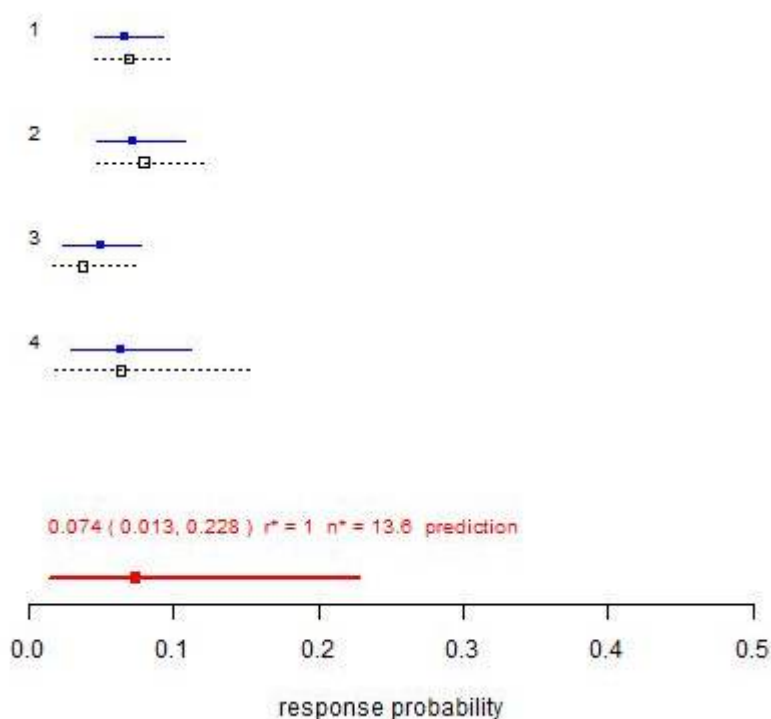


Figure 9-3 shows estimates of response rate and 95% credible intervals for each study based on study data alone (dashed lines) and from the meta-analysis (solid lines). The overall prediction for response rate in a future study is shown in red together with the mean and 95% credible interval from the posterior distributions and  $n^*$ , the prior number of observations that these data would contribute to a future analysis.

To allow for a simple randomization ratio for allocation of patients to treatment groups, it was decided to reduce the control arm to 15 patients, compared to 30 for the CFZ533 arms. Thus a prior beta distribution of Beta (1, 13) was chosen, which has a mean value of 7 with 95% CI (0.2, 24) and an approximate weight of 14 patients.

## 9.7 Power for analysis of key secondary variables

Table 9-2 provides 80% and 95% CIs for between-treatment difference (CFZ533-control regimen) based on an assumed SD and difference for  $eGFR_{MDRD}$ . Since this is an exploratory phase 2 trial, evidence of renal benefit will be based on a 80% CI. In line with the SYMPHONY study (Ekberg et al 2007), a difference of 6.5 mL/min/1.73m<sup>2</sup> between treatment regimens is considered to be the lower limit of clinically relevant benefit.

**Table 9-2 Two-sided 80 and 95 percent example CIs for between-treatment difference (CFZ533-Control regimen) of calculated  $eGFR$  (MDRD), assuming dropout rate = 30 percent (n = 53/group)**

Observed Standard Deviation	Observed difference in $eGFR_{MDRD}$ CFZ533 – control	80% CI	95% CI
16	4.0	(-0.0, 8.0)	(-2.2, 10.2)
	5.0	(1.0, 9.0)	(-1.2, 11.2)
	6.0	(2.0, 10.0)	(-0.2, 12.2)
	7.0	(3.0, 11.0)	(0.8, 13.2)
	8.0	(4.0, 12.0)	(1.8, 14.2)
18	4.0	(-0.5, 8.5)	(-3.0, 11.0)
	5.0	( 0.5, 9.5)	(-2.0, 12.0)
	6.0	( 1.5, 10.5)	(-1.0, 13.0)
	7.0	( 2.5, 11.5)	( 0.0, 14.0)
	8.0	( 3.5, 12.5)	( 1.0, 15.0)
20	4.0	(-1.0, 9.0)	(-3.7, 11.7)
	5.0	(-0.0, 10.0)	(-2.7, 12.7)
	6.0	(1.0, 11.0)	(-1.7, 13.7)
	7.0	(2.0, 12.0)	(-0.7, 14.7)
	8.0	(3.0, 13.0)	(0.3, 15.7)

## **10 Ethical considerations**

### **10.1 Regulatory and ethical compliance**

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

### **10.2 Informed consent procedures**

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the subject. In cases where the subject's representative gives consent, the subject should be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source documents.

Novartis will provide to Investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is

considered appropriate for this study. Any changes to the proposed consent form suggested by the Investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the subject will not reliably comply, they should not be entered in the study.

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In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or Ethics Committee approval will be obtained.

### **10.3 Responsibilities of the investigator and IRB/IEC**

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB, must be given to Novartis before study initiation. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform Novartis immediately that this request has been made.

### **10.4 Publication of study protocol and results**

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as [clinicaltrials.gov](http://clinicaltrials.gov). In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

## **11 Protocol adherence**

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances should an Investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If the Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

### **11.1 Protocol Amendments**

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for subject safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the Health Authorities (where required) and the IRB/IEC/REB at the study site should be informed within 10 working days or less, if required by local regulation.

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### 13 Appendix 1: Sample Log table – all matrices

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#### Blood Log (Part 1):

Visit	Study Day (Name or Time Post-Dose)	Serum pregnancy <sup>*</sup>	Local Labs <sup>^</sup>	Central Lab	Viral / TB serology / surveillance
		mL	mL	mL	mL
1	Day -28 to 1 (Screening)	5 <sup>#</sup>	19 <sup>#</sup>	6 <sup>#</sup>	5 <sup>#</sup>
99	Day -1 to 1 (Baseline)	5 <sup>#</sup>	19 <sup>#</sup>	6 <sup>#</sup>	20 <sup>#</sup>
101	Day 1 (Predose 1)		19 <sup>#</sup>	6 <sup>#</sup>	
101	Day 1 (EOI 1)†				
101	Day 1 (6 hrs)		19	6	
102	Day 2 (24 hrs)		19	6	
103	Day 3 (48 hrs)		19	6	
104	Day 4 (72 hrs)		19	6	
105	Day 8				
106	Day 10	5			
107	Day 15 (Predose 2)		19	6	
108	Day 22				10
109	Day 29 (Predose 3)		19	6	
110	Day 36				
111	Day 43 (Predose 4)				
112	Day 50				
113	Day 57	5	19	6	15
114	Day 64				
115	Day 71 (Predose 5)				
116	Day 85		19	6	
117	Day 99				
118	Day 113		19	6	
119	Day 127				
199	Day 155 / Study Completion	5	19	6	15
Study total		25	247	78	65
Total Blood Volume†					

DSA	Corporate Confidential Information	ac & MP trough levels
mL		mL
4 <sup>#</sup>		
4 <sup>#</sup>		
		6
		6
		6
		6
		6
		6
		6
		6
		6
		6
		6
		6
		6
		6
		6
4		6
12		96

sCD40	sCD154
Sample No.	Sample No.
mL	ml
1301	3 1401 4
1302	3 1402 4
1303	3 1403 4
1304	3 1404 4
1305	3 1405 4
1306	3 1406 4
1307	3 1407 4
1308	3 1408 4
1309	3 1409 4
1310	3 1410 4
1311	3 1411 4
1312	3 1412 4
1313	3 1413 4
1314	3 1414 4
1315	3 1415 4
1316	3 1416 4
1317	3 1417 4
1318	3 1418 4
1319	3 1419 4
1320	3 1420 4
1321	3 1421 4
1322	3 1422 4
	66 86

% Diagnostic point of care. Only collected in Part 3.

∞ As applicable based on randomization to treatment.

\* Only for females of child-bearing potential. Serum pregnancy tests should be carried out according to local practice.

<sup>^</sup> Local laboratory tests include: hematology, urinalysis, serum chemistries, renal function, systemic cytokines and coagulation parameters.

<sup>#</sup> Only need to be performed once in a 12-hour period if Screening, Baseline and Day 1 occur in close proximity.

† Total blood volume is obtained over approximately 6 months.

‡ EOI = End of Infusion (IV) or End of Injection (SC). Blood samples obtained immediately after infusion for IV-administered CFZ533 or immediately after injection for SC-administered CFZ533.

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DSA
mL
4 <sup>#</sup>
4 <sup>#</sup>
4
4
4
4
24

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Diagnostic Point-of-Care <sup>SM</sup>			PGx	
DRID	Sample No.	mL	Sample No.	mL
			2701	5
1	2601	3		
1	2602	3		
1	2603	3		
1	2604	3		
1	2605	3		
1	2606	3		
1	2607	3		
2	2608	3		
3	2609	3	2702	5
4	2610	3		
5	2611	3		
6	2612	3		
7	2613	3		
8	2614	3		
9	2615	3		
10	2616	3		
11	2617	3	2703	5
12	2618	3		
13	2619	3		
14	2620	3		
		60		15
				1152

\* Only for females of child-bearing potential. Pregnancy tests should be carried out ~~before and during treatment~~ before and after treatment.

# Only need to be performed once in a 12-hour period if Screening, Baseline and Day 1 occur in close proximity.

‡ EOI = End of Infusion (IV) or End of Injection (SC). Blood samples obtained immediately after infusion for IV-administered CFZ533 or immediately after injection for SC-administered CFZ533.

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## **14      Appendix 2:    US-Specific CellCept(R) Pregnancy and Safety Information**

- Use of CellCept® during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney.
- Females of reproductive potential must be made aware of the increased risk of first trimester pregnancy loss and congenital malformations with MPA products and must be counseled regarding pregnancy prevention and planning.
- For those females using CellCept® at any time during pregnancy and those becoming pregnant within 6 weeks of discontinuing therapy, the Investigator or healthcare practitioner should report the pregnancy to the Mycophenolate Pregnancy Registry (1-800-617-8191). The Investigator or healthcare practitioner should strongly encourage the patient to enroll in the pregnancy registry.
- Risks and benefits of CellCept® should be discussed with the patient. When appropriate, consider alternative immunosuppressants with less potential for embryofetal toxicity. In certain situations, the patient and her healthcare practitioner may decide that the maternal benefits outweigh the risks to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.
- To prevent unplanned exposure during pregnancy, females of reproductive potential should have a serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL immediately before starting CellCept®. Another pregnancy test with the same sensitivity should be done 8 to 10 days later. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the patient.
- Females of reproductive potential taking CellCept® must receive contraceptive counseling and use acceptable contraception (see [Table 14-1](#) for Acceptable Contraception Methods). Patients must use acceptable birth control during entire CellCept® therapy, and for 6 weeks after stopping CellCept®, unless the patient chooses abstinence (she chooses to avoid heterosexual intercourse completely).
- Patients should be aware that CellCept® reduces blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness.

**Table 14-1 Acceptable Contraception Methods for Females of Reproductive Potential\***

<b><u>Option 1</u></b> <b>Methods to Use Alone</b>	<ul style="list-style-type: none"><li>• Intrauterine device (IUD)</li><li>• Tubal sterilization</li><li>• Patient's partner had a vasectomy</li></ul>		
OR			
<b><u>Option 2</u></b> <b>Choose One Hormonal Method AND One Barrier Method</b>	<b>Hormone Methods</b> choose 1		<b>Barrier Methods</b> choose 1
	<b>Estrogen and Progesterone</b> <ul style="list-style-type: none"><li>• Oral contraceptive pill</li><li>• Transdermal patch</li><li>• Vaginal ring</li></ul> <b>Progesterone-only</b> <ul style="list-style-type: none"><li>• Injection</li><li>• Implant</li></ul>	<b>AND</b>	<ul style="list-style-type: none"><li>• Diaphragm with spermicide</li><li>• Cervical cap with spermicide</li><li>• Contraceptive sponge</li><li>• Male condom</li><li>• Female condom</li></ul>
OR			
<b><u>Option 3</u></b> <b>Choose One Barrier Method From Each Column (<i>must choose two methods</i>)</b>	<b>Barrier Methods</b> choose 1		<b>Barrier Methods</b> choose 1
	<ul style="list-style-type: none"><li>• Diaphragm with spermicide</li><li>• Cervical cap with spermicide</li><li>• Contraceptive sponge</li></ul>	<b>AND</b>	<ul style="list-style-type: none"><li>• Male condom</li><li>• Female condom</li></ul>

\*Females of reproductive potential include girls who have entered puberty and all women who have a uterus and have not passed through menopause.

## 15 Appendix 3: Stopping rules

Transition rules are based on both efficacy and safety results from Part 2. In Part 2, treatment arms are as follows:

- A: CFZ533 10mg/kg (IV);
- B is Control

Then the rules are as follows:

- If A is terminated for any reason, then STOP the study.

The following rules are for terminating treatment group(s) from Part 2:

### **For safety:**

- Terminate the treatment group if there are two (2) or more patients presenting with PTLD or PML in that group.
- For toxicities, AEs / infections, and causalities, case-by-case review is needed to determine any treatment group(s) should be terminated.

### **For efficacy (based on the number of patients with tBPAR):**

- If no tBPAR for SoC, then any group with  $tBPAR \geq 7$  will be terminated.
- If one tBPAR for SoC, then any group with  $tBPAR \geq 8$  will be terminated.
- If more than one tBPAR for SoC, then any group with  $tBPAR \geq 9$  will be terminated.

## 16 Appendix 4: Guidelines for MMF dose reduction

An Investigator may interrupt temporarily or reduce the dosage of study medication MMF if in his/her opinion this is clinically warranted, in response to any causally associated AE (e.g., neutropenia, thrombocytopenia, leucopenia, hyperlipidemia, hypertriglyceridemia or gastrointestinal intolerance). The following guidelines should be followed:

### **Dose reduction or temporary interruption may be performed for MMF**

Implementation of dose reduction will be based on thrombocytopenia, leukopenia, neutropenia, or other AEs which are suspected to be related to study medication, and in the opinion of the Investigator, are clinically warranted. The following guidelines should be used for both dose reduction and, once the event has resolved, restarting or increasing the dose of MMF back to original levels.

### **Dose Reduction Guidelines**

#### **Platelets**

- platelet count  $< 100,000/\text{mm}^3$  dose **may** be reduced at the discretion of the Investigator
- platelet count  $< 75,000/\text{mm}^3$  a second dose reduction should be **considered**
- platelet count  $< 50,000/\text{mm}^3$  **MANDATORY** interruption of medication

#### **WBC**

- WBC  $< 3500/\text{mm}^3$  dose **may** be reduced at the discretion of the Investigator
- WBC  $< 2500/\text{mm}^3$  a second dose reduction should be **considered**
- WBC  $< 2000/\text{mm}^3$  **MANDATORY** interruption of medication

All these changes must be recorded on the MMF Dosage Administration Record eCRF.

## **17      Appendix 5: Tacrolimus drug-drug interactions**

Please refer to most recent national prescribing information for current labeling recommendations.

### **Drug interactions**

Due to the potential for additive or synergistic impairment of renal function, care should be taken when administering Tac with drugs that may be associated with renal dysfunction. These include, but are not limited to, aminoglycosides, amphotericin B, and cisplatin. Initial clinical experience with the co-administration of Tac and cyclosporine resulted in additive/synergistic nephrotoxicity.

### **Drugs that may alter tacrolimus concentrations**

Since Tac is metabolized mainly by the CYP3A enzyme systems, substances known to inhibit these enzymes may decrease the metabolism or increase bioavailability of Tac as indicated by increased whole blood or plasma concentrations. Drugs known to induce these enzyme systems may result in an increased metabolism of Tac or decreased bioavailability as indicated by decreased whole blood or plasma concentrations. Monitoring of blood concentrations and appropriate dosage adjustments are essential when such drugs are used concomitantly.

**\*Drugs that may increase tacrolimus blood concentrations**

Calcium Channel Blockers	Antifungal Agents	Macrolide Antibiotics	Gastrointestinal Prokinetic Agents	Other Drugs
diltiazem	clotrimazole	clarithromycin	cisapride	bromocriptine
nicardipine	fluconazole	erythromycin	metoclopramide	chloramphenicol
nifedipine	itraconazole	troleandomycin		cimetidine
verapamil	ketoconazole**			cyclosporine
	voriconazole			danazol
				ethinyl estradiol
				methylprednisolone
				lansoprazole***
				omeprazole
				protease inhibitors
				nefazodone
				magnesium-aluminum hydroxide

\*\*In a study of 6 normal volunteers, a significant increase in Tac oral bioavailability ( $14\pm 5\%$  vs.  $30\pm 8\%$ ) was observed with concomitant ketoconazole administration (200 mg). The apparent oral clearance of Tac during ketoconazole administration was significantly decreased compared to Tac alone ( $0.430\pm 0.129$  L/hr/kg vs.  $0.148\pm 0.043$  L/hr/kg). Overall, IV clearance of Tac was not significantly changed by ketoconazole co-administration, although it was highly variable between patients.

\*\*\* Lansoprazole (CYP2C19, CYP3A4 substrate) may potentially inhibit CYP3A4-mediated metabolism of Tac and thereby substantially increase Tac whole blood concentrations, especially in transplant patients who are intermediate or poor CYP2C19 metabolizers, as compared to those patients who are efficient CYP2C19 metabolizers.

**\*Drugs that may decrease tacrolimus blood concentrations**

Anticonvulsants	Antimicrobials	Herbal Preparations	Other Drugs
carbamazepine	rifabutin	St. John's Wort	sirolimus
phenobarbital	caspofungin		
phenytoin	rifampin		

\* This table is not all inclusive.

St. John's Wort (*Hypericum perforatum*) induces CYP3A4 and P-glycoprotein. Since Tac is a substrate for CYP3A4, there is the potential that the use of St. John's Wort in patients receiving Tac could result in reduced Tac levels.

In a single-dose crossover study in healthy volunteers, co-administration of Tac and magnesium-aluminum hydroxide resulted in a 21% increase in the mean Tac AUC and a 10% decrease in the mean Tac C<sub>max</sub> relative to Tac administration alone.

In a study of 6 normal volunteers, a significant decrease in Tac oral bioavailability ( $14\pm 6\%$  vs.  $7\pm 3\%$ ) was observed with concomitant rifampin administration (600 mg). In addition, there was a significant increase in Tac clearance ( $0.036\pm 0.008$  L/hr/kg vs.  $0.053\pm 0.010$  L/hr/kg) with concomitant rifampin administration.

Interaction studies with drugs used in HIV therapy have not been conducted. However, care should be exercised when drugs that are nephrotoxic (e.g., ganciclovir) or that are metabolized by CYP3A (e.g., nelfinavir, ritonavir) are administered concomitantly with Tac. Similarly, care should be exercised when HCV protease inhibitors (e.g., boceprevir and telaprevir), also metabolized by CYP3A, are administered concomitantly with Tac.

Tac may affect the PK of other drugs (e.g., phenytoin) and increase their concentration. Grapefruit juice affects CYP3A-mediated metabolism and should be avoided.

### **Other Drug Interactions**

Immunosuppressants may affect vaccination. Therefore, during treatment with Tac, vaccination may be less effective. The use of live vaccines should be avoided; live vaccines may include, but are not limited to measles, mumps, rubella, oral polio, BCG, yellow fever, and TY 21a typhoid ([Prograf® PI 1994](#))

## 18 Appendix 6: Blinding and unblinding

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

**Table 18-1 Blinding levels**

Role	Time or Event						
	1	2	3	4	5	6	7
Drug Supply	UI	UI	UI	UI	UI	UI	UI
Randomization Office	UI	UI	UI	UI	UI	UI	UI
Subject	B	B	UI	UI	UI	UI	UI
Treating Physician	B	B	UI	UI	UI	UI	UI
Primary Investigator	B	B	UI	UI	UI	UI	UI
Study Monitor	B	B	UI	UI	UI	UI	UI
Clinical Trial Leader	B	B	B	UI	UI	UI	UI
Data Manager	B	B	UI	UI	UI	UI	UI
PK Bioanalytics	B	UI	UI	UI	UI	UI	UI
PK Expert	B	B	B	UI	UI	UI	UI
Statistician	B	B	B	UI	UI	UI	UI
Translational Medicine Expert	B	B	B	UI	UI	UI	UI
Modeler	B	B	B	UI	UI	UI	UI
Programmer	B	B	B	UI	UI	UI	UI
Data Monitoring Committee	B	B	B	UI	UI	UI	UI

UG Allowed to be unblinded on treatment group level

UI Allowed to be unblinded on individual patient level

B Remains blinded

1 Generation of randomization list, QC and lock randomization list

2 Patient allocation to treatment

3 Treatment administration

4 Safety emergency event (unblinding of a single subject)

5 Interim analysis (all patients included in the analysis have completed the study)

6 Interim analysis (some patients included in the analysis have not yet completed the study)

7 Database lock

## 19 Appendix 7: Clinically notable laboratory values

Laboratory variable	Standard units	SI units
Liver function and related variables		
SGOT (ASAT)	≥3 × ULN	≥3 × ULN
SGPT (ALAT)	≥3 × ULN	≥3 × ULN
Bilirubin	≥3 × ULN	≥3 × ULN
Renal function, metabolic and electrolyte variables		
Urea	≥5 × ULN	≥5 × ULN
Creatinine	After Wk4: ≥3 mg/dL OR >30% above value from preceding visit	After Wk4: ≥265 μmol/L OR >30% above value from preceding visit
Uric acid	M ≥12 mg/dL F ≥9 mg/dL	M ≥714 μmol/L F ≥535 μmol/L
Glucose	<45 mg/dL >250 mg/dL	<2.5 mmol/L >13.9 mmol/L
Cholesterol	≥350 mg/dL	≥9.1 mmol/L
Triglycerides	≥750 mg/dL	≥8.5 mmol/L
CK (MB)	None	None
Potassium	≤3.0 mEq/L ≥6.0 mEq/L	≤3 mmol/L ≥6 mmol/L
Calcium	≤6 mg/dL ≥13 mg/dL	≤1.5 mmol/L ≥3.2 mmol/L
Hematology variables		
Hemoglobin	<7 g/dL	<4.39 mmol/L
Platelets (thrombocytes)	<50 k/mm <sup>3</sup> ≥700 k/mm <sup>3</sup>	<50 × 10 <sup>9</sup> /L ≥700 × 10 <sup>9</sup> /L
Leukocytes (WBCs)	≤2.0 k/mm <sup>3</sup> ≥16 k/mm <sup>3</sup>	≤ 2.0 × 10 <sup>9</sup> /L ≥16 × 10 <sup>9</sup> /L
Hematology variables: differential		
Granulocytes (poly, neutrophils)	≤1,000/mm <sup>3</sup>	≤1 × 10 <sup>9</sup> /L
Eosinophils	≥12%	≥12%
Lymphocytes	≤1,000/mm <sup>3</sup>	≤1× 10 <sup>9</sup> /L
Vital sign variables		
Systolic BP (mm/Hg)	outside of 90≤ SBP ≥200 mm/Hg	
Diastolic BP (mm/Hg)	outside 50≤ DBP ≥120 mm/Hg	
Notable criteria		

## 20      **Appendix 8: Banff '09 Meeting Report: Antibody Mediated Graft Deterioration and Implementation of Banff Working Groups**<sup>1</sup>

- Normal
- Antibody-mediated rejection – due to circulating anti-donor antibodies, C4d, and allograft pathology:  
C4d deposition without morphologic evidence of acute rejection – C4d, anti-donor antibodies, no signs of acute or chronic rejection, no ATN-like minimal inflammation.  
Acute antibody-mediated rejection – C4d, anti-donor antibodies, and acute tissue injury, such as: (“suspicious for” if antibody not demonstrated)
  - Type I – ATN-like minimal inflammation
  - Type II – Capillary involvement and/or thromboses
  - Type III – Arterial changes
- Chronic antibody-mediated rejection – evidence of chronic tissue such as glomerular double contours, peritubular capillary basement membrane multilayering, interstitial fibrosis/tubular atrophy (IFTA), or fibrous intimal thickening in arteries. Borderline changes “suspicious” for acute T cell-mediated cellular rejection. No intimal arteritis present, but there are foci of mild tubulitis with mild interstitial infiltration. Threshold for rejection diagnosis is not met.
- T cell mediated rejection
  - Type IA - Significant interstitial infiltration (> 25% of parenchyma) and foci of moderate tubulitis (> 4 mononuclear cells/tubular cross section or group of 10 tubular cells).
  - Type IB - Significant interstitial infiltration (> 25% of parenchyma) and foci of severe tubulitis (> 10 mononuclear cells/tubular cross section or group of 10 tubular cells).
  - Type IIA - Mild to moderate intimal arteritis
  - Type IIB - Severe intimal arteritis comprising > 25% of the luminal area
  - Type III - Transmural (full vessel wall thickness) arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells (with accompanying lymphocytic inflammation)
- Interstitial fibrosis and tubular atrophy\*\*
  - Grade I - Mild interstitial fibrosis and tubular atrophy without (a) or with (b) specific changes suggesting chronic rejection
  - Grade II - Moderate interstitial fibrosis and tubular atrophy (a) or (b)
  - Grade E III - Severe interstitial fibrosis and tubular atrophy and tubular loss (a) or (b)

- Other: Changes not considered to be due to rejection (e.g., post-transplant lymphoproliferative disorder, nonspecific changes, acute tubular necrosis, etc.), specifically:
  - Chronic hypertension - Arterial/fibrointimal thickening with reduplication of elastica, usually with small artery and arteriolar hyaline changes.
  - Calcineurin toxicity - Arteriolar hyalinosis with peripheral hyaline nodules and/or progressive increase in the absence of hypertension or diabetes. Tubular cell injury with isometric vacuolization.
  - Chronic obstruction - Marked tubular dilatation. Large Tamm-Horsfall protein casts with extravasation into interstitium, and/or lymphatics.
  - Acute bacterial pyelonephritis - Intratubular and peritubular neutrophils with destruction of the tubular epithelium.
  - Viral infection - Viral inclusions on histology and immunohistology and/or electron microscopy.

\*The recommended format of report is a descriptive narrative signet followed by numerical codes (Banff '09) in parentheses. Categorization should in the first instance be based solely on pathologic changes, and then integrated with clinical data as a second step. More than one diagnostic category may be used if appropriate.

\*\*Glomerular and vascular lesions help define type of chronic nephropathy; chronic/recurrent rejection can be diagnosed if typical vascular lesions are seen. Grades I, II and III may include nonspecific vascular and glomerular sclerosis, but severity is graded by tubulointerstitial features.

<sup>1</sup> ([Sis et al 2010](#))