NOVARTIS

Clinical Development

RAD001A/everolimus

Protocol CRAD001A2433 / NCT01950819

A 24 month, multicenter, randomized, open-label safety and efficacy study of concentration-controlled everolimus with reduced calcineurin inhibitor vs mycophenolate with standard calcineurin inhibitor in *de novo* renal transplantation- *Advancing renal TRANSplant eFficacy and safety Outcomes with an eveRolimus-based regiMen (TRANSFORM)*

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List of abbreviations

AE	Adverse event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical therapeutic chemical (classification)
b.i.d.	bis in die/twice a day
BPAR	Biopsy Proven Acute Rejection
BKV	BK virus
C-0h	Whole blood concentration before morning dose
CI	Confidence interval
CMV	Cytomegalovirus
CKD	Chronic kidney disease
CNI	Calcineurin Inhibitor
CsA	Cyclosporine
CysC	Cystatin C
D	Death
DSE	Novartis Drug Safety & Epidemiology Department
eCRF	Electronic case report/record Form
ESRD	End stage renal disease
(e)GFR	(Estimated) Glomerular Filtration Rate
EVR	Everolimus
FAS	Full analysis set
FDA	US Food and Drug Administration
HbA1c	Glycosylated hemoglobin
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
ICH	International Conference on Harmonization

[redacted]

IEC	Independent Ethics Committee
IN	Investigator notification
ITT	Intent-to-treat
i.v.	intravenous(ly)
IRB	Institutional Review Board
IRT	Interactive Response Technology
KM	Kaplan Meier
LDL	Low density lipoprotein
MAR	Missing at random
MedDRA	Medical dictionary for regulatory activities
MDRD4	Abbreviated MDRD formula (4 variables)
MMF	Mycophenolate mofetil
MNAR	Missing not at random
MPA	Mycophenolic acid (MP used here to denote MMF or mycophenolate sodium)
mTORi	Mammalian target of rapamycin inhibitor
NG	Nasogastric
NI	Non inferiority
OC/RDC	Oracle clinical/remote data capture
p.o.	per os/by mouth/orally
PD	Pharmacodynamics
PPS	Per protocol set
RAD	40-O-2-hydroethyl-rapamycin, everolimus
RBC	Red blood cell
SAE	Serious adverse event
SAF	Safety set
SD	Standard deviation
TAC	Tacrolimus
tBPAR	treated Biopsy Proven Acute Rejection
TDM	Therapeutic drug monitoring
ULN	Upper limit of normal
WBC	White blood cell
WHO	World health organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Concentration controlled	Dosing regimen where the does is adjusted to achieve a given target level of drug in the blood
Control regimen	Drug regimen used post-randomization as a comparator to evaluate comparative effects of the investigational drug (i.e. the combination of MPA and a CNI- either tacrolimus or cyclosporine)
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)
Extension	Study period from Month 12 visit to completion of Month 24 visit regardless of treatment status (i.e. can be on or off randomized regimen)
Investigational regimen	The investigational drug regimen tested in the study post-randomization (i.e. the combination of everolimus and a CNI- either tacrolimus or cyclosporine)
Lost to follow-up	Those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw and cannot be contacted
Subject Number	A number assigned to each subject who enrolls into the study
Period	A distinct stage in the subjects' participation in the study, each period serves a purpose in the study as a whole
Premature subject withdrawal	Point when the subject exits from the study prior to the planned completion of all assessments, synonymous with study discontinuation, not the same as treatment discontinuation
Primary Treatment Period	Study period from randomization to completion of Month 12 visit, regardless of treatment status (i.e. can be on or off randomized regimen)
Screening period	Period from signing informed consent to successful completion of the transplant procedure
Study Completion	Point at which the subject came in for a final evaluation visit at Month 24 or complete discontinuation from the study if prior to Month 24
Study drug/ treatment	Any single drug or drug regimen administered to the subject as part of the required study procedures in any study period, includes everolimus, tacrolimus, cyclosporine, basiliximab, MPA and corticosteroids
Treated biopsy proved acute rejection (tBPAR)	An acute rejection episode documented by histological evidence for which anti-rejection therapy (e.g. steroids, antibody or increase in study regimen immunosuppression) was given.
Treatment discontinuation	Point when subject permanently stops taking study/investigational or control treatment drug/regimen for any reason, not the same as study discontinuation/premature subject withdrawal
Study Discontinuation	Point when subject permanently stops taking part in the study, also termed premature subject withdrawal, not the same as treatment discontinuation
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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Amendment 1

Amendment rationale

In response to the French Health Authorities (HA) request, the protocol is updated with the recent notifications for use of mycophenolate based on EMA's recommendation published on 23 Oct 2015, and the Dear Health Care Professional Letter (DHCPL) for CellCept that was distributed by Roche by 10-Nov-2015.

Mycophenolate (mycophenolate mofetil or mycophenolic acid) is a confirmed teratogen associated with an increased rate of spontaneous abortion and congenital malformation compared with other immunosuppressants. Therefore, investigators should ensure that female and male patients taking mycophenolate understand the risk of harm to the baby, the need for effective contraception, and the need to immediately consult responsible investigator if there is a possibility of pregnancy or a suspected gap of contraception.

Recommendations for female patients:

- Female patients sexually active should use two reliable methods of contraception simultaneously before starting and during therapy with mycophenolate, and for 6 weeks after stopping treatment following discontinuation of mycophenolate.
- Female patients should not donate blood during therapy with mycophenolate and at least 6 weeks following discontinuation of mycophenolate.

Recommendations for male patients:

- Male patients sexually active should use condom for sex during therapy with mycophenolate and at least 90 days following discontinuation of mycophenolate. Condom use applies for both reproductively competent and vasectomized male patients (due to the risks associated with the transfer of seminal fluid). In addition, female partners of male patients treated with mycophenolate are recommended to use highly effective contraception during treatment and for a total of 90 days after the last dose of mycophenolate.
- Male patients should not donate blood during therapy with mycophenolate and at least 6 weeks following discontinuation of mycophenolate.
- Male patients should not donate semen during therapy with mycophenolate and for 90 days following discontinuation of mycophenolate.

Changes to the protocol

The recommendations described above are now reflected in the corresponding protocol section (6.5.6 -Pregnancy and assessments of fertility).

The changes do not influence the study population, design of the study, safety considerations nor the integrity of the data analysis.

First Patient First Visit has occurred on December 3rd, 2013. Last Patient First Treatment has been completed on January 26th, 2016. At the time of amendment 1 release, 2037 patients were randomized.

[redacted]

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font for deletions~~ and red underlined for insertions.

Changes to the Inform Consent Form

[redacted] Novartis released on January 18th, 2016 a revised CRAD001A2433 Informed Consent Form (ICF) in order to inform the patients about the new warnings regarding the pregnancy risks.

All participating sites were required to submit for approval the revised versions and re-consented the patients.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and HA approval prior to implementation.

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Protocol synopsis

Protocol number	CRAD001A2433
Title	A 24 month, multicenter, randomized, open-label safety and efficacy study of concentration-controlled everolimus with reduced calcineurin inhibitor vs mycophenolate with standard calcineurin inhibitor in *de novo* renal transplantation
Brief title	Advancing renal TRANSplant eFficacy and safety Outcomes with an eveRolimus-based regiMen (TRANSFORM)
Sponsor and Clinical Phase	Novartis, Phase IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This study is designed to evaluate the impact of concentration-controlled everolimus with reduced exposure CNI, compared to mycophenolic acid (MPA) with standard exposure CNI, with respect to efficacy and safety in *de novo* renal transplant recipients. The primary endpoint combining efficacy (tBPAR) and graft function (eGFR) is consistent with recent Health Authority guidance on including an assessment of graft function as well as the traditional efficacy endpoints e.g. treated biopsy proven acute rejection, with or without clinical outcomes (i.e. Death and Graft loss). The endpoint represents an attempt to assess the clinical balance between having sufficient immunosuppression to prevent rejection while keeping CNI levels low enough to avoid nephrotoxicity.
Primary Objective, Key Secondary Objective	**Primary Objective-** To evaluate the effect of everolimus with reduced exposure CNI versus MPA with standard exposure CNI on the binary composite of treated biopsy-proven acute rejection (tBPAR) or eGFR < 50 mL/min/1.73m^2 (estimated glomerular filtration rate by MDRD4 formula) at Month 12 post-transplantation. **Key Secondary Objectives** To evaluate everolimus with reduced exposure CNI compared to MPA plus standard exposure CNI at 12 months post-transplantation with respect to the composite efficacy failure rate of (treated biopsy proven acute rejection (tBPAR), graft loss or death). To evaluate the binary composite endpoint of tBPAR or eGFR < 50 mL/min/1.73m2 (MDRD4) Month 12 among compliant subjects.
Secondary Objectives	To evaluate, by treatment group; • The incidence of composite endpoint of tBPAR or eGFR < 50 mL/min/1.73m^2 (MDRD4) at Month 24. • The incidence of composite endpoint of tBPAR (excluding Banff grade 1A acute rejections) or eGFR < 50 mL/min/1.73m^2 (MDRD4) at Month 24. • The incidence of composite endpoint of tBPAR or eGFR < 50 mL/min/1.73m^2 (MDRD4) at Month 12 by subgroup. • The incidence of composite endpoint of tBPAR, graft loss or death at Month 24.

[redacted]

	• The incidence of composite endpoint of tBPAR, graft loss, death, or loss to follow-up at Months 12 and 24. • The incidence of composite endpoint of tBPAR, graft loss, death or eGFR < 50 mL/min/1.73m^2 at Months 12 and 24. • The incidence of composite endpoint of graft loss or death at Month 12 and 24. • The incidence of individual endpoints of death, graft loss, tBPAR, BPAR, tAR, AR and humoral rejection at Months 12 and 24. • The incidence of tBPAR by severity and time to event. • The incidence of tBPAR excluding Banff 1A grade acute rejections • The incidence of transplant recipients with eGFR < 50 mL/min/1.73m^2 at Months 12 and 24. • Renal allograft function and change in renal allograft function from Month 1 (eGFR) at Months 12 and 24. • The evolution of renal function, as eGFR, over time by slope analysis. • Renal function by Cystatin C-based and other alternate formulae (e.g. CKD-EPI). • The incidence of adverse events, serious adverse events and adverse events leading to study regimen discontinuation. • The incidence of CMV and BKV, new onset diabetes mellitus, chronic kidney disease with associated proteinuria and CNI associated adverse events. • Urinary protein and albumin excretion by treatment estimated by urinary protein/creatinine and urinary albumin/creatinine ratios. • The incidence of major cardiovascular events. • The incidence of malignancies.
Study design	2-year, randomized, multicenter, open-label, 2-arm study evaluating the graft function of everolimus and reduced CNI versus MPA and standard CNI in adult *de novo* renal transplant recipients. Consented subjects (approximately 2040) meeting eligibility criteria will be randomized (1:1 between the two treatment groups) into the 24-month treatment period. Randomization will be stratified by donor type and CNI usage.
Population	Adult renal transplant recipients
Inclusion criteria (key)	1. Written informed consent obtained. 2. Male or female subject ≥ 18 years old 3. Subject randomized within 24 hr of completion of transplant surgery. 4. Recipient of a kidney with a cold ischemia time < 30 hr. 5. Recipient of a primary (or secondary, if first graft is not lost due to immunological reasons) renal transplant from a deceased heart beating, living unrelated, living related non-human leukocyte antigen identical or an expanded criteria donor.
Exclusion criteria (key)	1. Subject unable to tolerate oral medication at randomization. 2. Use of other investigational drugs at the time of enrollment, or within 30 days or five half-lives of enrollment, whichever is longer.

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	3. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes. 4. Subject is a multi-organ transplant recipient. 5. Recipient of ABO incompatible allograft or CDC crossmatch positive transplant. 6. Subject at high immunological risk for rejection as determined by local practice for assessment of anti-donor reactivity. 7. Subject who is HIV positive. 8. HBsAg and/or a HCV positive subject with evidence of elevated LFTs (ALT/AST levels ≥ 2.5 times ULN). Viral serology results obtained within 6 months prior to randomization are acceptable. 9. Recipient of a kidney from a donor who tests positive for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or anti-hepatitis C virus (HCV). 10. Subject with a BMI greater than 35. 11. Subject with severe systemic infections, current or within the two weeks prior to randomization. 12. Subject requiring systemic anticoagulation that cannot be temporarily interrupted and which would preclude renal biopsy. 13. 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. 14. Subject with severe restrictive or obstructive pulmonary disorders. 15. Subject with severe hypercholesterolemia or hypertriglyceridemia that cannot be controlled. 16. Subject with white blood cell (WBC) count ≤ 2,000 /mm^3 or with platelet count ≤ 50,000 /mm^3. 17. 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. 18. Women of child-bearing potential, unless they are using effective methods of contraception during dosing of study treatment.
Investigational and reference therapy	Investigational- everolimus plus reduced calcineurin inhibitor Reference- mycophenolate plus standard calcineurin inhibitor
Efficacy assessments	Treated, biopsy proven acute rejection (tBPAR), death, graft loss
Safety assessments	Renal function, adverse events, infections
Other assessments	None
Data analysis	The primary analysis will be performed on the Full Analysis Set following the intent-to-treat principle. The proportion of subjects with tBPAR or eGFR (MDRD4) < 50 mL/min/1.73m^2 at Month 12 will be compared for non-inferiority of EVR plus reduced CNI vs. MPA plus standard CNI using a 10% non-inferiority margin. The evaluation of non-inferiority for the key secondary endpoint, composite efficacy failure of tBPAR, graft loss, or death at Month 12, will only be assessed if EVR is shown to be non-inferior to MPA based on the

[redacted]

	primary endpoint of tBPAR or eGFR < 50 mL/min/1.73m^2 at Month 12. The rates of tBPAR, graft loss, or death based on Kaplan-Meier estimates will be compared to assess non-inferiority using a 10% non-inferiority margin using the Full Analysis Set. If non-inferiority of EVR plus reduced CNI vs. MPA plus standard CNI is achieved for both the primary and the key secondary endpoints, superiority of EVR plus reduced CNI to MPA plus standard CNI will be evaluated. The above hierarchical fixed hypothesis testing procedure will not inflate overall Type I error rate. Therefore, each hypothesis will be tested at the one-sided 0.025 significance level and no multiplicity adjustment is needed.
Key words	Transplantation, Kidney failure, renal failure, dialysis.

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1 Introduction

1.1 Background

Long-term graft survival in renal transplant recipients is dependent upon use of immunosuppressive agents. Despite improvements in current therapies, long-term transplantation outcomes have not significantly improved over the last decade.

In renal transplant patients, chronic allograft nephropathy (interstitial fibrosis and tubular atrophy) is the main cause of graft failure. A number of factors have been implicated, including donor age, acute rejection, vascular remodeling and calcineurin-inhibitor (CNI)-induced nephrotoxicity. CNI's represent the cornerstone of immunosuppressive therapy due to their efficacy in preventing acute rejection. However, CNIs have nephrotoxic side effects that can directly contribute to renal dysfunction and compromise long-term outcomes (Pascual 2009).

Several studies have shown that kidney allograft function is an important predictor of graft failure and that renal function is the best candidate for predicting long-term renal allograft survival. Several reports have shown that improvements in graft half-life are related to conservation of renal function within the first-year post-transplantation (Park 2012, Kasiske 2011, Wu 2010, Hariharan 2002). Therefore, treatment strategies that allow adequate immunosuppression to control rejection, avoid nephrotoxicity and improve long-term outcomes are sought.

Everolimus (RAD001) is an inhibitor of the mammalian target of rapamycin (mTORi) that has been developed in combination with cyclosporine for the prevention of rejection episodes following kidney, liver and heart transplantation. Everolimus has been proven to be effective in preventing acute rejection.

Initial phase III studies of fixed doses of everolimus versus mycophenolate mofetil (MMF) on combination with conventional exposure to cyclosporine have shown that everolimus is non-inferior to MMF in preventing biopsy proven acute rejection and graft loss (Vitko 2004). In these studies, the everolimus regimen was associated with impaired renal function which was thought to result from potentiation of cyclosporine nephrotoxicity.

Subsequently, 3 additional randomized studies demonstrated that de novo use of everolimus with concentration-controlled in combination with low exposure cyclosporine provided effective protection against rejection with good renal function (Nashan 2004, Vitko 2004, Tedesco 2010).

A recent analysis (Shihab 2012) from study CRAD001A2309 has shown that an exposure above 3 ng/mL is adequate in reducing the risk of tBPAR. Moreover, lowest rates of renal dysfunction (defined as poor renal function [estimated GFR, serum creatinine] or proteinuria), wound healing events, peripheral edema, new-onset diabetes mellitus, hypercholesterolemia and hypertriglyceridemia were generally observed with everolimus trough concentration in the range 3–8 ng/mL and CsA levels of <100 ng/mL.

Two short-term studies conducted in the US have evaluated the de novo use of everolimus in combination with tacrolimus. CRAD001AUS01 was a pharmacokinetic study of tacrolimus and everolimus in 8 maintenance renal patients with renal insufficiency that suggested no pharmacokinetic interactions between everolimus and tacrolimus when given simultaneously. CRAD001AUS09 was a prospective, multicenter, open-label, randomized, 6-month study of 92

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de novo renal transplant patients. This study also included PK assessments, which demonstrated no interaction between everolimus and tacrolimus. Patients received concentration-controlled everolimus, corticosteroids, and basiliximab with low exposure tacrolimus or standard exposure tacrolimus. Everolimus trough levels were to be maintained above 3ng/mL. Despite the reduction in tacrolimus exposure, the immunosuppressive regimen was associated with low BPAR rates in both study groups and an excellent graft function. The combination of everolimus and tacrolimus was found to be safe and well tolerated with no unanticipated safety issues.

Further evidence of the effectiveness of de novo everolimus in combination with tacrolimus was gained in the CRAD001A2426 (ASSET) study. ASSET was designed to determine whether concentration-controlled everolimus plus reduced exposure tacrolimus can preserve renal function in 199 de novo renal recipients. From the study, the authors concluded that use of EVR 1.5mg bid in combination with low or very low TAC was associated with a low rate of tissue regeneration complications (lymphocele, wound complications, wound dehiscence or incisional hernia) in both groups. At Month 12, mean eGFR was higher in the tacrolimus 1.5–3 ng/ml group versus the 4–7 ng/ml group (57.1 ± 19.5 vs. 51.7 ± 20 ml/min/1.73 m2, respectively. Efficacy outcomes were similar in both study groups (Langer 2012).

Currently, study CRAD001AUS92 (EMPEROR) is ongoing. The study is set to compare the efficacy and safety of concentration-controlled de novo everolimus with reduced tacrolimus versus mycophenolate mofetil with standard dose tacrolimus. The study was recently completed and analysis is ongoing.

The additional benefits of a de novo everolimus based regimen, which could translate in a better long-term patient and graft survival, have also been evaluated. A pooled analysis of several everolimus based studies showed that there is a decreased incidence of CMV events compared to MPA based regimen (Nashan 2012, Brennan 2011, Havenith 2013). In addition, a post-hoc analysis has suggested that everolimus trough levels of > 8 ng/mL were associated with proteinuria, but not with everolimus trough levels of 3-8 ng/mL (Wiseman 2013, Loriga 2010).

Other organ transplant indications beyond kidney provide additional evidence of the benefits of everolimus in transplantation. The anti-proliferative effects of everolimus, which may potentially support patient and graft survival, have been observed in the reduction of the risk for cardiac allograft vasculopathy (CAV) in heart transplant patients (Eisen 2003) and its use in drug-eluting stents (Grube 2004).

Additionally, superior renal function from randomization to month 12 (difference 8.50 mL/min/1.73 m^2) in de novo liver transplant recipients treated with everolimus in combination with reduced tacrolimus vs. tacrolimus alone has recently been reported (De Simone 2012).

The de novo use of everolimus with CNI minimization provides an opportunity to manage the risk of acute allograft rejection, reduce exposure to CNI nephrotoxicity without compromising efficacy and potentially provide long-term benefits. To date, in the above-mentioned studies, a regimen with de novo everolimus and CNI minimization is at least as effective as standard CNI-based regimens in terms of patient and allograft survival rates, with some improvements in renal function.

The present study builds on existing evidence and, with an innovative novel endpoint, combining renal function and allograft rejection, aims to demonstrate that de novo

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concentration-controlled everolimus, plus very low levels of CNI, will lead to better overall graft outcomes, as compared to current standard of care, being MPA plus standard dose CNI. The study will aim to prospectively confirm the utility of this novel endpoint, which was developed in exploratory analyses of previous everolimus studies.

1.2 Purpose

This study CRAD001A2433 is designed to evaluate the impact of concentration-controlled everolimus with reduced exposure CNI, compared to mycophenolic acid (MPA) with standard exposure CNI, with respect to efficacy and safety in *de novo* renal transplant recipients.

The primary endpoint combining efficacy (tBPAR) and graft function (eGFR) is consistent with recent Health Authority guidance on including an assessment of graft function as well as the traditional efficacy endpoints e.g. treated biopsy proven acute rejection, with or without clinical outcomes (i.e. Death and Graft loss). The endpoint represents an attempt to assess the clinical balance between having sufficient immunosuppression to prevent rejection while keeping CNI levels low enough to avoid nephrotoxicity.

The data will be published in order to support the validity of this endpoint in renal transplantation and the benefit of everolimus in this population.

2 Study objectives

2.1 Primary objective

To evaluate the effect of everolimus with reduced exposure CNI versus MPA with standard exposure CNI on the binary composite of treated biopsy-proven acute rejection (tBPAR) or eGFR < 50 mL/min/1.73m^2 (estimated glomerular filtration rate by MDRD4 formula) at Month 12 post-transplantation.

2.2 Secondary objectives

Key Secondary Objectives

- To evaluate everolimus with reduced exposure CNI compared to MPA plus standard exposure CNI at 12 months post-transplantation with respect to the composite efficacy failure rate of (treated biopsy proven acute rejection (tBPAR), graft loss or death).
- To evaluate the binary composite endpoint of tBPAR or eGFR < 50 mL/min/1.73m^2 (MDRD4) Month 12 among compliant subjects.

Other Secondary Objectives

To evaluate, by treatment group;

- The incidence of composite endpoint of tBPAR or eGFR < 50 mL/min/1.73m^2 (MDRD4) at Month 24.
- The incidence of composite endpoint of tBPAR (excluding Banff grade 1A acute rejections) or eGFR < 50 mL/min/1.73m^2 (MDRD4) at Month 24.
- The incidence of composite endpoint of tBPAR or eGFR < 50 mL/min/1.73m^2 (MDRD4) at Month 12 by subgroup (see Section 9.4.4).

[redacted]

- The incidence of composite endpoint of tBPAR, graft loss or death at Month 24.
- The incidence of composite endpoint of tBPAR, graft loss, death, or loss to follow-up at Months 12 and 24.
- The incidence of composite endpoint of tBPAR, graft loss, death or eGFR < 50 mL/min/1.73m^2 at Months 12 and 24.
- The incidence of composite endpoint of graft loss or death at Month 12 and 24.
- The incidence of individual endpoints of death, graft loss, tBPAR, BPAR, tAR, AR and humoral rejection at Months 12 and 24.
- The incidence of tBPAR by severity and time to event.
- The incidence of tBPAR excluding Banff 1A grade acute rejections
- The incidence of transplant recipients with eGFR < 50 mL/min/1.73m^2 at Months 12 and 24.
- Renal allograft function and change in renal allograft function from Month 1 (eGFR) at Months 12 and 24.
- The evolution of renal function, as eGFR, over time by slope analysis.
- Renal function by Cystatin C-based and other alternate formulae (e.g. CKD-EPI).
- The incidence of adverse events, serious adverse events and adverse events leading to study regimen discontinuation.
- The incidence of CMV and BKV, new onset diabetes mellitus, chronic kidney disease with associated proteinuria and CNI associated adverse events.
- Urinary protein and albumin excretion by treatment estimated by urinary protein/creatinine and urinary albumin/creatinine ratios.
- The incidence of major cardiovascular events.
- The incidence of malignancies.

[redacted]

3 Investigational plan

3.1 Study design

This is a 2-year, randomized, multicenter, open-label, 2-arm study evaluating graft function with everolimus and reduced CNI versus MPA and standard CNI in adult *de novo* renal transplant recipients (Figure 3-1). Consented subjects will enter the screening period and upon

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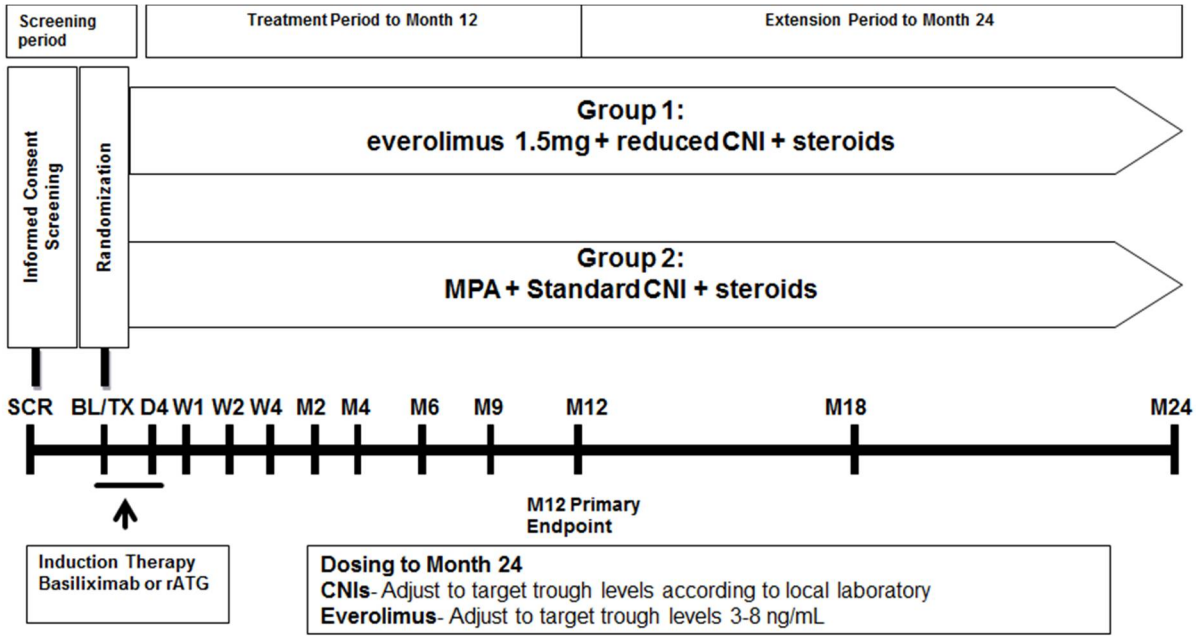
meeting eligibility criteria, including successful transplantation, will enter the initial 12 Month treatment period then continue in the next treatment period to Month 24.

Figure 3-1 Study design- Primary Treatment to M12, Extension to M24



Upon meeting eligibility criteria, approximately 2040 subjects (around 1020 per treatment arm) will be randomized (1:1) within 24 hr of transplantation, to the following treatment groups:

Group 1: Everolimus plus Reduced CNI (see Table 5-1 for CNI target trough levels)

Group 2: MPA plus Standard CNI (see Table 5-1 for CNI target trough levels)

Randomization will be stratified, within treatment groups, to balance; 1) recipients by donor type, living donors (LD), deceased standard criteria donors (SCD) and deceased expanded criteria donors ECD); 2) CNI usage, cyclosporine vs tacrolimus. The overall study population will contain no less than 50% recipients of living donor transplants and subjects taking cyclosporine will comprise no more than 20% of the population.

Subjects will commence the randomized study regimen within 24 hr post-reperfusion of the allograft and should continue on the assigned open-label study regimen until the Month 24 visit.

Induction therapy, with Basiliximab or rATG only, is mandatory for all subjects starting pre-or peri-operatively on the day of kidney transplant surgery (For details see Section 5.5.4). Corticosteroids are mandatory for all subjects through Month 24 and can be administered according to local practice but with a minimal daily dose of 5 mg prednisone, or equivalent. The study regimen/medication definition comprises either a) everolimus plus reduced CNI OR b) MPA plus standard CNI. Cyclosporine and tacrolimus dose adjustments will be made according to local trough values in order to maintain timely adherence to the protocol-specified ranges (See Table 5-1). Subjects are expected to remain on the original CNI (combined with everolimus or MPA) to which they were randomized until at least Month 24. However, if subjects discontinue either CNI due to AE/tolerability and can maintain everolimus or MPA

combined with the alternate CNI, within respective target levels as per protocol, they will not be considered to have discontinued study regimen/medication.

The primary analysis of the trial is planned when the last subject has completed the Month 12 visit. All subjects are expected to continue to Month 24 on the randomized study regimen. If subjects discontinue study medication (i.e. everolimus plus reduced CNI or MPA plus standard CNI) prior to Month 24 they should remain in study to Month 24 on standard of care immunosuppression.

It is planned that subjects completing the study to Month 24 on treatment may consent to participate in a separate three year observational study to Month 60 to allow validation of the composite endpoint with graft and subject outcomes up to 60 months post-transplant.

3.2 Rationale of study design

The controlled parallel group study design is well-established in *de novo* renal allograft recipients to evaluate an immunosuppressive drug regimen versus current standard treatment. As this trial uses three study drugs that need to be adjusted by therapeutic drug monitoring (TDM) to different target through levels, blinding is not possible due to the small therapeutic window and the burden of additional placebo drugs that subjects would need to take to finally ensure blinding of study drugs as well as the intention to have treatment arms close to clinical practice.

The primary endpoint combining efficacy (tBPAR) and graft function (eGFR) is consistent with recent HA guidance (CHMP/EWP/263148/06, effective February 2009) and discussions (FDA Workshop, 2012: Endpoints in Clinical Trials of Kidney Transplantation) on including an assessment of graft function as well as the traditional efficacy endpoints e.g. treated biopsy proven acute rejection, with or without clinical outcomes (i.e. Death and Graft loss). The endpoint represents an attempt to assess the clinical balance between having sufficient immunosuppression to prevent rejection while keeping CNI levels low enough to avoid nephrotoxicity.

The eGFR cutoff of 50 mL/min/1.73m^2 represents a moderate level of renal dysfunction according to the CKD staging criteria. As such it provides a surrogate for graft function and is expected to be sensitive both to the effects of acute and chronic rejection and nephrotoxic side-effects of immunosuppression. Analysis of previous renal transplant studies suggests that this cutoff, in combination with tBPAR, may provide a clinically meaningful approach to discriminate between immunosuppressive regimens in renal transplantation.

Recent reports have shown that renal function over the first year post transplant is predictive of long-term renal graft survival. eGFR at 12 months has been associated strongly with subsequent long-term graft survival post-transplant (Park 2012, Kasiske 2011, Wu 2010). Thus, eGFR at one year post-transplant may represent a surrogate for long term graft survival and is therefore a relevant component in the composite.

3.3 Rationale of dose/regimen, route of administration and duration of treatment

For everolimus the dosing will be as per the approved label for renal transplantation (including the target trough level of 3-8 ng/mL). The exposures of CNIs that are targeted will be lower

than the approved labels and will be designed to achieve significant reductions in CNI exposure compared to the control arm (see Table 5-1). The rationale is that this magnitude of reduction in CNI exposure can be achieved in combination with everolimus without impacting efficacy and with improved renal function since the CNI nephrotoxicity will be reduced. The inclusion of rabbit antithymocyte globulin (rATG) as an induction agent permits the inclusion of a broader range of centers and subjects and potentially higher risk subjects. rATG dose recommendations are based on practice according to a recent review but restricted in total dose in order to prevent over-immunosuppression (Deeks and Keating 2009). In addition, rATG may be used to provide immunological coverage for subjects with DGF. The assessment of efficacy and safety objectives at Month 12 post transplant with a longer term assessment at Month 24 are standard in the renal transplant indication.

Several studies have indicated that the Month 12 renal function has a strong correlation with long term graft and subject survival (Park 2012, Kasiske 2011, Wu 2012). It is planned to examine the correlation between renal function at Month 12 with Month 24 and longer-term clinical outcomes, the longer term outcomes may be evaluated by a separate extension study.

3.4 Rationale for choice of comparator

Cyclosporine and tacrolimus, both known as calcineurin inhibitors (CNIs), are at present the cornerstones in most of the immunosuppressive protocols used worldwide. In an effort to reflect current CNI usage as closely as possible, the ratio subjects receiving either tacrolimus or cyclosporine is anticipated to be approximately 4:1. MPA, cyclosporine, tacrolimus, basiliximab and rATG have each been approved for the prevention of acute rejection after kidney transplantation by health authorities in each participating country. The proposed standard target CNI levels are similar to those studied in previous clinical trials and are consistent with the updated prescribing information and reflect the current standard of care.

3.5 Purpose and timing of interim analyses/design adaptations

There will be a futility analysis when approximately 30% of subjects have completed 6 months on study. The primary analysis will be performed when the last subject completes 12 months on study. There will be a second analysis when the last subject completes 24 months on study to evaluate longer term outcomes.

3.6 Risks and benefits

In kidney transplantation there is a medical need for alternative immunosuppressive regimens which maintain the ability to prevent acute rejection while preserving renal function. A regimen that will maintain efficacy while allowing reduced CNI exposure to minimize or avoid CNI-associated adverse reactions (including nephrotoxicity) remains highly attractive.

Early renal transplantation studies using everolimus fixed doses with standard CNIs (CsA) exposure were associated with progressive deterioration of kidney function. This risk was addressed successfully when concentration controlled everolimus (3-8 ng/mL) was used with basiliximab induction and reduced exposure to CsA (Study CRAD001A2309, Tedesco 2010). The recently completed liver transplantation study (CRAD001H2304) also demonstrated that everolimus, in combination with reduced tacrolimus exposure and corticosteroids, showed

[redacted]

comparable efficacy and superior renal function versus the approved standard exposure tacrolimus at 12 months post liver transplantation (DeSimone 2012).

Everolimus, like all immunosuppressants, is associated with side effects. These effects are predominantly class-specific and well described; they are usually dose-related and prior experience has supported the value of therapeutic drug monitoring (TDM) for managing everolimus, similar to CNIs.

Overall, the safety findings in study CRAD001A2309 were consistent with the known safety profile of both everolimus and cyclosporine;

- Similar efficacy (tBPAR) compared to MPA plus standard cyclosporine control.
- Similar subject and graft survival compared to MPA plus standard cyclosporine control.
- Similar eGFR at Month 12 compared to MPA plus standard cyclosporine control.
- Increased incidence (more than 5% difference vs control) of hyperlipidemia, peripheral edema, dyslipidemia and stomatitis/mouth ulcerations with everolimus, these events being generally manageable in clinical practice.

The side effect profile of everolimus in combination with tacrolimus has been characterized in study CRAD001AUS09 of 92 renal transplant recipients where the combinations of everolimus combined with tacrolimus maintained control of rejection while providing for preservation of graft function. There were no unanticipated safety issues and the adverse events were consistent with everolimus and tacrolimus profiles. Currently, analysis of study CRAD001AUS92 with everolimus and reduced tacrolimus versus an MPA+standard tacrolimus control arm is in progress.

The benefits to subjects in this trial include potential improvement in renal function with preservation of graft survival, and increased medical monitoring and care. The risk to subjects in this trial will be minimized by compliance with the inclusion/exclusion criteria and particular compliance to the target levels for CNI and everolimus troughs (where non-compliance could cause over or under-immunosuppression). In addition to the site and CRA checking for compliance, the Novartis clinical team will also monitor compliance with the target levels and alert centers to correct out of range trough values.

4 Population

The study population will consist of male and female *de novo* renal transplant recipients. It is planned to randomize approximately 2040 subjects in around 200 centers worldwide. Since a 20% screening failure rate is expected, approximately 2550 subjects will have to be screened. The overall study population will contain no less than 50% recipients of living donor transplants and subjects taking cyclosporine will comprise no more than 20% of the population.

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 subject ≥ 18 years old.
3. Subject randomized within 24 hr of completion of transplant surgery.

[redacted]

4. Recipient of a kidney with a cold ischemia time < 30 hr.
5. Recipient of a primary (or secondary, if first graft is not lost due to immunological reasons) renal transplant from a deceased heart beating, living unrelated, living related non-human leukocyte antigen (HLA) identical or an expanded criteria donor (ECD, as defined below).

ECD is defined as:

- Brain-dead donor > 60 years old **OR**
- Donor age > 50 years old with two of the following criteria:
  - History of hypertension
  - Terminal serum creatinine ≥ 1.5 mg/dL
  - Death resulting from cerebrovascular accident

4.2 Exclusion criteria

Subjects fulfilling **any** of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects.

1. Subject unable to tolerate oral medication at time of randomization.
2. Use of other investigational drugs at the time of enrollment, or within 30 days or five half-lives of enrollment, whichever is longer, except for dialysis related drugs which are not expected to interact with the study regimens.
3. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
4. Subject is a multi-organ transplant recipient.
5. Recipient of ABO incompatible allograft or complement-dependent lymphocytotoxic (CDC) crossmatch positive transplant (isolated positive B-cell crossmatches are not an exclusion criterion).
6. Subject at high immunological risk for rejection as determined by local practice for assessment of anti-donor reactivity e.g. high PRA, presence of pre-existing DSA.
7. Subject who is HIV positive.
8. HBsAg and/or a HCV positive subject with evidence of elevated LFTs (ALT/AST levels ≥ 2.5 times ULN). Viral serology results obtained within 6 months prior to randomization are acceptable.
9. Recipient of a kidney from a donor who tests positive for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or anti-hepatitis C virus (HCV).
10. Subject with a BMI greater than 35.
11. Subject with severe systemic infections, current or within the two weeks prior to randomization.
12. Subject requiring systemic anticoagulation that cannot be temporarily interrupted and which would preclude renal biopsy.
13. 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.

[redacted]

14. Subject with severe restrictive or obstructive pulmonary disorders.
15. Subject with severe hypercholesterolemia or hypertriglyceridemia that cannot be controlled.
16. Subject with white blood cell (WBC) count ≤ 2,000 /mm^3 or with platelet count ≤ 50,000 /mm^3.
17. 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.
18. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment. 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 m prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository
    - 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
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS)

    In case of use of oral contraception women should have been stabile on the same pill 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.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational, control and concomitant drugs

The following immunosuppressive drugs will be used in this study and will be administered in accordance with this protocol (see Section 5.5.4, Instructions for prescribing and taking study

[redacted]

treatment), not all dosage forms listed are available in each country, dependent on local approval status and regulations.

Investigational drug

- Everolimus will be provided as 0.25, 0.5 and 0.75 and 1.0 mg tablets depending on locally approved dosage forms.

Control and concomitant drugs

- Basiliximab as 20 mg lyophilized vial for intravenous administration following reconstitution with sterile water.
- Rabbit anti-thymocyte globulin (rATG) will be provided locally as 25 mg lyophilized vial or as locally approved dosage form.
- MPA as either mycophenolic acid (sodium) 180 or 360mg enteric-coated tablets or mycophenolate mofetil 250 or 500 mg film coated tablets or 250mg capsules, depending on locally approved dosage forms.
- Cyclosporine as 10, 25, 50 and 100 mg capsules.
- Tacrolimus as 0.5, 1.0 mg and 5.0 mg capsules.

Corticosteroids for oral and i.v. administration will be supplied locally at the study centers.

5.1.2 Additional study treatment

No additional immunosuppressive agents may be used other than as per protocol. Concomitant therapies are as described below in Section 5.5.7.

5.2 Treatment arms

Subjects will be assigned to one of the following two treatment arms in a ratio of 1:1;

- Everolimus plus reduced CNI (EVR+rCNI)
- MPA plus standard CNI (MPA+sCNI)

5.3 Treatment assignment, randomization

At the Baseline Visit, within 24 hr of completion of transplant surgery, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. Randomization will be stratified, within the treatment groups, by donor type (living donors (LD), deceased standard criteria donors (SCD) and deceased expanded criteria donors (ECD)) and CNI usage, cyclosporine vs tacrolimus. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign the subject to a treatment arm and will specify the treatment to be dispensed to the subject. The randomization number will not be communicated to the caller. For subjects who are not eligible to be randomized post-transplantation the IRT must be informed that the subject is a screen failure and the screen failure recorded on the Screening disposition CRF.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates

[redacted]

the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms.

The randomization scheme for subjects will be reviewed and approved by a member of the IIS Randomization Group.

5.4 Treatment blinding

Not applicable, this is an open label study.

5.5 Treating the subject

5.5.1 Subject numbering

Each subject is uniquely identified by a Subject Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a subject, the Subject Number will not be reused.

Upon signing the informed consent form, the subject is assigned the next sequential number by the investigator. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the subject to register them into the IRT. The site should select the CRF book with a matching Subject Number from the EDC system to enter data.

If the subject fails screening and is not randomized for any reason, the IRT must be notified within 2 days that the subject was a screen failure/not randomized. The reason for not being randomized will be entered on the Screening Disposition CRF.

5.5.2 Dispensing the investigational treatment

Each patient will be supplied by the study site with commercial drugs. Commercial Novartis drugs and/or 3rd 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 by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all investigational treatment should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the investigational treatment but no information about the subject. The investigator must maintain an accurate record of the shipment and dispensing of investigational treatment in a drug accountability log. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial. Subjects will be asked to bring all unused investigational treatment and empty packaging at each visit and at the end of the study or at the time of discontinuation of investigational treatment.

[redacted]

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused investigational treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.4 Instructions for prescribing and taking study treatment

All dosages of everolimus, MPA, cyclosporine and tacrolimus and all dose changes during the study must be recorded, with reason for administration, on the corresponding Dosage Administration Record CRF. Dosages of basiliximab, rATG and steroids will be recorded on the Concomitant Medications CRF under the Immunosuppressive Mediations category.

Induction therapy, pre and post-transplant immunosuppression

CNI, MPA and/or steroids 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 all subjects must follow the assigned regimen. Pre-transplant immunosuppression, including induction therapy and any CNI or MPA should be recorded on the Concomitant medication CRF under the immunosuppressive category.

Basiliximab induction

All subjects are to receive 2 x 20-mg doses of basiliximab administered intravenously. The first dose is to be given within 2 hr prior to transplant surgery, and the second dose should be administered on Day 4, or each dose can be 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 i.v. 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. Dosing of basiliximab will be recorded in the Concomitant Medications CRF under the immunosuppressive category.

Rabbit anti-thymocyte globulin induction therapy

Administration of rabbit anti-thymocyte globulin (rATG) induction therapy should be given at 1.5 mg/kg/day and total dosage must not exceed 6 mg/kg. This dosing guidance is for Thymoglobulin®, where other rATG products are used usage should be consistent with local practice and approved labeling. rATG induction therapy can be administered from the day of transplant. Close attention should be paid to hematological parameters (e.g. lymphocytes, WBC and platelets) when administering rATG. Refer to manufacturer's product labeling for additional safety information. Dosing of rATG should be recorded on the Concomitant Medications CRF under the immunosuppressive category.

Initiation of everolimus with CNI

Within 24 hr of successful transplantation the subject will be randomized to receive a regimen of either everolimus or MPA in combination with the CNI drug as per center practice. The first post-randomization dose of everolimus in combination with CNI must be given immediately after randomization, within 24 hr of transplantation. All everolimus doses and dose changes should be recorded on the everolimus dose administration record eCRF.

[redacted]

Subjects will take everolimus twice daily in 12 hr intervals simultaneously with CNI, on a consistent schedule with regards to time of day and relation to meals. No grapefruit or grapefruit juice should be taken at all throughout the study.

The starting dose will be different based on CNI usage due to differential PK interactions and the suggested starting dose tablet strengths below may be modified according to locally available dosage forms and investigators' judgment to rapidly achieve a target trough level of 3-8 ng/mL. All everolimus dosing will be recorded on the dose administration record for everolimus.

For tacrolimus subjects the everolimus starting dose should be 3 mg/day as 1.5 mg bid: 1.5 mg everolimus in the morning, and 1.5 mg in the evening for all tacrolimus subjects.

For cyclosporine subjects the everolimus starting dose should be 1.5 mg/day as 0.75 mg bid: 0.75 mg everolimus in the morning, and 0.75 mg in the evening for all cyclosporine subjects.

Everolimus medication will be provided in 0.25, 0.5, 0.75 and 1.0 mg tablet strengths, depending on locally approved dosage forms.

The first everolimus trough level must be performed by Week 1, at the latest. If the everolimus trough level is below 3 ng/mL, the everolimus dose must be increased by at least 50%. Everolimus trough levels (C-0h) must be performed 5 days +/-2 days after any everolimus dose adjustment to confirm the levels are in the target range (3-8 ng/mL). The dose will be adjusted to maintain the everolimus levels in target (3-8 ng/mL), according to the local laboratory, for the duration of the study. The guidelines for everolimus dose reduction/interruption can be found in Table 5-2. The co-administration of drugs known to interfere with everolimus metabolism (see Appendix 2) should be avoided if possible. If these drugs are required, the investigator should carefully monitor everolimus and CNI trough levels.

In addition to the routine evaluations, everolimus trough blood levels must be monitored after each CNI dose reduction or after each CNI increase due to drug-drug interactions between these two compounds. Everolimus and CNI trough levels will be determined at the time points indicated in Table 6-1, for subjects in the investigational arm.

Initiation of MPA with CNI

Within 24 hr of successful transplantation the subject will be randomized to receive a regimen of either everolimus or MPA in combination with the CNI drug as per center practice. The first post-randomization dose of MPA in combination with CNI must be given immediately after randomization, within 24 hr of transplantation.

Dosing of MPA will be as follows:

- Enteric-coated mycophenolate sodium (Myfortic®) will be 2 tablets of 360 mg b.i.d. (1.44 g/day) for subjects randomized into the control group.
- Mycophenolate mofetil (MMF, Cellcept®) will be 2 tablets of 500 mg or 4 capsules of 250 mg b.i.d (2 g/day) for subjects randomized into the control group.

If a subject is treated with cyclosporine, the MPA dose should be maintained at these levels throughout the course of the study. If a subject is treated with tacrolimus, the MPA dose should be reduced after Week 2 to 1080 mg/day of Myfortic® or 1.5 g/day of MMF. The investigator is responsible for instructing the subjects regarding the exact dose and dosing schedule to be

followed. Dose adjustment/interruption guidance for MPA is provided in Appendix 3. All MPA doses and changes should be recorded on the MPA dose administration record eCRF.

Management of CNI targets

CNI should be adjusted to and maintained within the target ranges in Table 5-1.

Table 5-1 CNI trough target level ranges

Study Visit	Tacrolimus Ranges		Cyclosporine Ranges	
	EVR arm	MPA arm	EVR arm	MPA arm
Day 1 ≤ Month 2	4-7 ng/mL	8-12 ng/mL	100-150 ng/mL	200-300 ng/mL
Month 2 ≤ Month 6	2-5 ng/mL	6-10 ng/mL	50-100 ng/mL	150-200 ng/mL
Month 6 ≤ Month 24	2-4 ng/mL	5-8 ng/mL	25-50 ng/mL	100-200 ng/mL

Tacrolimus administration

Tacrolimus will be administered as capsules p.o., b.i.d.. Tacrolimus should be initiated as soon as possible and no later than 24 h after reperfusion of the graft. The lowest permitted dosing of tacrolimus in this study is 0.5 mg b.i.d. If tacrolimus is discontinued for more than 21 consecutive days, switching to cyclosporine may be considered, otherwise the study regimen must be discontinued. Subjects who discontinue their study regimen are expected to remain in study on Standard of care to Month 24. Visits and assessments for such subjects are described in Table 6-1.

Tacrolimus dosing will be modified by investigators as needed and recorded on the Tacrolimus Dosage Administration CRF at each visit. In the event of tacrolimus intolerance (e.g., nephrotoxicity, neurotoxicity) dose reduction of tacrolimus may be necessary. If it occurs that the tacrolimus trough level is outside the required target level, then the investigator will be asked to confirm the intended tacrolimus trough level, to record the start date and reason for dose reduction on the Tacrolimus Dosage Administration CRF.

The co-administration of drugs known to interfere with tacrolimus metabolism (see Appendix 4) should be avoided if possible. If these drugs are required, the investigator should carefully monitor tacrolimus and/or everolimus trough levels.

Cyclosporine administration

Cyclosporine will be administered as capsules p.o., b.i.d., unless an oral solution or i.v. administration of cyclosporine cannot be avoided. Cyclosporine should be initiated as soon as possible and no later than 24 h after reperfusion of the graft. The lowest permitted dosing of Cyclosporine in this study is 25 mg b.i.d. If cyclosporine is discontinued for more than 21 consecutive days, switching to tacrolimus may be considered, otherwise the study regimen must be discontinued. Subjects who discontinue their study regimen are expected to remain in study on Standard of care to Month 24. Visits and assessments for such subjects are described in Table 6-1.

Cyclosporine dosing will be modified by investigators as needed and recorded on the Cyclosporine Dosage Administration CRF at each visit. In the event of cyclosporine intolerance (e.g., nephrotoxicity) dose reduction of cyclosporine may be necessary. If it occurs that the cyclosporine trough level is below the required target level, then the investigator will be asked

[redacted]

to confirm the intended cyclosporine trough level, to record the start date and reason for dose reduction on the Cyclosporine Dosage Administration eCRF

The co-administration of drugs known to interfere with cyclosporine metabolism (see Appendix 5) should be avoided if possible. If these drugs are required, the investigator should carefully monitor CNI and/or everolimus trough levels.

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

5.5.5 Permitted dose adjustments and interruptions of study treatment

For all everolimus subjects who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the subject on investigational drug. The following guidelines should be followed (Table 5-2), for management of lipid elevations refer to Section 5.5.7 for initial approach, prior to considering dose reduction. The everolimus dose should be decreased by at least 0.25 mg b.i.d if a dose reduction is necessary. If a temporary reduction in everolimus level is needed, the everolimus trough blood level should still be maintained no lower than 3 ng/mL. Everolimus should be discontinued if a trough level ≥3 ng/mL cannot be maintained due to toxicity. Severe and unremitting changes may also lead to investigational drug discontinuation.

For subjects having rATG administered, whether as induction therapy, DGF or anti-rejection treatment the relative impact of all medications to reduced hematological parameters should be considered, thus everolimus dose reduction to these guidelines may not always be necessary under these circumstances.

Table 5-2 Guidelines for everolimus dose reduction/interruption

	Platelet count (/mm^3)	**Hemoglobin** (g/dL)	**WBC count** (/mm^3)	**Cholesterol** (mmol/L)	**Triglycerides** (mmol/L)
Dose reduction	≤ 75000	≤ 8	≤ 3000	> 9	> 8.5
Interruption	≤ 50000	≤ 6	≤ 2500	≥ 10	≥ 10.5

If everolimus is interrupted for safety reasons for longer than 21 consecutive days study regimen should be discontinued. Everolimus may be interrupted during antibody treatment of rejection episodes. In case of any planned or emergency surgery during the study treatment period, everolimus can be interrupted and a compensatory increase in CNI may be considered. In elective cases, this may be done 5 days before surgery which would allow restart of everolimus by 21 days post-surgery, in these cases everolimus must be re-introduced at the latest by day 27 after discontinuation.

For MPA, dose adjustment or interruption should follow Appendix 3. If MPA or either CNI is interrupted for more than 21 consecutive days the randomized study regimen must be discontinued. Subjects who discontinue their randomized study regimen are expected to remain in study with immunosuppression according to local practice until completing the treatment period at Month 24, visits and assessments for such subjects are described in Table 6-1. All immunosuppressive therapy administered post discontinuation of study regimen (i.e.

MPA+CNI or EVR+CNI) should be recorded on the concomitant Medications CRF under the immunosuppressive category.

For subjects having rATG administered, whether as induction therapy, DGF or anti-rejection treatment the relative impact of all medications to reduced hematological parameters should be considered, thus MPA dose reduction may not always be necessary under these circumstances.

All dose changes must be recorded on the everolimus or MPA Dosage Administration Record CRF as appropriate.

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 hr. All episodes of acute rejection must be entered on the corresponding CRF (e.g. Acute Rejection CRF, Kidney Allograft Biopsy CRF, etc.) preferably within 24 hr.

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

Other anti-rejection therapies (i.e. antibody therapy) should only be used in cases of steroid-resistant rejections, vascular rejections or rejections with a Banff grade $\geq$ 2B.

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

Treatment of Delayed Graft Function (DGF)

In case of DGF, treatment will be according to local practice, but the randomized study regimen cannot be interrupted for more than 21 consecutive days. DGF treatments must maintain sufficient immunological coverage for the graft and may include maintaining, interrupting or reducing the dose of CNI and the use of anti-thymocyte globulin. In case of use of depleting antibody hematological parameters (e.g. lymphocytes, WBC and platelets) must be monitored carefully. Use of MPA and everolimus in subjects randomized to the other treatment arm (i.e. everolimus or MPA respectively) is prohibited during any interruption whether for DGF or other reasons.

If a subject with DGF is not able to return to or maintain their randomized study regimen as per protocol after 21 consecutive days of interruption, the subject should be discontinued from the study. If a subject is placed on permanent dialysis (or retransplanted) the Graft Loss, and Adverse Event CRFs should be completed, as well as an SAE report of Graft Loss submitted. Dialysis treatments should be recorded on the Dialysis CRF. Retransplantation should be recorded on the surgical and medical procedures CRF.

5.5.6 Rescue medication

Not applicable.

[redacted]

5.5.7 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 CRF or the Surgical and Medical Procedures CRF respectively.

CMV prophylaxis

Cytomegalovirus (CMV) pre-emptive therapy and/or prophylaxis is recommended for all donor CMV positive/recipient CMV negative cases and considered for all recipients who are CMV positive. It is recommended that CMV prophylaxis be administered for a minimum of three months after transplantation. Prophylactic treatment with i.v. ganciclovir or oral valganciclovir is recommended and will be administered according to local practice, taking into account dose adjustments based on renal function. CMV prophylaxis is also recommended following antibody treatment of acute rejection episodes (see Section 5.5.5 above). Such prophylaxis should be recorded on the Concomitant Medications CRF.

Pneumocystis jirovecii (*Pneumocystis carinii*) pneumonia prophylaxis

All subjects will be started on trimethoprim-sulfamethoxazole, starting when oral medication can be tolerated and continuing until at least six months post-transplant. After six months, subjects will be treated per local practice. Aerosolized pentamidine or dapsone may be administered to subjects who are unable to tolerate trimethoprim-sulfamethoxazole.

These prophylactic treatments above must be applied consistently across the study population at each given center to avoid bias and confounding in the results. Such prophylaxis should be recorded on the Concomitant Medications CRF.

Treatment of hyperlipidemia

During the course of the study, the lipid profile will be monitored. Lipid lowering medications should be administered according to guidelines and local practice.

The combination of HMG-CoA reductase inhibitors concomitantly with fibrates should be avoided, due to the increased risk of myopathy and rhabdomyolysis in combination with cyclosporine. If combination therapy is needed, ezetimibe should be used in combination with statins. Lipid lowering therapy should be optimized before dosage reduction of study medication is considered.

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.

5.5.8 Prohibited Treatment

Use of the treatments displayed in Table 5-3 is NOT allowed after informed consent up to the end of the 24 Month treatment period. If the use of any of these medications or other non-protocol immunosuppressives is discovered prior to randomization subject must not be randomized and recorded as a screen failure. If discovered after randomization no further doses

[redacted]

are to be given and the subject should continue on the randomized treatment regimen, noting the protocol deviation.

Table 5-3 Prohibited medications

Medication	Action to be taken
Advagraf®	Discontinue Advagraf®, Subject to remain in study with protocol deviation.
Sirolimus	Discontinue sirolimus, Subject to remain in study with protocol deviation.
Belatacept	Discontinue belatacept, Subject to remain in study with protocol deviation.
Azathioprine	Discontinue azathioprine, Subject to remain in study with protocol deviation.
Induction therapy with Campath or other non-protocol antibody agents	Agent to be discontinued and subject to remain in study with protocol deviation.

5.5.9 Discontinuation of study treatment and discontinuation from study

Discontinuation of study regimen

The Dosage administration records for everolimus, MPA, tacrolimus and cyclosporine 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 problems
- 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.

If, at any time throughout the study, the randomized treatment regimen or any component of the regimen is interrupted for longer than 21 consecutive days, unless being held due to an elective surgical procedure then study regimen should be discontinued.

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 CRF, 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 their randomized study regimen (any component whether everolimus, MPA or the CNI) should remain in the study, if possible, and receive standard of care immunosuppression, according to local practice, until completing the study at Month 24. Visits and assessments for such subjects are described in Table 6-1. All immunosuppressants after

[redacted]

discontinuation of study regimen must be recorded on the Concomitant Medication CRF under the Immunosuppressive category.

Subjects are expected to remain on the original CNI (combined with everolimus or MPA) to which they were randomized until at least Month 24. However, if subjects discontinue either CNI due to AE/tolerability and maintain everolimus or MPA combined with the alternate CNI, administered to respective target levels per protocol, they will not be considered to have discontinued study regimen/medication.

Discontinuation from Study and Study/Period completion

Subjects who discontinue their study treatment regimen should NOT be considered withdrawn from the study. 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 24. See Table 6-1 for the required assessments of these subjects after discontinuation of study regimen.

The status of every randomized subject must be recorded on Month 12 and/or Month 24 Study Phase Completion CRFs as either completing or discontinuing from the respective study period, with reason for discontinuation.

Possible reasons for discontinuation from the study are:

- Technical problems
- Subject/Guardian Decision
- Lost to follow-up
- Death
- Graft Loss
- Study terminated by sponsor
- Pregnancy

Subjects may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a subject's premature withdrawal from the study and record this information on the Study Phase Completion CRF at Month 12 and/or Month 24 as applicable.

For subjects who are lost to follow-up (i.e. those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator must show "due diligence" by documenting in the source documents steps taken to contact the s ubject, e.g. dates of telephone calls, registered letters, etc.

Subjects who are prematurely withdrawn from the study will not be replaced.

5.5.10 Emergency breaking of treatment assignment

Not applicable.

[redacted]

5.5.11 Study completion and post-study treatment

Subject who successfully complete 24 months on treatment may be eligible to participate in a separate observational extension study for a further three years. Subjects who are prematurely withdrawn from the study should be treated according to local standard of care per investigator's judgment.

The study will be complete and ready for final analysis when the last active subject has completed their Month 24 visit.

5.5.12 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 for 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 schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "X" when the visits are to be performed. "A" indicates assessments only to be performed for subjects maintaining the study regimen (i.e. EVR+CNI or MPA+CNI). Subjects should be seen for all visits on the designated day or as close to it as possible.

The day of randomization will be considered to be study Day 1. Subjects will make scheduled study visits on Day 4, at the end of Weeks 1, 2 and 4 at the end of Months 2, 4, 6, 9, 12, 18 and 24. All randomized subjects are expected to continue in the study up to Month 24 regardless of being on or off randomized treatment status. 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 Table 6-1. 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.

At a minimum, subjects will be contacted for safety evaluations (SAEs) during the 30 days following the last study visit. Documentation of attempts to contact the subject should be recorded in the source documentation.

Table 6-1 Assessment schedule- Study Treatment to Month 24

Study Period	Screening[1]		Treatment to Month 12									Extension Treatment to Month 24	
Visit	**SCR**	**BL[2]**	**D4**	**W1**	**W2**	**W4**	**M2**	**M4**	**M6**	**M9**	**M12**	**M18**	**M24**
Visit Number	**1**	**99**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**199**	**201**	**299**
Informed Consent [1]	X												
Demographics	X												
Inclusion/ Exclusion	X	X											
Medical History	X												
Kidney Transplant Background Recipient/Donor		X											
Kidney Transplant Procedure		X											
Viral serology[3] Recipient/Donor		X											
Pregnancy test[4]	X								X		X	X	X
IRT call	S	S											
Screening Disposition[1]		X											
Vital signs	X	X	A	A	A	A	A	A	X	X	X	X	X
Physical exam	S										S		S
Tacrolimus dose administration record[5]			X	A	A	A	A	A	A	A	A	A	A
Tacrolimus trough level[6]				X	X	X	X	X	X	X	X	X	X
Cyclosporine dose administration record[5]			X	A	A	A	A	A	A	A	A	A	A
Cyclosporine trough level[6]				X	X	X	X	X	X	X	X	X	X
Everolimus dose administration record[5]			X	A	A	A	A	A	A	A	A	A	A
Everolimus trough level[6]				A	A	A	A	A	A	A	A	A	A
MPA Dose administration record[5]			X	A	A	A	A	A	A	A	A	A	A
Central Laboratory[7]		X		A	A	A	A	A	X	X	X	X	X
Concomitant medication[8]	As Needed												
Surgical and Medical Procedures	As Needed												
Adverse events[9]	As Needed												
CMV assessment			As Needed										
BKV assessment			As Needed										
Hospitalizations			As Needed										
Allograft rejection		As Needed											

[redacted]

Study Period	Screening[1]		Treatment to Month 12									Extension Treatment to Month 24	
Visit	**SCR**	**BL[2]**	**D4**	**W1**	**W2**	**W4**	**M2**	**M4**	**M6**	**M9**	**M12**	**M18**	**M24**
Visit Number	**1**	**99**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**199**	**201**	**299**
Kidney allograft biopsy		As Needed											
Graft loss			As Needed										
Dialysis log			As Needed										
Death	As Needed												
Withdrawal of Informed Consent	As Needed												
Month 12 Period Completion[10]			As Needed								X		
Month 24 Period Completion[10]											As needed		X
[redacted]													

X=assessment for all subjects in study regardless of on or off randomized study regimen, to be recorded in clinical data base
A=assessment ONLY for subjects maintaining their randomized study regimen, to be recorded on clinical data base
S=assessment to be recorded on source documentation

1. Informed consent should be obtained prior to performing any study-related procedures. 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 screen failure. For every consented subject the Screening period disposition CRF must be completed to indicate whether they were randomized or screening failures.

2. The Baseline visit covers the transplant period from 24 hr prior to surgery until randomization or randomization failure. Randomization must occur within 24 hr of completion of transplant surgery and post-transplant criteria for randomization (e.g. ability to take oral medication) must be met. Day 1 is the day of first dose of study drug post-randomization and for subsequent visits one week is 7 days and one month is 30 days, thus the Week 1 visit is on the seventh day from Day 1.

3. Viral serology includes HCV, HIV, HBV surface antigen, CMV and EBV. Measurements made within the last 6 months will be accepted, otherwise these tests should be performed within one week of randomization.

4. Only for females of child bearing potential, serum pregnancy tests should be carried out according to local practice. Local result must be available and negative prior to randomization.

5. First dose of everolimus or MPA together with applicable CNI (tacrolimus or cyclosporine) must be given immediately following randomization and within 24 hr of transplantation. Pre-transplant immunosuppression, including induction therapy and any CNI or MPA should be recorded on the Concomitant medication CRF under the immunosuppressive category.

6. Blood draws for everolimus, tacrolimus and cyclosporine (as applicable) trough concentrations should be performed locally as shown and additionally 5 days ± 2 days following each clinic visit in which tacrolimus, cyclosporine or everolimus doses are changed. Subject clinical management should be based on these local trough levels. At certain centers, by agreement with the sponsor, central analysis of everolimus may be performed.

7. Central laboratory tests at each visit indicated include: **Biochemistry** (sodium, potassium, chloride, calcium, Cystatin C, magnesium, inorganic phosphate, urea, creatinine, uric acid, AST, ALT, alkaline phosphatase, total bilirubin, CPK, lipase and amylase); **Hematology** (platelets, hemoglobin, red blood cell (RBC), white blood cell (WBC) and differential count): **Lipids:** total cholesterol, HDL, LDL and triglycerides **Urinalysis** (protein, creatinine, albumin, glucose; proteinuria and albuminuria per 24hr period will be estimated from spot protein/creatinine and albumin/creatinine ratios). For subjects who have discontinued study regimen who continue in the study to Month 24 all central laboratory assessments, **including serum creatinine** for renal function, should be performed, where no central laboratory serum creatinine is available **local laboratory serum creatinine** should be obtained. HbA1c and fasting plasma glucose will also be carried out by the central laboratory at Week 4 and Months 4, 6, 9, 12 18 and 24. At certain centers, in agreement with the sponsor, central analysis of everolimus levels may be performed.

8. Induction therapy (basiliximab or rATG) should be recorded on the Concomitant Medications CRF under the Immunosuppressive Medications category. Pre-transplant CNI or MPA, if used, should be also recorded on the Concomitant medication CRF under the immunosuppressive category.

9. All serious adverse events, serious infections and pregnancies must be reported from informed consent until 30 days after the last study visit post randomization (i.e. to the Month 12/24 visit or early discontinuation from study).

10. All subjects are expected to continue in the study to Month 24 regardless of whether they are on or off randomized study regimen, if subjects discontinue randomized study regimen they should continue on standard of care and attend study visits to M24. Any permanent discontinuation of the randomized study regimen should be recorded on the appropriate DAR(s) (everolimus MPA, tacrolimus or cyclosporine as needed). Post discontinuation of study regimen the immunosuppressive

[redacted]

Study Period	Screening[1]		Treatment to Month 12									Extension Treatment to Month 24	
Visit	SCR	BL[2]	D4	W1	W2	W4	M2	M4	M6	M9	M12	M18	M24
Visit Number	1	99	101	102	103	104	105	106	107	108	199	201	299

regimen prescribed should be recorded on the Concomitant medication CRF under the immunosuppressive category and any CNI trough levels should be recorded on the appropriate local lab trough CRF.

For subjects who have discontinued randomized study regimen, visits need only be completed at Months 6, 9, 12, 18 and 24.

For all subjects completing the study to Month 12 or discontinuing from the study prior to Month 12, the M12 Period completion form should be completed, regardless of on or off-treatment status. Similarly post-Month 12, for all subjects completing the study to Month 24 or discontinuing from the study prior to Month 24, the M24 Period completion form should be completed, regardless of on or off-treatment status.

[redacted]

6.1 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 12) will have the study completion CRF for the screening period, demographics (giving reason for screen failure), inclusion/exclusion and SAE data collected. Adverse events 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 interactive response technology (IRT) system at screening. For subjects who are not randomized the IRT and Screening Disposition CRF 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 enter the next period of the study (i.e. are randomized to treatment) will have all adverse events **occurring after informed consent is signed** recorded on the Adverse Event CRF.

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

6.2 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. Post-transplant, when all Inclusion/Exclusion criteria are met, the subject may be randomized. For randomization of subjects the IRT must be contacted, CNI and Donor status provided and the IRT will assign the treatment group. For all subjects regardless of randomization status the IRT and Screening Disposition CRF must be completed to

[redacted]

document all consented subjects as either randomized or as screen failures and the reason for screen failure recorded in the CRF.

6.3 Treatment exposure and compliance

All pre-transplant immunosuppression administered, such as basiliximab, rATG and any other agents (CNI, MPA and/or corticosteroids) administered pre-randomization will be recorded on the Concomitant Medications CRF under the immunosuppressive category.

All post-randomization doses of everolimus, MPA, tacrolimus and cyclosporine administered during the course of the study will be recorded on the corresponding Dosage Administration Record CRF.

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 therapy via an NG tube is administered the non-study drug usage of the immunosuppressive should be recorded on the Concomitant Medications CRF under the immunosuppressive category.

Tacrolimus and cyclosporine trough levels will be determined locally and recorded on the relevant CRF. The local trough values will be used to adjust the tacrolimus and cyclosporine dosing. Post-discontinuation of study regimen, for subject remaining in study to Month 24, the CNI trough levels should be recorded on the appropriate local lab CRF.

Everolimus trough levels will be determined by the local Laboratory. However, for sponsor agreed centers where subject management is not possible using a local laboratory, the samples should be sent to the Designated Central laboratory. All local everolimus levels must be completed for all visits on the local everolimus CRF.

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

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

6.4 Efficacy

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 6). 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 within 48 hrs. Biopsies will be read by the local pathologist according to the updated Banff 2009 criteria (Appendix 6). The results of the biopsy read by the local pathologist will be listed on the Kidney Allograft Biopsy CRF. The results will be used for subject management for acute rejection. The local pathologist will remain blinded to

[redacted]

treatment. Any biopsies performed according to local practice (e.g. not for cause) should also be recorded.

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 CRF. This will be reported on the M12 or M24 study completion CRF with Graft Loss as the reason for study discontinuation and on the appropriate Dosage Administration Record CRF(s) if death occurs while on randomized treatment. Graft loss is considered a Serious Adverse Event and should be reported on the Adverse Event CRF (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 hr.

Death

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

6.4.1 Appropriateness of efficacy assessments

The composite efficacy endpoint of treated BPAR and GFR< 50 mL/min/1.72 m^2 is novel in the kidney transplantation indication. This approach is consistent with recent HA guidance (CHMP/EWP/263148/06, effective February 2009) and discussions (FDA Workshop, 2012: Endpoints in Clinical Trials of Kidney Transplantation) on including an assessment of graft function as well as the traditional efficacy endpoints e.g. treated biopsy proven acute rejection with or without clinical outcomes (i.e. Death and Graft loss). The endpoint represents an attempt to assess the clinical balance between having sufficient immunosuppression to prevent rejection while keeping CNI levels low enough to avoid nephrotoxicity.

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.

6.5 Safety

Renal Function

Renal function by calculated eGFR using the MDRD4 formula (Coresh, 2003) from Randomization to Month 12 is a primary variable for assessment of renal function in this study. This will also be the primary method of assessment of renal function with respect to other renal endpoints.

6.5.1 Physical examination

A thorough physical assessment will be performed at Screening, Months 12 and 24 and the subject's final study visit in case of study discontinuation prior to Month 24.

[redacted]

Information about the physical examination must be present in the source documentation at the study site. Significant findings that are present prior to the start of the study must be included in the Relevant Medical History/Current Medical Conditions CRF. Significant findings made after the start of study medication which meet the definition of an AE must be recorded in the AE CRF.

6.5.2 Vital signs

Vital signs (radial pulse rate and blood pressure) will be recorded as indicated in Table 6-1. 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. The repeat sitting measurements will be made at 1-2 minute intervals and the mean of the three measurements will be recorded on the Vital Signs CRF. 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. Clinically notable vital signs are defined in Appendix 1.

6.5.3 Height and weight

Height will be recorded at Screening only, weight will be recorded at Screening, Baseline and at each subsequent visit. Results will be recorded on the Vital Signs CRF.

6.5.4 Laboratory evaluations

A central laboratory will be used for clinical chemistry, hematology and urinalysis as indicated in Table 6-1. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

6.5.4.1 Hematology

Hematological parameters will be analyzed as described in Table 6-1. Clinically notable laboratory findings are defined in Appendix 1.

6.5.4.2 Clinical chemistry

Clinical chemistry parameters will be analyzed as described in Table 6-1. Clinically notable laboratory findings are defined in Appendix 1.

6.5.4.3 Urinalysis

Urinalysis will be performed as described in Table 6-1.

6.5.5 Electrocardiogram (ECG)

Not applicable.

6.5.6 Pregnancy and assessments of fertility

Pregnancy testing (serum) must be carried out for all females of child-bearing potential as described in Table 6-1 or at premature discontinuation from the study.

Additional recommendations regarding pregnancy:

[redacted]

Mycophenolate (mycophenolate mofetil or mycophenolic acid) is a confirmed teratogen associated with an increased rate of spontaneous abortion and congenital malformation compared with other immunosuppressants. Therefore, investigators should ensure that female and male patients taking mycophenolate understand the risk of harm to the baby, the need for effective contraception, and the need to immediately consult the responsible investigator if there is a possibility of pregnancy or a suspected gap of contraception.

Recommendations for female patients:

- Female patients sexually active should use two reliable methods of contraception simultaneously before starting and during therapy with mycophenolate, and for 6 weeks after stopping treatment following discontinuation of mycophenolate.
- Female patients should not donate blood during therapy with mycophenolate and at least 6 weeks following discontinuation of mycophenolate.

Recommendations for male patients:

- Male patients sexually-active should use condom for sex during therapy with mycophenolate and at least 90 days following discontinuation of mycophenolate. Condom use applies for both reproductively competent and vasectomized male patients (due to the risks associated with the transfer of seminal fluid). In addition, female partners of male patients treated with mycophenolate are recommended to use highly effective contraception during treatment and for a total of 90 days after the last dose of mycophenolate.
- Male patients should not donate blood during therapy with mycophenolate and at least 6 weeks following discontinuation of mycophenolate.
- Male patients should not donate semen during therapy with mycophenolate and for 90 days following discontinuation of mycophenolate.

6.5.7 Appropriateness of safety measurements

The safety laboratory assessments (renal function, chemistry, hematology) selected are standard for the kidney transplant population. The blood levels of everolimus and CNIs are required for correct control of drug levels and dosing. The assessment of (serious) adverse events, including infections, graft loss, death, dialysis and details of certain viral infections (CMV and BKV) allow proper assessment safety related outcomes and side effects in this population.

6.6.1 Resource utilization

Resource utilization analysis may include hospitalization data, dialysis data and usage of Concomitant Medications, especially prophylaxis and with anti-CMV or anti-PCP agents.

6.6.2 Health-related Quality of Life

Not applicable.

6.6.3 Pharmacokinetics

Not applicable.

6.6.4 Pharmacogenetics/pharmacogenomics

Not applicable.

6.6.5 Other biomarkers

Not applicable.

7 Safety monitoring

7.1 Adverse events

An adverse event (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 after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product. The occurrence of adverse events should be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subject with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for labs and other test abnormalities are included in Appendix 1.

Adverse events should be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them accompanied by the following information.

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities

[redacted]

  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- possibility of relationship to the study treatment (no/yes)
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
- whether it constitutes a serious adverse event (SAE), if so report date should be provided
- action taken regarding study treatment
- whether other medication or therapies have been taken (concomitant medication/non-drug therapy)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

An SAE is any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria

- 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:
  - Renal allograft biopsy
  - Acute rejection treatment
  - 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
  - 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 subject 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 adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study treatment dosage adjusted/temporarily interrupted; study drug(s) permanently discontinued; concomitant medication given; non-drug therapy given. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

[redacted]

Once an adverse event 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 treatment, 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 subject informed consent and should be discussed with the subject during the study as needed.

The investigator should also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents, however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse event reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hr of learning of its occurrence. Any SAE experienced after the 30 day period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

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 hr 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 in English on the paper Serious Adverse Event Report Form or the electronic Serious Adverse Event Form within the OC/RDC system (where available). The Investigator must assess the relationship to each specific component of the study treatment (if the study treatment consists of several components).

SAEs (initial and follow-up) that are recorded on the paper SAE form should be faxed within 24 hr of 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

SAEs (initial and follow-up) that are recorded *electronically* in the OC/RDC system should be entered, saved and e-signed within 24 hr of awareness of the SAE or changes to an existing SAE. These data will automatically be submitted to Novartis Drug Safety & Epidemiology immediately after investigator signature or 24 hr after entry, whichever occurs first.

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

[redacted]

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 Directive 2001/20/EC or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

No additional testing other than in clinical chemistry as described in Table 6-1.

7.4 Pregnancy reporting

To ensure subject safety, each pregnancy occurring while the subject is on study treatment must be reported to Novartis within 24 hr 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 study treatment.

Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.5 Prospective suicidality assessment

Not applicable.

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 CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of subject records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

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

[redacted]

information, laboratory data and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form(s) 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 CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff will review the data entered into the CRFs 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 are required to respond to the query and confirm or correct the data.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

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

Randomization codes will be assigned using Interactive Response Technology (IRT). The IRT system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis.

Protocol deviations will be identified, documented and communicated as required throughout the study. At the conclusion of the study, the occurrence of relevant 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 after written agreement by Novartis Development management.

[redacted]

8.4 Data Monitoring Committee

Not applicable.

8.5 Adjudication Committee

Not applicable.

9 Data analysis

Statistical analysis and report writing will be performed when the last subject has completed 12 months on study. A second and final analysis will be performed when all subjects complete 24 months of the study.

9.1 Analysis sets

The **full analysis set** (FAS) consists of all randomized and transplanted subjects. Subjects randomized but not transplanted will be excluded from the FAS. Subjects who are misrandomized due to documented (IVRS) administrative error (eligibility criteria) and have no study drug received are excluded from the FAS. Following the intention-to-treat (ITT) principle, subjects will be analyzed according to their randomized treatment assignment and according to the actual stratum they belong to.

The **per-protocol set** (PPS) consists of all subjects in the FAS who complete the study without any major deviations from protocol procedures. Major deviations include:

- Subject had multiple transplants or has had previous transplants
- Renal cold ischemia time > 30 hr

Additional protocol deviations and final definition of the PPS will be made based on blinded examination of the data prior to the 12-month and 24-month database locks.

The **safety set** (SAF) consists of all subjects who received at least one dose of study drug. Subjects will be analyzed according to the treatment they actually received.

All safety analyses will be performed on the SAF. Generally safety analyses will use treatment - emergent data (on-treatment analysis by including data up to 2 days after the discontinuation of study drug). Selected variables will be analyzed using all available data including data assessed beyond study treatment discontinuation: AEs/infections and deaths.

9.2 Subject demographics and other baseline characteristics

Demographic and background information for the FAS population will be summarized using frequency distribution (for categorical variables) and descriptive statistics of mean, median, maximum, minimum and standard deviation (for continuous variables). Background information includes prior medication taken before study entry, past/current medical conditions and transplant history.

[redacted]

9.3 Treatments

Study medication

Duration of exposure to study regimen will be summarized in tables as follows. In addition to an overall summary of exposure duration for each study regimen, a separate summary will be made for CsA and TAC subgroups within a study regimen.

- Number and percentage of subjects being exposed for prespecified time intervals (e.g. 1-7 days, 8-14 days, 15-30 days, 31-60 days, etc) as well as cumulative exposure.
- Summary statistics (n, mean, SD, median, Q1, Q3, minimum, maximum) for duration of exposure will also be provided.

Average daily doses and body weight-adjusted average daily doses (for CsA and TAC only) by visit window and treatment group will also be calculated. In calculating average daily doses, zero doses will be used for periods of temporary interruption of study medication, regardless of whether this was due to safety reasons or non-compliance.

The number and percentage of subjects of remaining on their randomized CNI or switching CNI at least once during the study will be summarized for each study CNI-specific study regimen. This will be provided for each study period (up to Month 12, Month 12 to 24, and cumulatively).

Concomitant medication

Average daily doses and body weight-adjusted average daily doses by visit window will be summarized for corticosteroids (expressed in doses equivalent to prednisone) for each treatment group for subjects who are on study medication.

Medications will be identified using the NovDTD including Anatomical Therapeutic Chemical (ATC) code. Concomitant medications other than immunosuppressants, as well as the use of immunosuppressants other than study medication will also be summarized as follows.

- Medications will be presented in alphabetical order, by ATC codes and grouped by *anatomical main group* (the 1st level of the ATC codes). Tables will also show the overall number and percentage of subjects receiving at least one drug of a particular ATC code and at least one drug in a particular anatomical main group.

9.4 Analysis of the primary variable

9.4.1 Variable

The primary efficacy variable is a binary composite endpoint of tBPAR or eGFR (MDRD4) < 50 mL/min/1.73m^2 at Month 12 post-transplantation. The component of eGFR (MDRD4) < 50 mL/min/1.73m^2 at Month 12 is defined as an incidence of eGFR (MDRD4) < 50 mL/min/1.73m^2 in the Month 12 visit window.

9.4.2 Statistical model, hypothesis, and method of analysis

The primary analysis will be performed on the Full Analysis Set following the intent-to-treat principle. The proportion of subjects meeting the primary endpoint of tBPAR or eGFR (MDRD4) < 50 mL/min/1.73m^2 at Month 12 will be compared using a confidence interval approach.

[redacted]

Treatment by CNI interaction for the composite endpoint of tBPAR or eGFR (MDRD4) < 50 mL/min/1.73m^2 will be assessed using a logistic regression model (see Section 9.4.4 for risk factor analysis). If the interaction is not significant at the level of 0.10, i.e. the effects of treatment are similar for each CNI, then the primary analysis will be based on the pooled CNIs, i.e. everolimus plus reduced CNI (EVR+rCNI) vs. MPA plus standard CNI (MPA+sCNI). If this test shows significantly different event rates for tacrolimus vs. cyclosporine, then testing will be performed for the 2 CNIs separately, with the tacrolimus subgroup being considered primary [redacted]

Event rates will be compared between groups using the following hierarchical testing strategy:

a) Non-inferiority of EVR+rCNI vs. MPA+sCNI will be evaluated based on the primary endpoint of tBPAR or eGFR (MDRD4) < 50 mL/min/1.73m^2 at Month 12 using a 10% non-inferiority margin (see Section 9.4.2.1).

b) Non-inferiority of EVR+rCNI vs. MPA+sCNI will be evaluated with a 10% non-inferiority margin for the key secondary endpoint of tBPAR, graft loss or death at Month 12 (see Section 9.5.1).

c) Superiority of EVR+rCNI to MPA+sCNI will be evaluated based on the primary endpoint of tBPAR or eGFR (MDRD4) < 50 mL/min/1.73m^2 at Month 12 (see Section 9.4.2.2).

The above hierarchical fixed hypothesis testing procedure will not inflate overall Type I error rate. Therefore, each hypothesis will be tested at the one-sided 0.025 significance level and no multiplicity adjustment is needed.

9.4.2.1 Non-inferiority of everolimus plus reduced CNI to MPA plus standard CNI

The null hypothesis:

H_{01}: $R_{EVR+rCNI} - R_{MPA+sCNI} \geq 0.10$ (non-inferiority margin): the difference in proportion of subjects experiencing tBPAR or eGFR (MDRD4) < 50 mL/min/1.73m^2 at 12 months between the everolimus plus reduced CNI ($R_{EVR+rCNI}$) and the MPA plus standard CNI arm ($R_{MPA+sCNI}$) is at least 10%.

The alternative hypothesis:

H_{A1}: $R_{EVR+rCNI} - R_{MPA+sCNI} < 0.10$ (non-inferiority margin): The difference in proportion of subjects experiencing tBPAR or eGFR (MDRD4) < 50 mL/min/1.73m^2 at 12 months between the everolimus plus reduced CNI ($R_{EVR+rCNI}$) and the MPA plus standard CNI arm ($R_{MPA+sCNI}$) is less than 10%.

9.4.2.2 Superiority of everolimus plus reduced CNI to MPA plus standard CNI

The null hypothesis:

H_{03}: $R_{EVR+rCNI} - R_{MPA+sCNI} \geq 0$: the proportion of subjects experiencing tBPAR or eGFR (MDRD4) < 50 mL/min/1.73m^2 at 12 months in the everolimus plus reduced CNI ($R_{EVR+rCNI}$) arm is greater than or equal to that in the MPA plus standard CNI arm ($R_{MPA+sCNI}$) arm.

The alternative hypothesis:

[redacted]

H_{A3}: $R_{EVR+rCNI}$ - $R_{MPA+sCNI}$ < 0: the proportion of subjects experiencing tBPAR or eGFR (MDRD4) < 50 mL/min/1.73m^2 at 12 months in the everolimus plus reduced CNI ($R_{EVR+rCNI}$) arm is less than that in the MPA plus standard CNI arm ($R_{MPA+sCNI}$) arm.

Both hypotheses H_{01} and H_{03} will be tested at the significance level of $\alpha = 0.025$ (one-sided). A Z-test based 95% confidence interval will be constructed for the difference in proportion of subjects experiencing tBPAR or eGFR (MDRD4) < 50 mL/min/1.73m^2 at 12 months between the everolimus plus reduced CNI arm ($R_{EVR+rCNI}$) and the MPA plus standard CNI arm ($R_{MPA+sCNI}$). The everolimus plus reduced CNI arm will be claimed to have a non-inferior incidence of tBPAR or eGFR (MDRD4) < 50 mL/min/1.73m^2 compared to the MPA plus standard CNI arm if the upper limit of the 95% CI is below 10%. The everolimus plus reduced CNI arm will be claimed to be superior to the MPA plus standard CNI arm with respect to composite endpoint of tBPAR or eGFR (MDRD4) < 50 mL/min/1.73 m^2 at 12 months if the upper limit of the 95% CI is less than 0.

However, following the aforementioned hierarchical fixed hypothesis testing procedure, the hypothesis H_{03} for superiority of EVR plus reduced CNI to MPA plus standard CNI will be evaluated if non-inferiority of EVR plus reduced CNI vs. MPA plus standard CNI is achieved for the primary endpoint (rejecting the hypothesis H_{01}) and the key secondary endpoint of tBPAR, graft loss or death at Month 12 (rejecting the hypothesis H_{02}, see Section 9.5.1).

9.4.3 Handling of missing values/censoring/discontinuations

Since the subjects who have prematurely discontinued study regimen are followed on standard of care, renal function data (e.g. creatinine) and kidney allograft biopsy data will be collected post discontinuation of study regimen for these visits, it is expected that few subjects would be missing efficacy and/or renal function evaluation for the 12 month analysis.

To define the primary variable – composite endpoint of tBPAR or eGFR (MDRD4) < 50 mL/min/1.73m^2, the following imputation method will be applied for subjects with missing 12-month eGFR value. As allograft biopsy data will be collected on an as needed basis due to the nature of kidney transplant studies, no particular rule for missing biopsy will be applied.

- Under the assumption of missing not at random (MNAR), subjects who lost their grafts will be assigned a value of zero for their 12-month eGFR;
- Otherwise, under the assumption of missing at random (MAR), subjects who had missing values including those who died with a functioning graft will have a 12-month eGFR imputed using multiple imputation method based on the longitudinal eGFR (MDRD4) data at all available time points and covariates of randomization strata (donor type and CNI), HLA mismatches (≤3 vs >3) and induction.

9.4.4 Supportive analyses

The following analyses will serve as supportive analyses for the primary endpoint of tBPAR or eGFR (MDRD4)<50 mL/min/1.73m^2 at Month 12.

The analysis outlined for the primary endpoint in Section 9.4.2 will be repeated using compliant subjects in the FAS population.

[redacted]

Analysis on Per-Protocol Set

The analysis outlined for the primary endpoint in Section 9.4.2 will be repeated using the Per-Protocol Set.

Subgroup analysis

Subgroup analyses will be done for the primary composite endpoint of tBPAR or eGFR (MDRD4)<50 mL/min/1.73m^2 at 12 months for the subgroups defined by:

- recipient characteristics (recipient age group: <60 vs ≥60 yr, gender, race, region)
- donor/transplant characteristics (donor age group: <60 vs ≥60 yr, gender, cold ischemia time: < 20 vs ≥20 hr, end stage disease leading to transplant, donor type; living donor, standard criteria deceased donor and expanded criteria deceased donor; HLA mismatches: <=3 vs >3)
- CNI (tacrolimus vs. cyclosporine)
- Induction (basiliximab vs. rATG)
- Immunological risk (high vs. low)

Subgroup analyses will use the Z-test on event rates (proportions) and also present confidence intervals for the pairwise differences in proportions.

Risk factor analysis using a logistic regression model

To investigate prognostic variables that might have an impact on the primary efficacy endpoint, a logistic regression analysis will be performed to identify potential risk factors. For this analysis, the same variables to define the above subgroups as well as the interaction between treatment and CNI and the interaction between treatment and region will be used. In the model, recipient and donor age, cold ischemia time, and potentially HLA mismatches will be treated as continuous variables.

Analyses with other imputations for missing eGFR (MDRD4) at Month 12

In addition to the imputation method described in Section 9.4.3, the following imputation method will be used to impute missing 12-month eGFR value to define the primary variable – composite endpoint of tBPAR or eGFR (MDRD4) < 50 mL/min/1.73m^2. With these imputations, non-inferiority and superiority analyses described in Section 9.4.2 will be repeated.

- Subjects who lost their grafts will be assigned a value of zero for their 12-month eGFR;
- Otherwise, subject who had missing value including those who died with a functionin g graft will have a 12-month eGFR imputed using the following imputation methods:
    a) The last non-missing observation carried forward (LOCF);
    b) Penalty-adjusted imputation method: missing eGFR values will be imputed first under missing at random (MAR) assumption, then apply a multiplicative penalty factor to the imputed data for subjects who discontinued due to AE or death. For example, a penalty factor of 0.8 corresponds to a reduction of the MAR-imputed value by 20%. This penalty-adjusted imputation will be applied to both EVR + rCNI and MPA + sCNI arms. Penalty factors of 1.0, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, 0.1 and 0.0 will be used.

[redacted]

c) Impute missing eGFR values in EVR + rCNI arm based on the data from the control arm (MPA + sCNI) as everolimus subjects would switch to control (standard care) or control-like medication after they discontinue everolimus. The missing eGFR values in the control arm will be imputed under MAR assumption.

The purpose of imputation (a) is to compare with historical trials as this imputation was the main imputation method used in the past. To verify the MAR assumption used in Section 9.4.3 for multiple imputation, imputation methods (b) and (c) will be applied under the assumption of missing not at random (MNAR). These two imputations will be based on the longitudinal eGFR (MDRD4) data using all available time points and randomization strata (donor type and CNI), HLA mismatches (≤3 vs >3), and induction as covariates.

9.5 Analysis of secondary variables

9.5.1 Assessment of the key secondary endpoint of tBPAR, graft loss, or death

For the key secondary objective regarding the composite efficacy failure of tBPAR, graft loss or death, to evaluate whether everolimus plus reduced CNI is non-inferior to MPA plus standard CNI at 12 months post-transplantation, the following hypotheses will be evaluated (α=0.025, one-sided) based on the Full Analysis Set:

The null hypothesis:
H_{03}: $R_{EVR+rCNI} - R_{MPA+sCNI} \geq 0.10$ (non-inferiority margin): the difference in Kaplan-Meier event rate of the composite efficacy failure of tBPAR, graft loss or death at 12 months between the everolimus plus reduced CNI ($R_{EVR+rCNI}$) and the MPA plus standard CNI arm ($R_{MPA+sCNI}$) is at least 10%.

The alternative hypothesis:
H_{A3}: $R_{EVR+rCNI} - R_{MPA+sCNI} < 0.10$ (non-inferiority margin): the difference in Kaplan-Meier event rate of the composite efficacy failure of tBPAR, graft loss or death at 12 months between the everolimus plus reduced CNI ($R_{EVR+rCNI}$) and the MPA plus standard CNI arm ($R_{MPA+sCNI}$) is less than 10%.

For this analysis, the event rate of the composite efficacy failure of tBPAR, graft loss or death will be estimated with Kaplan-Meier product-limit formula. Greenwood's formula will be used to estimate variance of failure rates and to derive Z-test based confidence interval for the difference in failure rate between the everolimus plus reduced CNI and the MPA plus standard CNI arm.

Since the subjects who have prematurely discontinued study regimen are followed on standard of care, efficacy data including kidney allograft biopsies will be collected post-discontinuation of study regimen for these visits, it is expected that few subjects would be missing efficacy evaluation for the 12 months analysis. Subjects with missing efficacy evaluation for the 12 month analysis will be censored at the latest day known to be free of the event.

As supportive analyses, this non-inferiority analysis will be repeated using the Per-Protocol Set, and Kaplan-Meier event rates of this key secondary endpoint will be summarized for the subgroups defined in Section 9.4.4.

[redacted]

9.5.2 Other secondary efficacy variables

Other secondary efficacy variables to be considered are as follows:

(1) Composite endpoint of tBPAR or eGFR (MDRD4) < 50 mL/min/1.73m^2 at Month 24;

(2) Composite endpoint of tBPAR excluding grade IA rejections or eGFR (MDRD4) < 50 mL/min/1.73m^2 at Months 12 and 24

(3) Composite efficacy failure of tBPAR, graft loss, or death at Month 24;

(4) Composite efficacy failure of tBPAR, graft loss, death, or loss to follow-up at Month 12 and 24;

(5) Components of composite efficacy failure as well as BPAR, AR, tAR at Month 12 and Month 24;

a) AR

b) tAR

c) BPAR;

d) tBPAR;

e) tBPAR excluding grade IA rejections;

f) Humoral rejection

g) Graft loss;

h) Death.

(6) composite endpoint of tBPAR, graft loss, death or eGFR < 50 mL/min/1.73m^2 at Months 12 and 24;

(7) Composite endpoint of graft loss or death at Month 12 and Month 24;

(8) Composite endpoint of BPAR, graft loss or death at Month 12 and Month 24;

(9) eGFR (MDRD4) < 50 mL/min/1.73m^2 at Month 12 and Month 24;

(10) Renal function (eGFR by MDRD4, CKD-EPI and Cystatin C-based formulae) at Month 12 and Month 24;

(11) Renal function change from Month 1 (Week 4) to Month 12 and Month 24;

(12) Evolution of renal function (eGFR by MDRD4) from Month 1 to Month 12 and Month 24 (slope analyses).

The analyses on efficacy endpoints and renal function will be based on the Full Analysis Set. Selected parameters will be analyzed on the Per-Protocol Set as well.

A Z-test based comparison will be performed for the following composite endpoints: tBPAR or eGFR (MDRD4) < 50 mL/min/1.73m^2 at Month 24, composite endpoint of tBPAR excluding grade IA rejections or eGFR (MDRD4) < 50 mL/min/1.73m^2 at Months 12 and 24, endpoint of tBPAR, graft loss, death or eGFR < 50 mL/min/1.73m^2 at Months 12 and 24, and endpoint of tBPAR, graft loss, death, or loss to follow-up at Months 12 and 24.

[redacted]

For the composite efficacy failure (tBPAR, graft loss or death) at Month 24 and the composite endpoint of BPAR, graft loss or death at Month 12 and Month 24, Kaplan-Meier event rates will be estimated and compared between the everolimus plus reduced CNI and the MPA plus standard CNI arm. Similarly Kaplan-Meier event rates will be estimated and compared for AR, tAR, BPAR, tBPAR, humoral rejection, graft loss, death and the composite endpoint of graft loss or death. To assess time-to-event occurrence of efficacy endpoints, Kaplan-Meier plots will be produced and the log-rank test will be performed. A forest plot of KM event rate differences for efficacy endpoints will be produced. Severity of tBPAR will be tabulated by treatment.

As a key component of the primary endpoint (tBPAR or eGFR (MDRD4) < 50 mL/min/1.73m ^{2}), the endpoint of eGFR (MDRD4) < 50 mL/min/1.73m^2 will be summarized with raw incidence rates and compared. A Z-test based 95% confidence interval will be provided.

For eGFR(MDRD4) at Month 12 and Month 24, analysis of covariance (ANCOVA) will be performed with treatment (everolimus vs MPA), CNI (CsA vs TAC), interaction of treatment and CNI, region, interaction of treatment and region, induction, donor type (living donor, deceased standard criteria donor and deceased expanded criteria donor), recipient gender and donor gender as factors, and recipient age and BMI, donor age, cold ischemic time and eGFR(MDRD4) at Month 1 as covariates. The missing Month 12 or Month 24 values will be imputed using the same methods as described in Section 9.4.3 and Section 9.4.4 except LOCF approach for Month 24, for which a Month 24 eGFR value will be imputed using the last non-missing observation carried forward (LOCF) from Month 6 onwards as subjects will be maintained in the same CNI target range since Month 6.

Renal function and change from Month 1 (Week 4) will be summarized by visit with descriptive statistics and graphically presented by visit.

The evolution of renal function (eGFR by MDRD4) will be evaluated via a mixed effect model with intercept and subject as random effects and using with the same covariates/factors as used for the ANCOVA model. Based on the mixed effect model, the treatment groups will be compared, and slope of renal function evolution for each treatment group will be assessed.

9.5.3 Safety variables

Safety variables to be assessed include discontinuation from study, discontinuation from treatment, AE/infection, SAE, notable events, laboratory tests, and vital signs. All safety analyses will be done on the safety set. Generally safety analyses will use treatment -emergent data (on-treatment analysis by including data up to 2 days after the discontinuation of study drug). Selected variables will be analyzed using all available data including data assessed beyond study treatment discontinuation: AEs/infections and deaths.

As subjects may not necessarily visit the clinics at the exact scheduled time, it may be misleading to lump all data with the same nominal visit number into the same visit in a by-visit analysis. Thus, all data are to be "re-aligned" by referencing their visit date to the date of initial dose. Visit-based time windows will be defined for data analysis.

The Baseline value is represented by the last observation during the Baseline period.

[redacted]

Assessment of premature study and study treatment discontinuation

Incidence rate of subjects who prematurely discontinue study medication or study will be summarized by frequency tables.

AEs/infections

Generally, infection data are analyzed together with AE data. In addition, infection data will be analyzed separately. Micro-organism will be additionally coded with NovORG dictionary.

The incidence of treatment-emergent AEs will be summarized by body system, severity and relationship to study drug. The type (viral, bacterial, fungal, and others) and micro-organism of infections will be tabulated. In addition, AEs/infections will be summarized per SMQ narrow search.

[redacted]

All information pertaining to AEs noted during the study will be listed by subject, detailing AE (verbatim given by the investigator as well as the preferred term according to the MedDRA dictionary), body system, date starting and ending, causality, severity and drug-relatedness.

Notable events

Notable events include death, non-fatal SAEs (including infections and rejections reported as SAE), AEs (including infections and rejections) leading to discontinuation from the study, and drop-outs due to notable events as reported on the Treatment/Study completion CRF): a) adverse event(s); b) abnormal laboratory result(s); c) abnormal test procedure result(s).

Vital signs

Vital signs variables include measurements of oral body temperature, systolic and diastolic blood pressures, pulse and body weight. Vital signs will be examined for abnormal values and change from baseline according to pre-specified clinically notable criteria. Appropriate incidence rates of clinically notable abnormalities will be provided. Further, descriptive statistics of all vital signs variables as well as the changes from baseline will be presented by visit. A by-subject listing of all vital signs (with clinically notable abnormalities being flagged) will be generated.

Laboratory data

Descriptive statistics (mean, standard deviation, minimum, median and maximum) of quantitative laboratory variables, including change from Baseline, will be generated by visit for laboratory parameters. Categorical levels of urinary protein/creatinine ratio (<30, 30 - <500, 500 - <1000, 1000 - <3000, >=3000 mg/g) will additionally summarized by visit.

Abnormalities according to the clinical notable criteria (see Appendix 1) will be identified and tabulated for each applicable lab parameter. Lipids levels are categorized based on the following criteria per American Heart Association (Adult treatment panel III 2002). A by-subject listing of individual subject laboratory data will be generated; values outside of clinical notable will be flagged.

[redacted]

- Triglycerides
  - Normal: < 150 mg/dL
  - Borderline high: 150 – <200 mg/dL
  - High: 200 – <500 mg/dL
  - Very high: ≥ 500 mg/dL
- Total cholesterol
  - Normal: < 200 mg/dL
  - Borderline high: 200 – <240 mg/dL
  - High: ≥240 mg/dL
- HDL cholesterol
  - Low: < 40 mg/dL for men, <50 mg/dL for women
  - Normal: 40 – <60 mg/dL for men, 50 – <60 mg/dL for women
  - Optimal: ≥60 mg/dL
- LDL cholesterol
  - Optimal: < 100 mg/dL
  - Near or above optimal: 100 – <130 mg/dL
  - Borderline high: 130 – <160 mg/dL
  - High: 160 – <190 mg/dL
  - Very high: ≥ 190 mg/dL

Total cholesterol /HDL ratio level is defined as

- Normal: <5
- High: >=5 but <=7
- Very High: >7

Tolerability

Tolerability of the regimens is assessed by summarizing the percentage of subjects requiring dose adjustment or interruption and premature treatment discontinuations due to adverse events by treatment group.

9.5.4 Resource utilization

Data relating to resource utilization will be used for the purpose of economic evaluation, which will be carried out and reported as a separate activity.

9.5.5 Health-related Quality of Life

Not applicable.

9.5.6 Pharmacokinetics

Not applicable.

9.5.7 Pharmacogenetics/pharmacogenomics

Not applicable.

[redacted]

9.5.8 Biomarkers

Not applicable.

9.5.9 PK/PD

Not applicable.

9.6 Interim analyses

A futility analysis will be performed when approximately 30% of subjects have completed 6 months on study. The unblinded futility analysis results will be reviewed and considered together with other efficacy and safety data by an unblinded team. At their discretion, the unblinded team will make a recommendation regarding trial continuation/amendment/ termination. No stringent (binding) futility boundary is pre-specified. The details of the futility analysis will be provided in a separate document.

The primary analysis will be at Month 12 and the final analysis will be at Month 24.

9.7 Sample size calculation

The sample size for this study was chosen with the goals to (1) have high power to evaluate non-inferiority in both the overall population *and* the TAC alone population and (2) have adequate power to evaluate superiority in the both the overall population *and* the TAC alone population.

As shown in Table 9-1, with a sample size of n=1020 randomized per arm (EVR, MPA), the study has at least 95% power to demonstrate non-inferiority (α=0.025, one-sided) in the overall and TAC alone populations at Month 12. There are at least 73% and 63% power (α=0.025, one-sided) to demonstrate superiority of 7% or more in the overall and TAC alone populations, respectively.

The calculations are based on the following assumptions:

- 80% of subjects are randomized to tacrolimus, 20% of subjects are randomized to cyclosporine
- 20% and 30% subjects are excluded from the PP population at Months 12 and 24 respectively
- For non-inferiority, the event rate in each arm is 50%, based on study results from RAD001A2309 and Ekberg 2007, and the non-inferiority margin for the primary composite endpoint is 10%.
- For the evaluation of superiority, the event rate in the MPA + sCNI arm is 50%.

Table 9-1 Power for non-inferiority and superiority testing: Overall population and TAC alone population

Population	Analysis Set	Time Point (N evaluable per group)	Power: Non-inferiority	Power for Superiority: difference from MPA + sCNI			
				-5%	-6%	-7%	-8%

Overall	FAS	Month 12 or 24 (N=1020)	>99	60	76	87	94
	PPS	Month 12 (N=816)	98	50	66	79	89
		Month 24 (N=714)	97	45	60	73	84
TAC	FAS	Month 12 or 24 (N=816)	98	50	66	79	89
	PPS	Month 12 (N=653)	95	41	56	69	81
		Month 24 (N=571)	92	37	50	63	75

All sample size calculations were performed using NQuery Advisor, Version 7.0 (modules PTE1b-1 and PTT1-1).

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 treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception 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.

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) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC 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, 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. 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

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as requests to approve deviations will not be granted.

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

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 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. Only amendments that are required for subject safety may be implemented prior to IRB/IEC 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 IRB/IEC at the study site should be informed within 10 working days or less, if required by local regulations.

12 References (available upon request)

Brennan DC, Legendre C, Patel D, Mange K, Wiland A, McCague K, Shihab FS (2011) Cytomegalovirus Incidence Between Everolimus Versus Mycophenolate in De Novo Renal Transplants: Pooled Analysis of Three Clinical Trials. Am J Transplant; 11(11):2453-62.

[redacted]

CHMP guideline on clinical investigation of immunosuppressants in solid organ transplantation (2009) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003593.pdf (accessed 7th June 2013)

Coresh J, Astor BC, Greene T, Garabed E, Levey AS (2003) Prevalence of chronic kidney disease and decreased kidney function in adult US population: Third national health and nutrition examination survey. Am J Kidney Dis; 41(1): 1-12.

De Simone P, Nevens F, De Carlis L, Metselaar HJ, Beckebaum S, Saliba F, Jonas S, Sudan D, Fung J, Fischer L, Duvoux C, Chavin KD, Koneru B, Huang MA, Chapman WC, Foltys D, Witte S, Jiang H, Hexham JM, Junge G; for the H2304 Study Group (2012) Everolimus With Reduced Tacrolimus Improves Renal Function in De Novo Liver Transplant Recipients: A Randomized Controlled Trial. Am J Transplant. 12:3008-3020.

Deeks ED and Keating GM (2009) Rabbit antithymocyte globulin: A review of its use in the prevention and treatment of acute renal allograft rejection. Drugs 69;1485-1512.

Eisen HJ, Tuzcu EM, Dorent R, Kobashigawa J, Mancini D, Valantine-von Kaeppler HA, Starling RC, Sørensen K, Hummel M, Lind JM, Abeywickrama KH, Bernhardt P; RAD B253 Study Group (2003) Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. N Engl J Med; 349(9):847-58.

Ekberg H, Tedesco-Silva H, Demirbas A, Vítko S, Nashan B, Gürkan A, Margreiter R, Hugo C, Grinyó JM, Frei U, Vanrenterghem Y, Daloze P, Halloran PF; ELITE-Symphony Study (2007) Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med; 357(25):2562-75.

FDA Workshop, 2012: Endpoints in Clinical Trials of Kidney Transplantation. Transcript at http://www.fda.gov/Drugs/NewsEvents/ucm305308.htm

Grube E, Sonoda S, Ikeno F, Honda Y, Kar S, Chan C, Gerckens U, Lansky AJ, Fitzgerald PJ (2004) Six- and twelve-month results from first human experience using everolimus-eluting stents with bioabsorbable polymer. Circulation; 109(18):2168-71.

Hariharan S, McBride MA, Cherikh WS, Tolleris CB, Bresnahan BA, Johnson CP (2002) Post-transplant renal function in the first year predicts long-term kidney transplant survival. Kidney Int; 62(1):311-8.

Havenith SH, Yong SL, van Donselaar-van der Pant KA, van Lier RA, ten Berge IJ, Bemelman FJ (2013) Everolimus-treated renal transplant recipients have a more robust CMV-specific CD8+ T-cell response compared with cyclosporine- or mycophenolate-treated patients. Transplantation; 95(1):184-91.

Kasiske BL, Israni AK, Snyder JJ, Skeans MA; Patient Outcomes in Renal Transplantation (PORT) Investigators (2011) The relationship between kidney function and long-term graft survival after kidney transplant. Am J Kidney Dis; 57(3):466-75.

Langer RM, Hené R, Vitko S, Christiaans M, Tedesco-Silva H Jr, Ciechanowski K, Cassuto E, Rostaing L, Vilatoba M, Machein U, Ulbricht B, Junge G, Dong G, Pascual J. (2012) Everolimus plus early tacrolimus minimization: a phase III, randomized, open-label, multicentre trial in renal transplantation. Transplant Int. 25:592-602.

[redacted]

Loriga G, Ciccarese M, Pala PG, Satta RP, Fanelli V, Manca ML, Serra G, Dessole P, Cossu M (2010) De novo everolimus-based therapy in renal transplant recipients: effect on proteinuria and renal prognosis. Transplant Proc; 42(4):1297-302.

Nashan B, Curtis J, Ponticelli C, Mourad G, Jaffe J, Haas T (2004) Everolimus and reduced-exposure cyclosporine in de novo renal-transplant recipients: a three-year phase II, randomized, multicenter, open-label study. Transplantation, 78:1332-40.

Nashan B, Gaston R, Emery V, Saemann MD, Mueller NJ, Couzi L, Dantal J, Shihab F, Mulgaonkar S, Seun Kim Y, Brennan DC (2012) Review of cytomegalovirus infection findings with mammalian target of rapamycin inhibitor-based immunosuppressive therapy in de novo renal transplant recipients. Transplantation; 93(11):1075-85.

National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report (2002) Circulation. 106:3143–3421

Park WD, Larson TS, Griffin MD, Stegall MD (2012) Identification and Characterization of Kidney Transplants With Good Glomerular Filtration Rate at 1 Year But Subsequent Progressive Loss of Renal Function. Transplantation 94:931-939

Pascual J (2009) The use of everolimus in renal-transplant patients. Int J Nephrol Renovasc Dis; 2: 9–21.

Shihab FS, Cibrik D, Chan L, Kim YS, Carmellini M, Walker R, Zibari G, Pattison J, Cornu-Artis C, Wang Z, Tedesco-Silva Jr H (2012) Association of clinical events with everolimus exposure in kidney transplant patients receiving reduced cyclosporine. Clin Transplant. 2012.

Tedesco Silva H Jr, Cibrik D, Johnston T, Lackova E, Mange K, Panis C, Walker R, Wang Z, Zibari G, Kim YS. (2010) Everolimus plus reduced-exposure CsA versus mycophenolic acid plus standard-exposure CsA in renal-transplant recipients. Am J Transplant. 10:1401-13.

Vitko S, Tedesco H, Eris J, Pascual J, Whelchel J, Magee JC, Campbell S, Civati G, Bourbigot B, Alves Filho G, Leone J, Garcia VD, Rigotti P, Esmeraldo R, Cambi V, Haas T, Jappe A, Bernhardt P, Geissler J, Cretin N (2004) Everolimus with optimized cyclosporine dosing in renal transplant recipients: 6-month safety and efficacy results of two randomized studies. Am J Transplant. 4:626-35.

Wiseman AC, McCague K, Kim Y, Geissler F, Cooper M (2013) The effect of everolimus versus mycophenolate upon proteinuria following kidney transplant and relationship to graft outcomes. Am J Transplant; 13(2):442-9.

Wu J, Li H, Huang H, Wang R, Wang Y, He Q, Chen J (2010) Slope of changes in renal function in the first year post-transplantation and one-yr estimated glomerular filtration rate together predict long-term renal allograft survival. Clin Transplant; 24(6):862-8.

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13 Appendix 1: 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^3 ≥700 k/mm^3	<50 × 10^9/L ≥700 × 10^9/L
Leukocytes (WBCs)	≤2.0 k/mm^3 ≥16 k/mm^3	≤ 2.0 × 10^9/L ≥16 × 10^9/L
Hematology variables: differential		
Granulocytes (poly, neutrophils)	≤1,000/mm^3	≤1 x 10^9/L
Eosinophils	≥12%	≥12%
Lymphocytes	≤1,000/mm^3	≤1× 10^9/L

Vital sign variables	Notable criteria
Systolic BP (mm/Hg)	Either an increase of ≥30 that results in ≥180 or >200(mm/Hg) OR a decrease of ≥30 that results in ≤90 or <75 (mm/Hg)
Diastolic BP (mm/Hg)	Either an increase of ≥20 that results in ≥105 or >115 (mm/Hg) OR a decrease of ≥20 that results in ≤50 or <40 (mm/Hg)

[redacted]

14 Appendix 2: Everolimus drug-drug interactions

Drugs to be avoided:

Coadministration of everolimus with strong inhibitors and inducers of CYP3A4 is not recommended unless the benefit outweighs the risk.

- **Strong CYP3A4 inhibitors:** ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, telithromycin, ritonavir, atazanavir, saquinavir, darunavir
- **Strong CYP3A4 inducers:** rifampicin, rifabutin
- **Foods:** Grapefruit and grapefruit juice

Drugs to coadminister with caution:

In vitro, everolimus was a competitive inhibitor of CYP3A4 and of CYP2D6, potentially increasing the concentrations of medicinal products eliminated by these enzymes. Therefore, caution should be exercised when coadministering everolimus with 3A4- and 2D6 substrates with a narrow therapeutic index.

- CYP3A4 substrates that may prolong QT interval: terfenadine, astemizole, cisapride
- CYP2D6 substrates with narrow therapeutic index: quinidine, thioridazine

Perform everolimus therapeutic drug monitoring when initiating or discontinuing these drugs from the regimen:

Moderate inhibitors of CYP3A4 and P-glycoprotein may increase everolimus blood levels such as:

- **Antifungals:** fluconazole
- **Macrolide antibiotics:** erythromycin
- **Calcium channel blockers:** verapamil, nicardipin, diltiazem
- **HIV protease inhibitors:** nelfinavir, indinavir, amprenavir

Moderate inducers of CYP3A4 may increase the metabolism of everolimus and decrease everolimus blood levels such as:

- **Anticonvulsants:** carbamazepine, phenobarbital, phenytoin
- **HIV protease inhibitors:** efavirenz, nevirapine
- **Herbals:** St. John's wort (*Hypericum perforatum*)

[redacted]

15 Appendix 3: Dose reduction guidance for MPA

Dose reduction or temporary interruption may be performed for MPA

Implementation of dose reduction will be based on thrombocytopenia, leukopenia, neutropenia, or other adverse events 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 MPA back to original levels.

Dose Reduction Guidelines

Platelets

- platelet count < 100,000/mm³ dose **may** be reduced at the discretion of the investigator
- platelet count < 75,000/mm³ a second dose reduction should be **considered**
- platelet count < 50,000/mm³ **MANDATORY** interruption of medication

WBC

- WBC < 3500/mm³ dose **may** be reduced at the discretion of the investigator
- WBC < 2500/mm³ a second dose reduction should be **considered**
- WBC < 2000/mm³ **MANDATORY** interruption of medication

All these changes must be recorded on the MPA Dosage Administration Record CRF.

[redacted]

16 Appendix 4: 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 tacrolimus 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 tacrolimus and cyclosporine resulted in additive/synergistic nephrotoxicity.

Drugs that may alter tacrolimus concentrations

Since tacrolimus is metabolized mainly by the CYP3A enzyme systems, substances known to inhibit these enzymes may decrease the metabolism or increase bioavailability of tacrolimus as indicated by increased whole blood or plasma concentrations. Drugs known to induce these enzyme systems may result in an increased metabolism of tacrolimus 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 tacrolimus oral bioavailability (14±5% vs. 30±8%) was observed with concomitant ketoconazole administration (200 mg). The apparent oral clearance of tacrolimus during ketoconazole administration was significantly decreased compared to tacrolimus alone (0.430±0.129 L/hr/kg vs. 0.148±0.043 L/hr/kg). Overall, IV clearance of tacrolimus 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 tacrolimus and thereby substantially increase tacrolimus whole blood concentrations, especially in transplant patients who are intermediate or poor CYP2C19 metabolizers, as compared to those patients who are efficient CYP2C19 metabolizers.

[redacted]

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

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

* This table is not all inclusive.

§ Sirolimus is prohibited in this study.

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

In a single-dose crossover study in healthy volunteers, co-administration of tacrolimus and magnesium-aluminum hydroxide resulted in a 21% increase in the mean tacrolimus AUC and a 10% decrease in the mean tacrolimus Cmax relative to tacrolimus administration alone.

In a study of 6 normal volunteers, a significant decrease in tacrolimus oral bioavailability (14±6% vs. 7±3%) was observed with concomitant rifampin administration (600 mg). In addition, there was a significant increase in tacrolimus clearance (0.036±0.008 L/hr/kg vs. 0.053±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 tacrolimus. Similarly, care should be exercised when HCV protease inhibitors (e.g. boceprevir and telaprevir), also metabolized by CYP3A, are administered concomitantly with tacrolimus.

Tacrolimus may affect the pharmacokinetics of other drugs (e.g., phenytoin) and increase their concentration. Grapefruit juice affects CYP3A-mediated metabolism and should be avoided (see Dosage Administration).

Other Drug Interactions

Immunosuppressants may affect vaccination. Therefore, during treatment with tacrolimus, 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.[1]

[1]Reference: Prograf™ package Insert, Revised August 2012.

[redacted]

17 Appendix 5 : Cyclosporine drug-drug interactions

Please refer to most recent national prescribing information for current labeling recommendations. All the individual drugs cited below are well substantiated to interact with cyclosporine. In addition, concomitant non-steroidal anti-inflammatory drugs, particularly in the setting of dehydration, may potentiate renal dysfunction.

Drugs that may potentiate renal dysfunction

Antibiotics	Antifungals	Gastrointestinal Agents
gentamicin	amphotericin B	cimetidine
tobramycin	ketoconazole	ranitidine
vancomycin		
trimethoprim with sulfamethoxazole		
Antineoplastics	**Anti-Inflammatory Drugs**	**Immunosuppressives**
melphalan	azapropazone	tacrolimus
	diclofenac	
	naproxen	
	sulindac	
	colchicine	

Drugs that alter cyclosporine concentration

Compounds that decrease cyclosporine absorption such as orlistat should be avoided. Cyclosporine is extensively metabolized by cytochrome P-450 3-A. Substances that inhibit this enzyme could decrease metabolism and increase cyclosporine concentrations. Substances that are inducers of cytochrome P-450 activity could increase metabolism and decrease cyclosporine concentrations. Appropriate cyclosporine dosage adjustment to achieve the desired cyclosporine concentrations is essential when drugs that significantly alter cyclosporine concentrations are used concomitantly.

Monitoring of circulating cyclosporine concentrations and appropriate dosage adjustments are essential when these drugs are used concomitantly.

Drugs that increase cyclosporine concentration

Calcium Channel Blockers	Antifungals	Antibiotics
diltiazem	ketoconazole	clarithromycin
nicardipine	fluconazole	erythromycin
verapamil	itraconazole	quinupristin/ daldopristin
Glucocorticoids	**Other Drugs**	
methylprednisolone	allopurinol	
	bromocriptine	
	danazol	
	metoclopramide	
	colchicine	
	amiodarone	

[redacted]

Grapefruit and grapefruit juice affect metabolism, increasing blood concentrations of CsA, thus should be avoided.

Prophylactic treatment with systemic antifungal agents (i.e., ketoconazole, itraconazole, and fluconazole) will not be allowed. If azoles are used during the study for the treatment of active infections, CsA levels should be carefully monitored and dose adjustments may be necessary.

Drugs that decrease cyclosporine concentration

Antibiotics	Anticonvulsants	Other Drugs
nafcillin	carbamazepine	octreotide
rifampin	phenobarbital	ticlopidine
	phenytoin	orlistat
		St. John's Wort

There have been reports of serious drug interaction between cyclosporine and the herbal dietary supplement, St. John's Wort. This interaction has been reported to produce a marked reduction in the blood concentrations of cyclosporine, resulting in subtherapeutic levels, rejection of transplanted organs, and graft loss.

Rifabutin is known to increase the metabolism of other drugs metabolized by the cytochrome P-450 system. The interaction between rifabutin and cyclosporine has not been studied. Care should be exercised when these two drugs are administered concomitantly.

Other drug-drug interactions

Pharmacodynamic interactions have been reported to occur between cyclosporine and both naproxen and sulindac, in that concomitant use is associated with additive decreases in renal function, as determined by 99 mTc-diethylenetriaminepentaacetic acid (DTPA) and (p-aminohippuric acid) PAH clearances. Although concomitant administration of diclofenac does not affect blood levels of cyclosporine, it has been associated with approximate doubling of diclofenac blood levels and occasional reports of reversible decreases in renal function. Consequently, the dose of diclofenac should be in the lower end of the therapeutic range.

Cyclosporine may reduce the clearance of digoxin, colchicine, prednisolone, HMG-CoA reductase inhibitors (statins), aliskiren, repaglinide, NSAIDs, sirolimus, etoposide, and other drugs. Severe digitalis toxicity has been seen within days of starting cyclosporine in several patients taking digoxin. There are also reports on the potential of cyclosporine to enhance the toxic effects of colchicine such as myopathy and neuropathy, especially in patients with renal dysfunction. If digoxin or colchicine are used concurrently with cyclosporine, close clinical observation is required in order to enable early detection of toxic manifestations of digoxin or colchicine, followed by reduction of dosage or its withdrawal. If digoxin is used concurrently with cyclosporine, serum digoxin concentrations should be monitored.

Literature and postmarketing cases of myotoxicity, including pain and weakness, myositis, and rhabdomyolysis, have been reported with concomitant administration of cyclosporine with lovastatin, simvastatin, atorvastatin, pravastatin, and, rarely fluvastatin. When concurrently administered with cyclosporine, the dosage of these statins should be reduced according to label recommendations. Statin therapy needs to be temporarily withheld or discontinued in patients with signs and symptoms of myopathy or those with risk factors predisposing to severe renal injury, including renal failure, secondary to rhabdomyolysis.

[redacted]

Cyclosporine should not be used with potassium-sparing diuretics because hyperkalemia can occur.

During treatment with cyclosporine, vaccination may be less effective. The use of live vaccines should be avoided. Frequent gingival hyperplasia with nifedipine, and convulsions with high dose methylprednisolone have been reported. The concomitant use of nifedipine should be avoided in patients in whom gingival hyperplasia develops as a side effect of cyclosporine

[redacted]

18 Appendix 6: Banff '09 Meeting Report: Antibody Mediated Graft Deterioration and Implementation of Banff Working Groups [1]

1. Normal
2. 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
3. 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.
4. 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 lumenal 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)
5. 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)
6. Other: Changes not considered to be due to rejection (e.g., post-transplant lymphoproliferative disorder, nonspecific changes, acute tubular necrosis, etc.), specifically:

[redacted]

- 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.

[1] Sis B, Mengel M, Haas M, Colvin RB, Halloran PF, Racusen LC, Solez K, Baldwin W, Bracamonte ER, Broecker V, Cosio F, Demetris AJ, Drachenberg C, Einecke G, Gloor J, Glotz D, Kraus E, Legendre C, Liapis H, Mannon RB, Nankivell BJ, Nickeleit V, Papadimitriou JC, Randhawa P, Regele H, Renaudin K, Rodriguez ER, Seron D, Seshan S, Suthanthiran M, Wasowska BA, Zachary A, Zeevi (2008) A Banff 07 classification of renal allograft pathology: updates and future directions. Am. J. Transplant. 8:753-60.

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