NOVARTIS

Everolimus

CRAD001ADE14 / NCT00862979

A multi-center, randomized, open-label, parallel group study investigating the renal tolerability, efficacy and safety of a CNI-free regimen (Everolimus and MPA) versus a CNI-regimen with Everolimus in heart transplant recipients

MANDELA – TRIAL

Author(s) [redacted]

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List of abbreviations

AE	Adverse Event
ALT (SGPT)	Alanine Aminotransferase (Serum Glutamate Pyruvate Transaminase)
AST (SGOT)	Aspartate Aminotransferase (Serum Glutamatoxalacetate Transaminase)
ATC	Anatomical Therapeutic Chemical dictionary
ATG	Antithymocyte Globulin
AUC	Area Under the Curve
Bid	*bis in diem*/twice a day (12 hours apart)
BPAR	Biopsy-Proven Acute Rejection
CAV	Cardiac allograft valsculopahty
CI	Confidence Interval
Cmax	Maximum Plasma Concentration
CMV	Cytomegalovirus
CNI	Calcineurin Inhibitor
CPK	Creatinine Phosphokinase
CR	Clinical Research
CRF	Case Report/Record Form
CRO	Clinical Research Organization
CRP	C-Reactive Protein
CsA	Cylcosporine A
[redacted]	[redacted]
DSMB	Drug Safety Monitoring Board
EBV	Epstein Barr virus
ECG	Electrocardiogram
ENR	Enrolled Patient Population
EC-MPS	Enteric Coated Mycophenolate Sodium
FSH	Follicle Stimulating Hormone
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL	High-Density Lipoproteine Cholesterine
HLA	Human leukocyte antigen
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMPDH	Inosine 5'-Monophosphate Dehydrogenase
IRB	Institutional Review Board

ITT	Intention-to-Treat
LAD	Left Anterior Descending
LDL	Low-Density Lipoproteine Cholesterine
LH	Luteinizing Hormone
LLN	Lower limit of normal
MACE	Major Adverse Cardiac Events
MDRD	Modification of Diet in Renal Disease Study Group
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MIT	Maximal Intimal Thickness
mmHg	Millimeters of Mercury
MMF	Mycophenolate Mofetil
mTOR	Mammalian Target of Rapamycin
MPA	Mycophenolic Acid
NRP	Non-Randomized Patient Group
NSAID	Non-Steroidal Anti-Inflammatory Drug
PCP	Pneumocystis carinii pneumonia
PK	Pharmacokinetics
PP	Per-Protocol
PRA	Panel reactive antibody
RAD	Everolimus
RAN	Randomized Patients Population (at Baseline Visit 2)
SAE	Serious Adverse Event
SAF	Safety Population
SIMO	Sandimmun® Optoral
SL	Serum Level
SNOMED	Systematized Nomenclature of Medicine
SOP	Standard Operating Procedures
SRL	Sirolimus
Tac	Tacrolimus
TL	Trough Level
Tmax	Time until Maximum Plasma Concentration
TSH	Thyroid-Stimulating Hormone
Tx	Transplantation
ULN	Upper Limit of Normal
WBC	White blood cells
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control; control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Randomization number	A unique identifier on the label of each medication package in studies that dispense medication using an IVR system
Patient number	A unique identifier assigned to each patient who enrolls in the study
Phase	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments
Premature patient Withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned
Study drug	Any drug administered to the patient as part of the required study procedures; includes investigational drug and any control drugs
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

Signature Pages

Everolimus

Protocol number: **CRAD001ADE14**

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EudraCT-No.: **2007-002671-14**

Approved by the following

Signatures of Novartis Personnel:

[redacted] _____ _____
signature Date

[redacted] _____ _____
signature Date

[redacted] _____ _____
signature Date

Signature of Co-ordinating Investigator:

[redacted] _____ _____
signature Date

Signature Page for Investigator

Everolimus

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I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with the principles outlined in the Declaration of Helsinki.

(Investigator) _____ Signature _____ Date

Amendment 2

Amendment rationale

The purpose of this amendment is to provide clarification with regard to protocol misunderstandings that were identified after an internal reassessment of the protocol. In particular, two exclusion criteria who were either missing in the synopsis (page 13) or protocol text (page 22) but mentioned in the corresponding part, were completed.

Table 4-1 (Study Outline) was adapted to clearly indicate the timely application of medication. Additionally, the required time frames of SAE reporting have been clarified (section 7.1).

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.

This amended protocol will not be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities due to the non substantial nature.

Amendment 3

Amendment rationale

In response to German health authority's request, the protocol was modified to implement most recent notifications for use of MPA based on the dear health care professional letter (DHCPL) that was sent out for CellCept® by Roche on 12-Dec-2014. In detail the study medication stopping rules were adopted to clearly follow the recommendations given in the DHCPL. This information was added to sections 6.5.1 (Study drug administration), 6.5.2 (Permitted study drug adjustments), 6.5.6 (Premature patient withdrawal from study treatment) and to Appendix 5 (Dose Reduction of Everolimus and MPA).

Further, two exclusion criteria were amended for enhanced study feasibility in line with clinical praxis and patients' de facto condition as follows:

Exclusion criterion 10 (enrollment) and exclusion criterion 4 (baseline) were modified to allow for inclusion of patients with leukocytes ≥3000/mm^3 (see Protocol Synopsis and Section 5).

Exclusion criterion 17 (enrollment) was removed. (see Protocol Synopsis and Section 5).

Corrections of typos were made for clarification of visit schedule (see Section 7, Table 7.1).

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.

This amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities for approval. The changes described in this amended protocol require IEC approval prior to implementation.

Amendment 4

Amendment rationale

This amendment addresses the size of study population. In the study protocol 200 patients were intended to be randomized. Recruitment of study has been ongoing since 2009. Due to ongoing slow recruitment the planned sample size of 200 patients cannot be achieved in a considerable amount of time. Thus, enrollment will be terminated by 31st December 2015. At timepoint of preparation of this amendment 4 to protocol n = 160 patients have been randomized into this study.

A comment was added to section 10.8. (Sample size calculation)

Further, in response to German Health Authority's request, the protocol was modified to implement most recent notifications for use of MPA based on the dear health care professional letter (DHCPL) that was sent out for CellCept® by Roche 10-Nov-2015.

The novel safety informations were added to section 6.5.1. (Study drug administration). Additional pregnancy ß-HCG tests were implemented into section 7 (Visit schedule and assessments) and into the assessment schedule (Table 7-1) and are mandatory for all female patients of child bearing potential at screening, baseline, switch and every study visit.

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.

This amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities for approval. The changes described in this amended protocol require IEC approval prior to implementation.

Protocol Synopsis

Title of study:

A multi-center, randomized, open-label, parallel group study investigating the renal tolerability, efficacy, and safety of a CNI-free regimen (Everolimus and MPA) versus a CNI regimen with Everolimus in heart transplant recipients

Study purpose:

To assess whether a CNI-free regimen with Everolimus and MPA is associated with a better renal outcome as compared to the CNI regimen and Everolimus; while both treatments are expected to be comparable with respect to efficacy.

Objectives:

Primary
- Renal function assessed as glomerula filtration rate (GFR) – MDRD formula – 18 months after heart transplantation

Secondary
- To assess occurrence of treatment failures up to or at Month 18 post Tx, while treatment failure is defined as a composite endpoint of biopsy proven acute rejection of ISHLT 1990 grade ≥ 3A (ISHLT 2004 grade ≥ 2R), acute rejection episodes associated with hemodynamic compromise, graft loss / re-transplant, death, loss to follow-up (at least one condition must be present)
- To assess incidence of MACE and each of its components at Month 18 post Tx
- To assess renal function by GFR – Cockcroft-Gault method – at Month 12 and 18 post Tx
- To assess renal function (serum creatinine) and evolution of renal function between Month 6 and Month 18 post Tx (creatinine slope)
- To assess safety and tolerability at Month 6, 9 and 18 post Tx (acc. to safety parameters specified in section 7.6)

Population:

The study population will consist of a representative group of 200 heart transplant patients (i.e. 200 patients will be randomized at Month 6 post Tx to either the CNI-free or the CNI-based treatment group; 100 patients in each group). Enrollment will be continued until the required sample size will be achieved.

The patients will be recruited from about 10 transplant centers in Germany.

Inclusion/Exclusion criteria:

To be fulfilled at Enrollment (Month 3 post Tx)

Inclusion Criteria

1. Males or females, aged 18 – 70 years
2. Recipients of de novo cardiac transplants, 3 months prior to enrollment
3. Patients with sufficient renal function, i.e. GFR >30 and <100 mL/min
4. Patients who are willing and able to participate in the study and from whom written informed consent has been obtained.
5. Women of childbearing potential should have a negative serum or urine pregnancy test within 7 days prior to or at screening. Females are eligible if they are postmenopausal for at least 24 months past last natural menses. Study medication should not be administered until a negative

pregnancy test report is obtained. Two or more acceptable methods of contraception should be started 1 month prior to beginning study drug unless abstinence is the chosen method, during therapy, and for 3 months after stopping the study. Abstinence is an allowed contraceptive method if in the judgment of the investigator the patient is reliably abstaining. Acceptable forms of birth control include any two or more of the following methods: surgical sterilization (e.g. bilateral tubal ligation, hysterectomy), hormonal contraception (implantable, patch, oral), IUD and barrier methods (male or female condom with spermicidal gel, diaphragm, sponge, cervical cap). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

1. Multi-organ recipients, re-transplantation, or previous transplant with any other organ.
2. Donor age: < 5 years or > 70 years
3. Patients who are recipients of A-B-O incompatible transplants
4. Calculated ischemia time > 6 hours (calculated ischemia time = total ischemia time MINUS time of the transplant in the OCS (Organ Care System)
5. Patients with a historical or current peak PRA of > 25% at time of transplantation
6. Patients with already existing antibodies against the HLA-type of the receiving transplant
7. Patients with insufficient graft function, i.e. who suffered from severe rejection (i.e. more than 2 episodes of ISHLT 1990 > Grade 2 resp. ISHLT 2004 > Grade 1R), recurrent acute rejection, or steroid resistant acute rejection during the first 3 months post Tx
8. Patients with any known hypersensitivity to Everolimus, mycophenolic acid, Cyclosporin A, Tacrolimus, other drugs similar to Everolimus (e.g. macrolides), or other components of the formulations (e.g. lactose)
9. Patients who have received an investigational drug within four weeks prior to study entry (Screening Visit - Month 3 post Tx)
10. Patients with thrombocytopenia (platelets < 50,000/mm³), with an absolute neutrophil count of < 1,500/mm³ or leucopenia (leucocytes < 3,000/mm³), or hemoglobin < 6 g/dL
11. Patients with symptoms of significant somatic or mental illness. Inability to cooperate or communicate with the investigator, who are unlikely to comply with the study requirements, or who are unable to give informed consent
12. Patients with a history of malignancy during the last five years, except squamous or basal cell carcinoma of the skin
13. Patients who are HIV positive or Hepatitis B surface antigen positive or Hepatitis C (PCR+ only) virus positive. Laboratory results obtained within 6 months prior to study entry are acceptable.
14. Recipients of organs from donors who test positive for Hepatitis B surface antigen or Hepatitis C.
15. Evidence of severe liver disease (incl. abnormal liver enzyme profile, i.e. AST, ALT or total bilirubin > 3 times UNL)
16. Presence of severe hypercholesterolemia (≥ 350 mg/dL; ≥ 9 mmol/L) or hypertriglyceridemia (≥ 750 mg/dL; ≥ 8.5 mmol/L)
17. Females of childbearing potential who are planning to become pregnant, who are pregnant or lactating, and/or who are unwilling to use effective means of contraception
18. Presence of a clinically significant infection requiring continued therapy, severe diarrhea, active peptic ulcer disease, or uncontrolled diabetes mellitus that in the opinion of the investigator would interfere with the appropriate conduct of the study
19. Evidence of drug or alcohol abuse
20. Patients receiving drugs known to significantly interact with CsA and/or Everolimus according to the list provided in Appendix 3 to this protocol. Especially the administration of terfenadine, astemizole, or cisapride as well as strong inducers or inhibitors of cytochrome P450 3A4 will not be allowed.

To be fulfilled at Baseline (Month 6 post Tx - prior to randomization)
In addition to the above criteria the following must be met at Baseline (Month 6 post Tx) prior to randomization.

Inclusion Criteria
1. Patients with sufficient renal function, i.e. GFR >30 mL/min

Exclusion Criteria
1. Graft loss / re-transplantation or death
2. Changes to the immunosuppressive regimen prior to randomization due to immunologic reasons
3. Patients who suffered from more than 2 severe rejections (more than ISHLT 1990 Grade 2 resp. ISHLT 2004 Grade 1R), recurrent acute rejection, or steroid resistant acute rejection
4. Patients with thrombocytopenia (platelets < 50,000/mm³), with an absolute neutrophil count of < 1,500/mm³ or leucopenia (leucocytes < 3,000/mm³), or hemoglobin < 6 g/dL
5. Evidence of severe liver disease (incl. abnormal liver enzyme profile, i.e. AST, ALT or total bilirubin > 3 times ULN)
6. Patients with clinically significant infection requiring continued therapy which would interfere with the objectives of the study
7. Presence of intractable immunosuppresant complications or side effects (e.g. severe gastrointestinal adverse events) at randomization visit (Month 6 post Tx)

Investigational and reference therapy

Investigational drug

- **Certican®**

Active ingredient:	Everolimus (RAD001)
Galenic form:	tablets
Dose:	one tablet containing 0.25 mg, 0.75 mg, or 1.0 mg
Dosing schedule:	based on blood level (5 - 10 ng/mL)
Packaging:	blisters of 10 tablets

Other components of the immunosuppressive regimen

- **Prograf®**

Active ingredient:	Tacrolimus
Galenic form:	capsules
Dose:	one capsule containing 0.5 mg, 1.0 mg and 5.0 mg
Dosing schedule:	according to blood level
Packaging:	trade ware will be used

- **Sandimmun® Optoral**

Active ingredient:	Cyclosporin A
Galenic form:	capsules
Dose:	one capsule containing 10 mg, 25 mg, 50 mg, or 100 mg
Dosing schedule:	according to blood level
Packaging:	trade ware will be used

- **Mycophenolic Acid (MPA)**
  based on investigator's decision, one of the following drugs will be used:

  Myfortic®

Active ingredient:	Enteric Coated Mycophenolate Sodium (EC-MPS)
Galenic form:	tablets

Dose:	one tablet containing 180 mg or 360 mg
Dosing schedule:	1440 - 2880 mg/day
Packaging:	trade ware will be used

CellCept®

Active ingredient:	Mycophenolate Mofetil (MMF)
Galenic form:	capsules / tablets
Dose:	one capsule containing 250 mg or one tablet containing 500 mg
Dosing schedule:	1500 - 3000 mg/day, if tolerated
Packaging:	trade ware will be used

- **Corticosteroids**
  according to local standard. A dose of 0.05 - 0.3 mg/kg prednisolone or equivalent should be continued throughout the trial.

Study design

Prospective, multi-center, randomized, controlled, parallel group, open-label study in heart transplant recipients.

During the first 3 months post Tx the patients will be treated outside this clinical study and according to center standards.

Subjects who are fulfilling all inclusion criteria and none of the exclusion criteria will be enrolled into the trial 3 Months post transplantation.

During a **Run in phase** (Month 3 - 6 month post transplantation), all patients will be treated with CNI (Tacrolimus or Cyclosporin A) + Everolimus or MPA + corticosteroids.

At Baseline (Month 6 post Tx) all eligible patients (according to inclusion and exclusion criteria) will be randomized to one of the two treatment groups in a 1:1 ratio:

Group 1: CNI-group	**Maintenance of immunosuppressive CNI-based regimen (CNI-group) consisting of** Tacrolimus (C0: 3 - 8 ng/mL) or Cyclosporin A (C0: 50 - 150 ng/mL) + Everolimus (C0: 5 - 10 ng/mL) + corticosteroids
Group 2: CNI-free-group	**Switch immunosuppressive therapy to a CNI-free regimen consisting of** MPA (MMF 1500 - 3000 mg/day OR EC-MPS 1440 - 2880 mg/day) + Everolimus (C0: 5 - 10 ng/mL) + corticosteroids INCLUDING during switch phase (months 6-9) (see table 4-1): Cyclosporin A ≤ 75 ng/mL (according to C0-level) or Tacrolimus ≤ 5 ng/mL (according to C0) **The therapy switch will start the day after randomization (Month 6) and should be completed by Month 9 post Tx.**

The established treatment will be continued until Month 18 post Tx (final assessment). Control assessments will be performed at Month 10 and 12 after Tx. Renal function (GFR) as well as efficacy (BPAR, graft loss, death) will be assessed at every study visit.

Obligatory biopsies will be obtained at Month 6, 9, 12, 18. However, facultative biospsies may be obtained at every study visit.

Assessments of renal tolerability

- Glomerular Filtration Rate (GFR), calculated according to MDRD-method (primary endpoint), and Cockcroft-Gault method
- Serum creatinine and slope of creatinine

Efficacy assessments

- Death / graft loss / re-transplantation / acute rejection associated with hemodynamic compromise / biopsy proven acute rejection of ISHLT 1990 grade ≥ 3A resp. ISHLT 2004 grade ≥ 2R / treated acute rejection / loss to follow-up as well as treatment failure as a composite endpoint.
- Major Adverse Cardiac Events (MACE)
- Electrocardiogram (ECG)
- Echocardiogram

Safety assessments

- Infections
- (Serious) Adverse Events
- Physical Examination
- Vital Signs
- (Safety) Laboratory evaluation

Pharmakokinetic assessments

- Blood trough levels (C0-h) of Cyclosporin A, Tacrolimus, MPA and Everolimus

Data analysis

Statistical analysis and report writing will be performed when all patients have completed Month 18 after Tx assessment.

Change in glomerular filtration rate (MDRD method) will be used as the primary criterion in order to demonstrate the CNI-free regimen is superior to the CNI-based regimen regarding the prevention of renal failure. Primary analysis will be perfomed with the ITT population.

Type I error probability is set to 0.05, two-sided.

All other safety and efficacy variables will be presented by descriptive statistics and compared between both treatments using suitably chosen tests for unpaired or paired (laboratory data and vital signs) observations. Categorial variables will be analyzed with the chi^2-test or Fisher's exact test. Event data will be assessed by Kaplan-Meier statistics and compared between the two groups with the logrank test. In addition to the comparison of the two treatment groups, further comparisons will be made with the group of patients who were not eligible for randomization at Baseline visit 2.

Sample size

The probable difference between the CNI-free - and the CNI-group in the GFR is estimated as δ = 8 ml/min with σ = 16 ml/min. With α=.05 (two sided significance level) and 1-β = 90% (power), n=86 patients per group are required to demonstrate superior efficacy of the CNI-free regimen compared to the CNI-group in the GFR using the t-test [redacted]. To compensate for some uncertainty of the assumptions for sample size calculation, the calculated sample size is increased by ≈ 15%. Therefore, a total number of N=200 patients (n=100 per treatment group) will be randomized and treated in both treatment arms after Baseline visit 2.

1 Background

The ultimate aim of immunosuppressive therapy in transplantation is to provide an efficacious regimen while minimizing (long-term) non-immune toxicities and without compromising safety. By combining synergistic drugs, it may be possible to reduce the exposure to individual agents and therefore avoid adverse effects whilst maintaining favorable clinical outcomes.

Progress has been made in transplantation medicine with the introduction of calcineurin inhibitors (CNIs) such as **Cyclosporin A** (CsA) and **Tacrolimus**. Owing to the benefits of this drug class, the survival rates after heart transplantation markedly improved (Eisen H et al., 2005; Organ Procurement and Transplantation Network reports 1996-2001); however, with the increase in use, the side effects of this drug group became more evident (Keogh A, 2004; Eisen H et al., 2005; Schweiger M et al., 2005). Impairment of renal function was one of the major side effects associated with CNI-based immunosuppression (Lindenfeld JA et al., 2004). It is known that CNIs trigger arterial hypertension and, therefore, additional treatment is required to overcome this effect (Lindenfeld JA et al., 2004, Dalla Pozza R et al., 2006). Furthermore, the incidence of tremor and cosmetic side effects (hirsutism and gingival hyperplasia) are common with CNI immunosuppression (Lindenfeld JA et al., 2004). There has, therefore, been an increasing interest to explore combinations of treatment that allow for reduction in CNI exposure, as this may potentially enhance favorable long term outcomes.

The immunosuppressant Everolimus is a proliferation signal inhibitor (PSI) with potent immunosuppressant activity that has been introduced since April 2005 in over 60 countries for prophylaxis of organ rejection in adult renal and heart transplant recipients (Vitko S et al., 2004 and 2005; Krämer BK et al., 2005; Monaco AP et al., 2005; Lober MI et al., 2005; Eisen HJ et al., 2003; Tendesco H, et al., in press). According to licensing, Everolimus should be administered with Cyclosporin A and steroids.

Everolimus metabolism, via CYP3A4 in the liver, seems to cause less renal toxicity than calcineurin inhibitors. Promising data are available for 3- and 4-year treatment in renal transplant recipients (Vitko S et al., 2005; Lober MI et al., 2005; Tedesco H et al., 2006).

First, CNI-free immunosuppression with a proliferation signal inhibitor was focused on the use of sirolimus (Rapamune), with studies demonstrating an improvement in renal function with sirolimus and mycophenolate mofetil (MMF) immunosuppression in heart transplant recipients (Lyster H et al., 2004; Groetzner J et al., 2004).

Between June 2004 and July 2005 Lehmkuhl et al. (2007) conducted a single-center observational study with Everolimus in combination with low-dose Cyclosporin A in de novo heart transplant recipients. The findings demonstrated that use of Everolimus at a dose of 0.75 mg directly before engraftment allows for a pronounced reduction in CsA exposure post-transplant. Furthermore, this regimen preserves

renal function without loss of immunosuppressive efficacy and without a significant effect on post-transplant CK and cholesterol levels, suggesting that Everolimus and low-dose CsA may have an important role as part of the primary immunosuppressive strategy in de novo heart transplant recipients.

The effects of CNI-free immunosuppression using Everolimus were investigated in a mulit-center trial including 60 maintenance heart transplant recipients (5.4 ± 3.2 years post transplant) (Rothenburger et.al, 2007a). Reasons for switching to Everolimus were side effects associated with prior CNI immunosuppression. All patients underwent standardized switching protocols to reach the CNI-free immunosuppressive regimen consisting of Everolimus (target blood level: 4 – 8 ng/mL), MMF (1000 mg twice daily), and prednisone (5 mg/day). All patients completed 6 months of follow-up. After switching to Everolimus, most patients recovered from the side effects associated with CNIs. Renal function improved significantly after 6 months (creatinine, 2.1 ± 0.6 mg/dl vs. 1.5 ± 0.9 mg/dL, p=0.001; creatinine clearance, 42.2 ± 21.6 mL/[min * 1.73 m²] vs. 61.8 ± 23.4 mL/[min * 1.73 m²], p=0.018). Arterial hypertension improved after 3 months and remained decreased during the observation period. Tremor, peripheral edema, hirsutism, and gingival hyperplasia markedly improved. Adverse events occurred in 8 patients (13.3%), including interstitial pneumonia (n=2), skin disorders (n=2), reactive hepatitis B (n=1), and fever of unknown origin (n=3). Summarizing the preliminary data it was concluded that CNI-free immunosuppression using Everolimus may be safe, with excellent efficacy in maintenance heart transplant recipients.

Since the publication of the results of the 2003 Certican consensus Meeting (Hummel M, 2005), clinical experience with the use of Everolimus has grown. An increasing number of patients treated outside of clinical studies have provided more information about the efficacy and safety of Everolimus. Based on these recent data, a second Certican Consensus Conference was held in January 2006 (Rothenburger et al., 2007b). The main goal of the meeting was to discuss new areas for the application and indication of Everolimus in cardiac transplantation. The resulting report summarized the conclusions of the meeting and also brought fourth adaptations and changes in recommendations for the use of Everolimus:

Key Considerations when using Everolimus (Rothenburger et al., 2007b, Table 1)

CNI minimization:

- Maintain target Everolimus trough blood levels 3 – 8 ng/mL
- Monitor Everolimus trough blood levels after changes in dose
- Avoid CYP3A4 inducers or inhibitors where possible
- Statins should be given concomitantly with Everolimus and CsA
- Target CsA C0 trough blood levels of 120 – 150 ng/mL after 3 months and 50 - 100 ng/mL after 6 months

CNI-free:

- Maintain target Everolimus trough blood levels 3 – 8 ng/mL
- Do not eliminate before 6 months post-transplantation
- Closely monitor rejection episodes especially within the first year post-transplantation.

However, further research is needed to address effectiveness of CNI-free immunosuppressive regimen based on Everolimus. The design chosen for the current study follows the abovementioned recommendations. A CNI-free regimen with Everolimus and MPA will be compared with a low-dose CNI regimen and Everolimus. It is expected, that the CNI-free regimen will result in superior renal function, when compared to the CNI-based regimen, while it is expected to be as efficacious and safe as the CNI-based regimen with regard to occurrence of biopsy proven acute rejection episodes, graft loss, and death.

2 Study purpose

This phase IV study is designed to show that an early onset of a CNI-free regimen with MPA and Everolimus in heart transplant patients may be associated with better renal outcome, and similar efficacy as compared to a CNI-based regimen and Everolimus.

3 Objectives

The primary objective of this trial is to demonstrate superiority of a CNI-free regimen with respect to the renal function at Month 18 post Tx assessed by glomerular filtration rate – MDRD method – as compared to the standard CNI-based regimen in heart transplant patients.

Secondary objectives of this trial are:

- to asses occurrence of treatment failures up to or at Month 18 post Tx, while treatment failure is defined as a composite endpoint of biopsy proven acute rejection of ISHLT 1990 grade ≥ 3A (ISHLT 2004 grade ≥ 2R), acute rejection episodes associated with hemodynamic compromise, graft loss / re-transplant, death, loss to follow up (at least one condition must be present)
- to assess incidence of MACE and each of its components at Month 18 post Tx
- to assess renal function by glomerular filtration rate - Cockcroft-Gault method - at Month 12 and 18 post Tx
- to assess renal function (serum creatinine) and evolution of renal function between Month 6 and 18 post Tx (creatinine slope)
- to assess safety and tolerability at Month 6, 9 and 18 post Tx (according to safety parameters specified in section 7.6)

4 Study design

This is a prospective, multi-center, randomized, controlled, parallel group, open label study in heart transplant recipients. A total of 200 patients fulfilling the inclusion and exclusion criteria at Baseline visit (Month 6 post Tx) will be randomized to the two treatment groups. Enrollment will be continued until the required sample size is achieved.

Once consent is obtained, screening data will be collected to determine each patient's eligibility for study participation. Screening assessment will be performed at Month 3 post Tx and relevant data from transplantation will be recorded retrospectively.

During the first three months post Tx the patients may be treated according to center standards. Latest after study inclusion (Month 3 post Tx ±2 weeks), the patients should receive an immunosuppressive regimen consisting of Cyclosporin A (based on C0-h level) or Tacrolimus (based on C0-h level) + Everolimus (target C0-h level: 5 – 10 ng/mL) or MPA + corticosteroids.

At Month 6 (±1 week) post transplantation (Baseline), patients whose eligibility is confirmed by additional in- and exclusion criteria will be randomized and hence allocated to one of the two treatment groups in a 1:1 ratio. Patients will then either receive an immunosuppressive regimen consisting of a CNI (Tacrolimus or Cyclosporin A) with Everolimus with corticosteroids or be switched to the CNI-free regimen in the following way:

Starting the day following the Month 6 assessment, Cyclosporin A will be reduced to ≤75 ng/mL (according to C0 level) or Tacrolimus will be reduced to ≤5 ng/mL (according to C0 level) for 8 weeks and subsequently removed completely. Depending on the initial immunosuppression either MPA or Everolimus will be added to the patient´s immunosuppressive regimen. Consequently, patients receive a transitional immunosuppressive regimen of Cyclosporin A or Tacrolimus and Everolimus and MPA or MMF until complete switch to the CNI-free regimen is achieved at 9 months post Tx.

Dose increase / adjustment of MPA should be performed based on the investigator's experience and the given clinical conditions, adverse events, etc. The CNI-free regimen should be achieved after a maximum of 3 months and be stable by Month 9. During the therapy-switch a control assessment will be performed at Month 8.

In all patients, further control assessments will be performed at Month 9, 10, 12 and 18 (end of study and early discontinuation) post Tx.

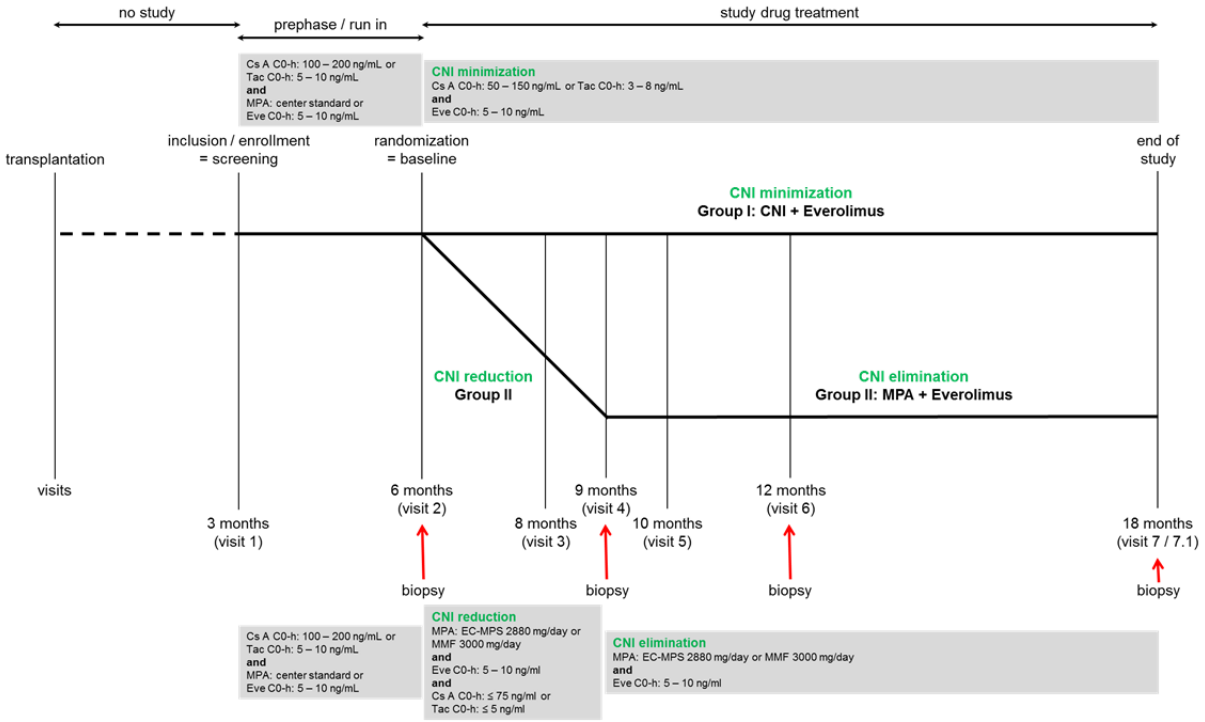
Corticosteroids must be added to the immunosuppressive regimen in all patients, according to local standard. A dose of 0.05 – 0.3 mg/kg prednisolone or equivalent should be continued throughout the whole study.

Obligatory biopsies will be obtained at Month 6, 9, 12, 18. Facultatively biospsies may be obtained at every study visit.

Statistical analysis and report writing will be performed when all patients have completed Month 18 after Tx assessment.

An external and independent Data Safety Monitoring Board (DSMB) will be instituted. The DSMB will review safety-related issues and will be entitled to make recommendations for changes in study conduct. Details on the function of the DSMB will be laid out in a separate DSMB Charter.

Table 4-1 Study outline



Patients should be seen for all visits on the designated day or as close to it as possible.

Baseline visit assessments and randomization (Month 6 post Tx) may be performed within a time window of ± 1 week.

5 Population

The study population will consist of 200 de novo heart transplant patients (100 patients per treatment group) who are randomized to the two treatment groups at Baseline visit (Month 6 post Tx). The patients will be recruited from about 10 transplant centers in Germany.

Inclusion / Exclusion criteria for Enrollment (Month 3 post Tx)

The investigator must ensure that all patients who meet the following inclusion criteria and none of the exclusion criteria are offered enrollment in the study. No additional exclusions can be applied by the investigator, in order that the study population will be representative of all eligible patients.

Inclusion Criteria

The following inclusion criteria must be present at enrollment (Month 3 post Tx)

1. Males or females, aged 18 – 70 years
2. Recipients of de novo cardiac transplants, 3 months prior to enrollment
3. Patients with sufficient renal function, i.e. GFR >30 and <100mL/min
4. Patients who are willing and able to participate in the study and from whom written informed consent has been obtained.
5. Women of childbearing potential should have a negative serum or urine pregnancy test within 7 days prior to or at screening. Females are eligible if they are postmenopausal for at least 24 months past last natural menses. Study medication should not be administered until a negative pregnancy test report is obtained. Two or more acceptable methods of contraception should be started 1 month prior to beginning study drug unless abstinence is the chosen method, during therapy, and for 3 months after stopping the study. Abstinence is an allowed contraceptive method if in the judgment of the investigator the patient is reliably abstaining. Acceptable forms of birth control include any two or more of the following methods: surgical sterilization (e.g. bilateral tubal ligation, hysterectomy), hormonal contraception (implantable, patch, oral), IUD and barrier methods (male or female condom with spermicidal gel, diaphragm, sponge, cervical cap). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

The following exclusion criteria must not be present at enrollment (Month 3 post Tx)

1. Multi-organ recipients, re-transplantation, or previous transplant with any other organ.
2. Donor age: < 5 years or > 70 years
3. Patients who are recipients of A-B-O incompatible transplants
4. Calculated ischemia time >6 hours (calculated ischemia time = total ischemia time MINUS time of the transplant in the OCS (Organ Care System)
5. Patients with a historical or current peak PRA of > 25% at time of transplantation
6. Patients with already existing antibodies against the HLA-type of the receiving transplant
7. Patients with insufficient graft function, i.e. who suffered from severe rejection (i.e. more than 2 episodes of ISHLT 1990 > Grade 2 resp. ISHLT 2004 > Grade 1R),

recurrent acute rejection, or steroid resistant acute rejection during the first 3 months post Tx

8. Patients with any known hypersensitivity to Everolimus, mycophenolic acid, Tacrolimus, Cyclosporin A, other drugs similar to Everolimus (e.g. macrolides), or other components of the formulations (e.g. lactose)
9. Patients who have received an investigational drug within four weeks prior to study entry (Screening Visit - Month 3 post Tx)
10. Patients with thrombocytopenia (platelets < 50,000/mm³), with an absolute neutrophil count of < 1,500/mm³ or leucopenia (leucocytes < 3,000/mm³), or hemoglobin < 6 g/dL
11. Patients with symptoms of significant somatic or mental illness. Inability to cooperate or communicate with the investigator, who are unlikely to comply with the study requirements, or who are unable to give informed consent
12. Patients with a history of malignancy during the last five years, except squamous or basal cell carcinoma of the skin
13. Patients who are HIV positive or Hepatitis B surface antigen positive or Hepatitis C (PCR+ only) virus positive. Laboratory results obtained within 6 months prior to study entry are acceptable.
14. Recipients of organs from donors who test positive for Hepatitis B surface antigen or Hepatitis C.
15. Evidence of severe liver disease (incl. abnormal liver enzyme profile, i.e. AST, ALT or total bilirubin > 3 times UNL)
16. Presence of severe hypercholesterolemia (≥ 350 mg/dL; ≥9 mmol/L) or hypertriglyceridemia (≥ 750 mg/dL; ≥ 8.5 mmol/L)
17. Females of childbearing potential who are planning to become pregnant, who are pregnant or lactating, and/or who are unwilling to use effective means of contraception
18. Presence of a clinically significant infection requiring continued therapy, severe diarrhea, active peptic ulcer disease, or uncontrolled diabetes mellitus that in the opinion of the investigator would interfere with the appropriate conduct of the study
19. Evidence of drug or alcohol abuse
20. Patients receiving drugs known to significantly interact with CsA and/or Everolimus according to the list provided in Appendix 3 to this protocol. Especially the administration of terfenadine, astemizole, or cisapride as well as strong inducers or inhibitors of cytochrome P450 3A4 will not be allowed.

Inclusion / Exclusion criteria for Baseline (Month 6 post Tx – prior to randomization)

Of all patients included into the study at Month 3 post Tx, those can continue into the randomized study period, in whom the following condition is observed at Baseline (Month 6 post Tx), prior to randomization.

Inclusion Criteria

1. Patients with sufficient renal function, i.e. GFR > 30 and < 100 mL/min

Exclusion Criteria

Of all patients included into the study at Month 3 post Tx, those can not continue into the randomized study period, in whom one or more of the following criteria are met at Baseline (Month 6 post Tx), prior to randomization:

1. Graft loss / re-transplantation or death
2. Changes to the immunosuppressive regimen prior to randomization due to immunologic reasons
3. Patients who suffered from more than 2 severe rejections (more than ISHLT 1990 Grade 2 resp. ISHLT 2004 Grade 1R), recurrent acute rejection, or steroid resistant acute rejection
4. Patients with thrombocytopenia (platelets < 50,000/mm³), with an absolute neutrophil count of < 1,500/mm³ or leucopenia (leucocytes < 3,000/mm³), or hemoglobin < 6 g/dL
5. Evidence of severe liver disease (incl. abnormal liver enzyme profile, i.e. AST, ALT or total bilirubin > 3 times ULN)
6. Patients with clinically significant infection requiring continued therapy which would interfere with the objectives of the study
7. Presence of intractable immunosuppressant complications or side effects (e.g. severe gastrointestinal adverse events) at randomization visit (Month 6 post Tx)

6 Treatment

6.1 Investigational and control drugs

Investigational drug

- **Certican®**

Active ingredient:	Everolimus (RAD001)
Galenic form:	tablets
Dose:	one tablet containing 0.25 mg, 0.75 mg or 1.0 mg
Dosing schedule:	based on drug level (5 – 10 ng/mL).
Packaging:	blisters of 10 tablets

Other components of the immunosuppressive regimen

- **Prograf®**

Active ingredient:	Tacrolimus
Galenic form:	capsules

Dose: one capsule containing 0.5 mg, 1.0 mg and 5.0 mg
Dosing schedule: according to blood level
Packaging: trade ware will be used

- **Sandimmun® Optoral**
  Active ingredient: Cyclosporin A
  Galenic form: capsules
  Dose: one capsule containing 10 mg, 25 mg, 50 mg, or 100 mg
  Dosing schedule: according to blood levels (cf. Table 4-1 and section 6.5.2)
  Packaging: trade ware will be used

- **Mycophenolic Acid (MPA)**
  based on investigator's decision, one of the following drugs will be used:

  Myfortic®
  Active ingredient: Enteric Coated Mycophenolate Sodium (EC-MPS)
  Galenic form: tablets
  Dose: one tablet containing 180 mg or 360 mg
  Dosing schedule: 1440 – 2880 mg/day, if tolerated
  Packaging: trade ware will be used

  CellCept®
  Active ingredient: Mycophenolate Mofetil (MMF)
  Galenic form: capsules / tablets
  Dose: one capsule containing 250 mg or
  one tablet containing 500 mg
  Dosing schedule: 1500 – 3000 mg/day, if tolerated
  Packaging: trade ware will be used

- **Corticosteroids**
  according to local standard. A dose of 0.05 – 0.3 mg/kg prednisolone or equivalent should be continued throughout the trial.

6.2 Treatment groups

The day after Screening visit, during the run in phase, all patients will receive the following immunosuppressive therapy:

Cyclosporin A (C0level: 100-200 ng/mL) or Tacrolimus (C0level: 5 - 10 ng/mL) and Everolimus (C0level: 5-10 ng/mL) or MPA and corticosteroids.

At Baseline visit (Month 6 post Tx) patients will be assigned to one of the following two treatment groups in a ratio of 1:1:

- **Maintenance** of immunosuppressive **CNI-based regimen** (CNI group):
  Cyclosporin A (C0: 50 – 150 ng/mL) or Tacrolimus (C0: 3 – 8 ng/mL)+
  Everolimus (C0: 5 – 10 ng/mL) +
  Corticosteroids
- **Switch** to **CNI-free regimen** (CNI-free group):
  MPA (MMF 1500 - 3000 mg/day OR EC-MPS 1440 - 2880 mg/day) +
  Everolimus (C0: 5 – 10 ng/mL) +
  Corticosteroids +
  Cyclosporin A ≤ 75 ng/mL (according to -evel) (months 6-9) or Tacrolimus ≤ 5 ng/mL (according to C0) (months 6-9)

6.3 Treatment assignment

A randomization list will be produced by or under the responsibility of Novartis Biometrics Department using a validated system that automates the random assignment of treatment groups to randomization numbers in the specified 1:1 ratio (CNI group, CNI-free group). The randomization scheme will be reviewed and locked after approval. According to the recommendations given in the ICH E9 Guideline "Statistical Principles for Clinical Trials" (CPMP, 1998), the used block length is specified in a separate document which is withhold from the study centers. The randomization list will be kept sealed in a secure location.

At Enrollment (Screening Visit – Month 3 post Tx), patients will be assigned a unique patient identification number by the investigator. The patient identification number has two parts. The first part is the four-digit center number, which is assigned by Novartis. The second part will be assigned by the investigator starting with number "00001" in each study site. Once assigned to a patient, the patient identification number will not be reused. If the patient fails to be enrolled into the study for any reason, the patient's identification number and the reason for not being enrolled will be entered on the Screening Failure Log. Note: The patient identification number is different from the randomization number.

At Baseline visit (Month 6 post Tx), all eligible patients will be given a randomization number that assigns them to one of the treatment groups. The randomization numbers are sequentially allocated to the patients per center in the order of inclusion in the randomized treatment period.

Randomization of individual patients will be performed centrally by a CRO [redacted]. Allocation of a patient to one of the two treatment groups will be performed in the following steps.

1. Information about patient enrollment (Screening Visit – Month 3 post Tx):
   Study sites will inform the randomization department of the [redacted] about each patient inclusion via fax.

2. Randomization (Baseline Visit – Month 6 post Tx):
   At day of randomization, the site will provide the information of eligible patient to [redacted] by fax.
   [redacted] randomization department will allocate the patient the next free consecutive randomization number allocated to the site. Randomization number and allocated treatment (according to the randomization list) will be provided to the site by fax.

The randomization number will be entered on the CRF of an individual patient.

6.4 Treatment blinding

This is an open-label study.

6.5 Treating the patient

6.5.1 Study drug administration

Everolimus is study drug from month 3 (visit 1). Before month 3 the patient will receive a prescription for Everolimus, the use of Everolimus before visit 1 is not excluded. Each study site will be supplied by Novartis with study drug (Everolimus). Study drug will be provided as tablets, packaged in boxes containing strips of blister packed tablets, and labeled as RAD001 Tablets. Study drug will be available in 0.25, 0.75, and 1.0 mg strength. One component of the box consists of a 2-part label which includes an identifier of each single box of study medication. Before dispensing the study medication to an individual patient, investigator staff must enter the 4-digit patient number and the date of dispensing of the medication box on both parts of the label. The outer part of the label will be detached from the packaging and affixed to the source document (Drug Label Form in the CRF) containing that patient's unique patient number.

For the other immunosuppressive drugs (Cyclosporin A, Tacrolimus, MPA, corticosteroids) the patient will receive a prescription.

The prescribed total daily dosage of the immunosuppressive drugs should be divided in two (equal) doses, applied 12 hours apart (i.e. 08:00 a.m. and 08:00 p.m.).

The investigator should instruct the patient to take the study drug exactly as prescribed in order to promote compliance. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

In patients randomized to the CNI-free group, withdrawal of Cyclosporin A or Tacrolimus and commencement of MPA or Everolimus will be performed starting the day after randomization at Month 6 post Tx.

In a first step the Cyclosporin A should be decreased to a dose resulting in a C0 blood level of ≤ 75 ng/mL for 8 weeks, and Tacrolimus should be decreased to a dose resulting in a level of ≤ 5 ng/mL. MPA or Everolimus should be introduced. Further increase / adjustment of MPA or Everolimus and removal of Cyclosporin A or Tacrolimus should be performed based on the investigator's experience and the given clinical conditions, adverse events, etc. The CNI-free regimen should be achieved after a CNI reduction / elimination period of maximum of 3 months (starting from Month 6 post Tx and be stable by Month 9 post Tx).

In cases of recurrent infections serum antibody concentration should be measured; if hypogammaglobulinemia presents as persistent and clinically significant, patients should be examined accurately and appropriate actions should be taken; dose reduction or change of immunosuppression should be taken into consideration.

Patients with recurrent pulmonary disorders e.g. cough/dyspnea should as soon as possible be examined accurately for signs of bronchiectasis; dose reduction or change of immunosuppression should be taken into consideration.

Corticosteroids must be added to the immunosuppressive regimen in all patients, according to local standard. A dose of 0.05 – 0.3 mg/kg prednisolone or equivalent should be continued throughout the whole study.

Safety recommendations regarding the use of MPA:

MPA is a powerful human teratogen, which increases the risk of spontaneous abortions and congenital malformations in case of exposure during pregnancy. Therefore following safety recommendations should be followed for all patients that are receiving MPA (f.ex. CellCept or myfortic).

Investigators should ensure that women and men that are receiving MPA 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. In addition, patients should not donate blood during therapy or for at least 6 weeks following discontinuation of MPA.

Recommendations for female patients:

Before starting treatment with MPA, women of child bearing potential must have undergone pregnancy testing, i.e. done at Screening, Baseline, Switch and following study visits (Assessment Schedule Table 7-1) in order to exclude unintended exposure of the embryo to mycophenolate. A pregnancy ß-HCG test is mandatory for all female patients in this trial at all indicated visits (Table 7-1).

Pregnancy tests should be repeated as clinically required (e.g. after any gap in contraception is reported). Results of all pregnancy tests should be discussed with the patient.

Women of childbearing potential should use two reliable forms of contraception simultaneously before starting therapy, during therapy, and for six weeks after stopping treatment with MPA.

Recommendations for male patients

Sexually active men (including vasectomized men) are recommended to use condoms during treatment and for at least 90 days after cessation of treatment. In addition, female partners of male patients treated with MPA are recommended to use highly effective contraception during treatment and for a total of 90 days after the last dose.

Men should not donate semen during therapy with MPA or for 90 days following discontinuation of MPA.

Table 6-1 Schematic diagram of medication administration

Phase	No Study	Prephase	Study Drug Treatment					
Period		Run In	BL	Switch	Maintenance			
Visit		1	2	3	4	5	6	7
Month post Tx	0 - 3	3	6	8	9	10	12	18
Randomization			X					

Treatments				
CNI group				
- Everolimus		center practice	C0-h level: 5 – 10 ng/mL	
- CNI (Cyclosporin A/ Tacrolimus)		acc. to blood level *	acc. to blood level *	acc. to blood level *
- MPA		center practice	none	None
- Steroids		0.05 – 0.3 mg/kg	0.05 – 0.3 mg/kg Prednisolone or equivalent	
CNI-free group				
- Everolimus		center practice	C0-h level: 5 – 10 ng/mL	
- CNI (Cyclosporin A/Tacrolimus)	)	acc. to blood level *	CyA: C0 level of ≤ 75 ng/mL for 8 weeks, then removal Tac: C0 level of ≤ 5 ng/mL for 8 weeks, then removal	None

- MPA		center practice	MMF 1.5 – 3 g/d OR EC-MPS 1440 – 2880 mg/d	MMF 1.5 – 3 g/d OR EC-MPS 1440 – 2880 mg/d
- Steroids		0.05 – 0.3 mg/kg	0.05 – 0.3 mg/kg Prednisolone or equivalent	

BL = Baseline visit: day of randomization – Month 6 post Tx

CNI Group: treatment post randomization: Everolimus + Cyclosporin A/Tacrolimus + corticosteroids

Cyclosporin A Dosage: Month 1 - 6: C0-h levels 100 – 200 ng/mL
Month >6: C0-h levels 50 – 150 ng/mL
(cf. section 6.5.2)

Tacrolimus Dosage: Month 1 - 6: C0-h levels 5 - 10 ng/mL
Month >6: C0-h levels 3 - 8 ng/mL

CNI-free Group: treatment post randomization: Everolimus + MPA + corticosteroids

Cyclosporin A Dosage: Month 1 - 6: C0-h levels 100 – 200 ng/mL
Month 6 - 9: C0-h levels ≤75 ng/mL
(cf. section 6.5.2)

Tacrolimus Dosage: Month 1 - 6: C0-h levels 5-10 ng/mL
Month 6 - 9: C0-h levels ≤5 ng/mL

6.5.2 Permitted study drug adjustments

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on study drug. The recommendations described below should be followed as far as clinically feasible.

All immunosuppressive medication, with single dose, unit, frequency, route of administration, indication, start and end dates will be recorded in the Immunosuppressive Therapies CRF. Only approved but no investigational drugs are permitted.

Oral corticosteroids will be given at a dose of 0.03 – 0.5 mg/kg prednisolone or equivalent throughout the whole trial. If possible, it should remain stable during the entire course of the study. However, dose adjustments for medically indicated reasons will be possible.

Everolimus

Because Everolimus is the mainstay of immunosuppression, Everolimus dose should be continued on a stable level according to trough levels. Dose reductions should only be performed if the symptoms do not respond to other measures (e.g. reduction of MPA dose).

Target therapeutic ranges for Everolimus whole blood trough levels should be 5 - 10 ng/mL.

Dose adjustments may be performed if Everolimus whole blood trough levels outside the target range are measured. Dose adjustments of Everolimus should be monitored 7 days later by a measurement of the Everolimus blood trough level.

In both renal and heart transplantation, Everolimus trough concentrations ≤ 3 ng/mL were associated with a significantly lower protection from acute rejection compared with trough levels > 3 ng/mL. Although hyperlipidemias were common over the full exposure range, they responded to corticosteroid dose reduction, dietary management, and lipid-lowering therapies, and were, therefore, not dose-limiting. The incidence of leukocytopenia did not show any exposure-response relationship to Everolimus trough concentrations. The incidence of notable thrombocytopenia (< 100 x 10^9/L) increased with Everolimus exposure; however, the incidence of clinically meaningful platelet reductions (< 75 x 10^9/L) was generally low.

If Everolimus medication is interrupted for safety related considerations for more than 2 weeks during the Run in phase (Month 3 to Month 6 post Tx) or 4 consecutive weeks within the 12 months study treatment (or cumulative for more than 8 weeks), discontinuation of the medication should be considered and the patient should be withdrawn from study treatment. Appropriate information needs to be recorded on the Dosage Administration CRF.

Cyclosporin A

Target therapeutic range for Cyclosporin A whole blood levels should be the following.

Timepoint	C0-h levels [ng/mL]
Month 3 – 6	100 – 200
Month > 6	50 – 150

Dose adjustments may be performed if Cyclosporin A whole blood levels outside the target range are measured. In case of severe CsA toxicity, dose reductions below the target levels may be performed on the investigator's discretion.

In the CNI-free group the Cyclosporin A will be reduced to a dose resulting in a C0 level of ≤ 75 ng/mL starting at Month 6 post Tx and finally (after 8 weeks of reduced dosage) removed completely. At the latest at Month 9, Cyclosporin A should be withdrawn completely from the immunosuppressive regimen in the CNI-free group.

If Cyclosporin A medication is interrupted for safety related considerations for more than 4 consecutive weeks or more than 8 cumulative weeks after randomization, discontinuation of the medication should be considered and the patient should be

withdrawn from study treatment. Appropriate information needs to be recorded on the Dosage Administration CRF.

Tacrolimus

Target therapeutic range for Tacrolimus whole blood levels should be the following.

Timepoint	C0-h levels [ng/mL]
Month 3 – 6	5 – 10
Month > 6	3 – 8

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 below 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.

In the CNI-free group the Tacrolimus will be reduced to a dose resulting in a C0 level of ≤5 ng/mL starting at Month 6 post Tx and finally (after 8 weeks of reduced dosage) removed completely. At the latest at Month 9, Cyclosporin A or Tacrolimus should be withdrawn completely from the immunosuppressive regimen in the CNI-free group.

If Tacrolimus medication is interrupted for safety related considerations for more than 4 consecutive weeks or more than 8 cumulative weeks after randomization, discontinuation of the medication should be considered and the patient should be withdrawn from study treatment. Appropriate information needs to be recorded on the Dosage Administration CRF.

The co-administration of drugs known to interfere with Tacrolimus metabolism should be avoided if possible. If these drugs are required, the investigator must monitor Tacrolimus and/or Everolimus trough levels (Appendices 3 and 4).

Mycophenolic Acid (MPA)

In patients randomized to the CNI-free group, treatment with MPA will be introduced starting the day after Baseline (Month 6 post Tx) assessment (see section 6.5.1). Either Mycophenolate Mofetil (MMF) or Enteric-Coated Mycophenolate Sodium (EC-MPS) may be applied.

In case of leukopenia (leukocyte count < 3,000/mm^3), neutropenia (neutrophil count < 1,500/mm^3), or anemia, MPA medication doses may be reduced at the discretion of

the investigator or eliminated completely until the event resolves. Furthermore, for any other moderate/severe AE which in the opinion of the investigator warrants a dose reduction or temporary interruption of the medication, this will be allowed. However, the MPA medication should be restarted once the AE has resolved or returned to an acceptable grading (see instructions given in Appendix 5).

If MPA medication is interrupted for safety related considerations more than 2 weeks during the run in phase (Month 3 to Month 6 post Tx) or for more than 4 consecutive weeks or more than 8 cumulative weeks, discontinuation of the medication should be considered and the patient should be withdrawn from study treatment. Appropriate information needs to be recorded on the Dosage Administration CRF.

The Month 18 assessments will be performed and documented for all patients who are withdrawn prematurely from the treatment at timepoint of discontinuation and again at month 18 after Tx.

In cases of recurrent infections serum antibody concentration should be measured; if hypogammaglobulinemia presents as persistent and clinically significant, patients should be examined accurately and appropriate actions should be taken; dose reduction or change of immunosuppression should be taken into consideration.

Patients with recurrent pulmonary disorders e.g. cough/dyspnea should as soon as possible be examined accurately for signs of bronchiectasis; dose reduction or change of immunosuppression should be taken into consideration.

6.5.3 Rescue medication

Treatment for acute rejection episodes

Patients with presumed acute rejection episodes must undergo endomyocardial biopsy within 48 h (regardless of initiation of anti-rejection treatment) and echocardiogram as needed. If the patient is not stable, the biopsy will be done within 24 hours after the patient has been stabilized. The acute rejection is to be treated according to the following table, or according to local practice. The randomized immunosuppressive regimen should not be changed, unless a second Grade 3A rejection episode with or without hemodynamic compromise occurs or a second rejection episode associated with hemodynamic compromise occurs. If either situation occurs and the investigator chooses to change the randomized immunosuppressive regimen, the patient will be removed from study treatment.

Table 6-2 Acute cellular rejection – diagnosis and treatment

ISHLT biopsy grade 1990 (2004)	Hemodynamic compromise*	
	Absent	Present
Grade 1A, 1B Mild (1R, mild)	No treatment	1-2 mg/kg oral corticosteroids for 3 - 5 days followed by 5 to 10 day taper or immediate return to baseline oral corticosteroids And/or

		High dose IV corticosteroids with or without anti-lymphocyte antibody therapy
Grade 2 Focal Moderate (1R, mild)	No treatment	High dose corticosteroids for 3 days followed by taper or by immediate return to baseline oral corticosteroids And/or High dose IV corticosteroids with or without anti-lymphocyte antibody therapy
Grade 3A, 3B Multifocal or diffuse (2R, moderate or 3R, severe)	1 - 4 mg/kg oral corticosteroids for 3-5 days followed by 5 to 10 day taper or immediate return to baseline oral corticosteroids Or High dose IV corticosteroids for 3 days followed by immediate return to baseline oral corticosteroids	High dose corticosteroids for 3 days with or without 7 - 14 days of anti-lymphocyte antibody therapy followed by a taper or immediate return to baseline oral corticosteroids And/or High dose IV corticosteroids with or without anti-lymphocyte antibody therapy
Grade 4 Diffuse, polymorphous with or without edema, hemorrhage, vasculitis (3R, severe)	High dose IV corticosteroids and anti-lymphocyte antibody therapy	High dose IV corticosteroids with or without anti-lymphocyte antibody therapy

* Hemodynamic compromise is considered to be present if one or more of the following conditions are met:
Ejection fraction ≤ 30% or 25% lower than baseline or
Fractional shortening ≤ 20% or 25% lower than baseline and/or Inotrope treatment
Baseline is defined as Visit 1

Treatment of CMV

Treatment with gancyclovir, cytomegalovirus hyperimmune globulin, valgancyclovir or valcyclovir is permitted and will be at the investigator's discretion per standard practice of the individual centers. Non-high risk patients will be treated according to local practice. CMV prophylaxis is also recommended following any antibody treatment of acute rejection episodes.

Treatment of Pneumocystis carinii

All patients should receive prophylactic treatment for Pneumocystis carinii Pneumonia (PcP) with trimethoprim/sulfamethoxazole (e.g. Bactrim® or Cotrim®) according to local practice. Duration and dosage depend on the discretion of the investigator. Aerosolized pentamidine or dapsone may be administered to patients unable to tolerate oral formulations.

Treatment of Candida

Nystatin for oral thrush (Candida) will be used in a swish and swallow regimen. Routine use of systemic antifungal agents (i.e., ketoconazole, itraconazole, and fluconazole) will not be allowed unless patients are systemically infected. Administration of azoles may increase blood concentrations of Cyclosporin A, Tacrolimus and Everolimus; therefore their use should be minimized. Particular attention to side effects is required. If such agents are to be used, additional drug monitoring Cyclosporin A, Tacrolimus and Everolimus are recommended at start and end of treatment.

Treatment of hyperlipidemia

Lipid lowering medications (e.g. fluvastatin, Lescol®) are to be administered to all patients even if the patient does not have an elevated LDL-cholesterol or triglyceride levels at baseline. Initiation of treatment should follow the National Cholesterol Educating Program (NCEP) guidelines (Appendix 6).

The daily starting dose should be the equivalent of 20 mg pravastatin, 5 mg simvastatin, 10 mg atorvastatin, or 20 mg fluvastatin, and may be increased to target and maintain a LDL level of < 130 mg/dL. In case of simvastatin, dose should not exeed 10 mg/day to account for the increased risk of myophathy/rhabdomyolysis, when combined with Cyclosporin A.

When HMG-CoA reductase inhibitors are used concomitantly with gemfibrozil (and probably other fibrates), Cyclosporin A or erythromycin, myopathy and rhabdomyolysis have been reported. **Therefore, the use of lovastatin will be prohibited in this study.**

Lipid lowering medications should be optimized prior to reduction of study medication. If the elevation of cholesterol and/or triglyceride levels persists, the dosing of study medication will be adjusted following the recommendations in Appendix 5.

6.5.4 Other concomitant treatment

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be listed on the Prior-/Concomitant medications/Significant non-drug therapies CRF. If required for an AE, such concomitant medication should be cross-referenced on the AE CRF under “action taken”, appropriately coded for “concomitant medication taken”.

Inducers of CYP3A4 (e.g. rifampin, carbamazepine, phenytoin, and barbiturates) have been shown or have the potential to decrease exposure to Everolimus. If these drugs are necessary, Everolimus doses may have to be increased. Potent inhibitors of CYP3A4 such as ketoconazole, itraconazole and fluconazole should be avoided

while the patient is on study medication. Everolimus has the potential to increase the exposure to terfenadine, astemizole and cisapride; hence these drugs should be avoided. In vitro data suggested that everolimus may have the potential to interact with quinidine, fluoxetine and paroxetine, and alternative medications should be considered. Since the potential for drug interaction with digoxin has not been evaluated, patients on digoxin should have periodic measurement of digoxin levels.

The concomitant administration of nephrotoxic drugs (e.g. aminoglycosides, NSAIDs) and drugs known to interfere with Cyclosporin A and Tacrolimus pharmacokinetics (i.e., ketoconazole, erythromycin, phenytoin, barbiturates, carbamazepine, diltiazem, verapamil, rifampin) should be associated with a careful monitoring of renal function and Cyclosporin A / Tacrolimus blood trough levels. In addition, drugs known to interfere with Everolimus or MPA should be avoided (see Appendix 5 for possible drug interactions).

6.5.5 Study drug discontinuation

In case of platelet count < 50,000/mm³, leukocyte count < 3,000/mm^3 or neutrophil count < 1,500/mm^3, at the discretion of the investigator, MPA medication dose may be reduced by half, or eliminated completely until the event resolves. In case of dose reduction, MPA should be reduced according to the guidelines given in Appendix 5. Everolimus should be continued on a stable dose level and reduced only if the symptoms do not respond to the reduction of the MPA dosage.

In case of elevated cholesterol and/or triglyceride levels, lipid lowering medications should be maximized. If the elevation persists, the dosing of Everolimus should be adjusted following the recommendations given in Appendix 5.

Dose reduction may be performed for those patients with other moderate/severe AEs according to the investigator's judgment. Also in these cases, the medication doses can be reduced by half or interrupted completely until event resolves.

If the MPA or Everolimus medication is interrupted for more than 2 weeks during the run in phase (Month 3 to Month 6 post Tx) or for more than 4 consecutive weeks or more than 8 cumulative weeks within the 12 months study treatment, discontinuation of the respective medication should be considered and the patient withdrawn from study treatment.

Patients who discontinue study drug before completing the maintenance period at Month 18 post Tx should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit (Month 18) will be performed. Month 18 assessments should be repeated at the initially planned timepoint, 18 months post transplantation.

At a minimum, all patients who discontinue study drug, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of study drug.

Patients who discontinue study drug should be considered withdrawn from the study only after the final visit assessments (month 18 post Tx) are performed or when it is clear that the patient will not return for these assessments.

6.5.6 Premature patient withdrawal from study treatment

Patients *may* voluntarily withdraw from study treatment or study treatment may be discontinued at the discretion of the investigator at any time.Patients *must* be withdrawn prematurely from the study treatment if any of the following occur:

- premature discontinuation of study drug (see section 6.5.5)
- pregnancy
- graft loss / re-transplantation
- third severe rejection episode (ISHLT 1990 grade ≥ 3A resp. ISHLT 2004 grade ≥ 2R) with or without hemodynamic compromise or rejection episode requiring change in baseline immunosuppressive therapy according to this protocol or any rejection ISHLT 1990 grade ≥ 3A resp. ISHLT 2004 grade ≥ 2R within months 6 – 9 **(as assessed by per protocol biopsies)**
- occurrence or detection of severe medical disorder jeopardizing the life of the patient in the immediate future

If such premature withdrawal from study treatment occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study / Treatment Completion CRF.

Patients *may* be withdrawn from the study treatment prematurely at the investigator's discretion for one of the following reasons:

1. adverse event(s)
2. abnormal laboratory value(s)
3. abnormal test procedure result(s)
4. unsatisfactory therapeutic effect (e.g. severe rejecetion)
5. protocol violation
6. administrative problems
7. patient's condition no longer requires study treatment

In cases of recurrent infections serum antibody concentration should be measured; if hypogammaglobulinemia presents as persistent and clinically significant, patients should be examined accurately and appropriate actions should be taken; MPA dose reduction or change of MPA-based immunosuppression should be taken into consideration.

Patients with recurrent pulmonary disorders e.g. cough/dyspnea should as soon as possible be examined accurately for signs of bronchiectasis; MPA dose reduction or change of MPA-based immunosuppression should be taken into consideration.

For patients who are lost to follow-up, the investigator should show “due diligence” by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

Patients who discontinue participation in the trial for any reason will not be replaced.

All patients who prematurely discontinue study treatment should still attend the final visit at Month 18 post transplantation to obtain follow up information on rejection episodes, allograft and patient survival, hospitalizations, malignancies and immunosuppressive medication.

The CRFs Study Completion Page should be completed at month 18 or earlier if the patient can no longer be followed, e.g. due to death, withdrawal of consent, or loss to follow-up.

6.5.7 Emergency unblinding of treatment assignment

Not applicable, since this is an open-label trial.

7 Visit schedule and assessments

Table 7-1 lists all of the assessments and indicates with an “X” the visits when they are performed. All these obtained data must be supported in the patient’s source documentation.

Table 7-1 Assessment schedule

Phase	Prephase	Study Drug Treatment					
Period	SCR	BL	Switch	Maintenance			
Visit	1	2	3	4	5	6	7[1]/7.1[2]
Month post Tx	3	6	8	9	10	12	18
Informed consent	X						
Inclusion/ exclusion	X	X					
Randomization		X					
Demography	X						
General medical history	X						
Renal history **(information on dialysis etc.)**	X						
Transplantation information	X						
Physical examination	X	X		X			X
Vital signs	X	X	X	X	X	X	X
Endomyocardial biopsy		X		X		X	X
ECG	X	X		X		X	X
Study medication check		X	X	X	X	X	X
Laboratory test:							
- Hemat. / Biochemistry	X	X	X	X	X	X	X
- Viral Serology	X	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
- Pregnancy test[4] (β-HCG)	X	X	X	X	X	X	X
- Blood sampling for frozen storage **(2-5 mL EDTA blood)**	X	X		X			X
- Urinalysis (proteinuria)	X	X		X			X
Drug concentration (C0-h)							
Tacrolimus/ Cyclosporin A[5]	X	X	X	X	X	X	X
Everolimus	X	X	X	X	X	X	X
Comments	← as necessary →						
Echocardiogram	← as necessary →						
Hospitalization[6]	← as necessary →						
AEs	← as necessary →						
SAEs	← as necessary →						
Infections	← as necessary →						
Concomitant therapy	← as necessary →						
Positive inotropic effect or vasoactive treatment	← as necessary →						
Immunosuppressive therapy	← as necessary →						
Rejection episodes	← as necessary →						
Hemodynamic compromise	← as necessary →						
MACE	← as necessary →						
End of study[1/2]							X

SCR: Screening visit: Month 3 post Tx BL: Baseline visit: day of randomization, Month 6 post Tx

1) At end of study (Month 18 post Tx) or at timepoint of discontinuation for patients with premature discontinuation of per protocol treatment
2) At Month 18 post Tx: Only for patients who prematurely discontinued the per protocol treatment
3) Only CMV-status (including pp65 Ag)
4) Only in women of childbearing potential
5) To be assessed only if Cyclosporin A or Tacrolimus is administered at that visit. C0-h levels have to be determined at all indicated timepoints.
6) Hospitalization: see section 7.8, Resource utilization

Patients should be seen for all visits on the designated day or as close to it as possible. However, timely intervals of ± 1 week will be regarded acceptable.

Screening Visit - Visit 1 (Month 3 post Tx)

This visit may be performed within a time window of ± 2 weeks.

1. Patient signs informed consent.
2. Patient's eligibility for the study according to in- and exclusion criteria will be checked.
3. Demographic data will be recorded (sex, age, ethnic origin).
4. Relevant medical history as well as renal history **(especially information on dialysis)** will be obtained and recorded.
5. Transplantation information will be recorded (donor and recipient information, including viral serology; initiated immunosuppressive regimen, including induction therapy).
6. A complete physical examination will be performed.
7. Vital signs will be measured.
8. A 12-lead ECG will be written.
9. Venous blood will be drawn for measurement of hematology and biochemistry.
10. Viral serology of CMV (including pp65 Ag), Hepatitis B (HbsAg), Hepatitis C, and HIV will be recorded. Results from ≤ 6 months prior Screening visit will be acceptable.
11. Venous blood will be drawn for measurement of the C0-h levels of Cyclosporin A or Tacrolimus and Everolimus.
12. Venous blood will be drawn for frozen storage until end of trial (2 EDTA-tubes**, 2-5 mL**); only as a backup to repeat laboratory measurements if necessary).
13. In woman of childbearing potential a pregnancy test will be performed (β-HCG).
14. Urinalysis for proteinuria will be performed (spot urine sample for protein/creatinine ratio may be used).
15. Prior and concomitant medications / significant non-drug therapies will be recorded.
16. Immunosuppressive medication taken at M3 post Tx and any dose adjustments that were performed within the five days preceding the Screening visit will be recorded.

17. Information on rejection episodes and MACE that occurred since transplantation will be recorded.

Baseline Visit - Visit 2 (Month 6 post Tx)

This visit may be performed within a time window of ± 1 week.

1. Patient's eligibility for the study according to in- and exclusion criteria will be checked
2. The patient will be randomized to one of the two treatment arms.
3. A complete physical examination will be performed.
4. Vital signs will be measured.
5. An endomyocardial biopsy will be performed.
6. A 12-lead ECG will be written.
7. Venous blood will be drawn for measurement of hematology and biochemistry.
8. Venous blood will be drawn for measurement of viral serology (CMV status including pp65 Ag).
9. Venous blood will be drawn for measurement of the C0-h levels of Cyclosporin A or Tacrolimus and Everolimus.
10. Venous blood will be drawn for frozen storage until end of trial (2 EDTA-tubes**, 2-5 mL**).
11. In woman of childbearing potential a pregnancy test will be performed (β-HCG).
12. Urinalysis for proteinuria will be performed (spot urine sample for protein/creatinine ratio may be used).
13. Changes in Concomitant medications / significant non-drug therapies will be recorded.
14. (Changes in) immunosuppressive medication will be recorded.
15. Information on rejection episodes, hemodynamic compromise, MACE, hospitalization, infections, and other (S)AEs that occurred since the last visit will be recorded.

Switch of immunosuppressive regimen - Visit 3 (Month 8 post Tx)

This visit may be performed within a time window of ± 1 week.

1. Vital signs will be measured.
2. Venous blood will be drawn for measurement of hematology and biochemistry.
3. In woman of childbearing potential a pregnancy test will be performed (β-HCG).
4. Venous blood will be drawn for measurement of viral serology (CMV status including pp65 Ag)
5. Venous blood will be drawn for measurement of
   - Everolimus C0-h level in all patients
   - Cyclosporin A C0-h level, only in patients of the CNI group

- Tacrolimus C0-h level, only in patients of the CNI group

6. Changes in concomitant medications / significant non-drug therapies will be recorded.
7. Changes in immunosuppressive medication (including study drug dosage) will be recorded.
8. Information on rejection episodes, hemodynamic compromise, MACE, hospitalization, infections, and other (S)AEs that occurred since the last visit will be recorded.

Maintenance Period - Visits 4, 5 and 6 (Month 9, 10, 12 post Tx)

These visits may be performed within a time window of ± 1 week.

1. Vital signs will be measured.
2. An endomyocardial biopsy will be performed (only visits 4 and 6).
3. A 12-lead ECG will be written (not at month 10, Visit 5).
4. Venous blood will be drawn for measurement of hematology and biochemistry.
5. Venous blood will be drawn for the measurement of viral serology (only CMV-status including pp65 Ag).
6. Venous blood will be drawn for measurement of
   - Everolimus C0-h level in all patients
   - Cyclosporin A C0-h level, only in patients of the CNI group
   - Tacrolimus C0-h level, only in patients of the CNI group
7. In woman of childbearing potential a pregnancy test will be performed (β-HCG).
8. Changes in concomitant medications / significant non-drug therapies will be recorded.
9. Changes in immunosuppressive medication (including study drug dosage) will be recorded.
10. Information on rejection episodes, hemodynamic compromise, MACE, hospitalization, infections, and other (S)AEs that occurred since the last visit will be recorded.

<u>Only at Vist 4, Month 9</u>

11. A complete physical examination will be performed.
12. Venous blood will be drawn for frozen storage until end of trial (2 EDTA-tubes**, 2-5 mL**).
13. Urinalysis for proteinuria will be performed (spot urine sample for protein/creatinine ratio may be used).

End of Study - Visit 7 (Month 18 and early discontinuation)

In case of early discontinuation, Month 18 assessments need to be performed
- as soon as possible after study drug discontinuation
- additionally at the originally planned timepoint, i.e. 18 months after transplantation

1. A complete physical examination will be performed.
2. Vital signs will be measured.
3. An endomyocardial biopsy will be performed.
4. A 12-lead ECG will be written.
5. Venous blood will be drawn for measurement of hematology and biochemistry.
6. In woman of childbearing potential a pregnancy test will be performed (β-HCG).
7. Venous blood will be drawn for measurement of viral serology (CMV-status including pp65 Ag).
8. Venous blood will be drawn for measurement of
   - Everolimus C0-h level in all patients
   - Cyclosporin A C0-h level, only in patients of the CNI group
   - Tacrolimus C0-h level, only in patients of the CNI group
9. Venous blood will be drawn for frozen storage until end of trial (2 EDTA-tubes).
10. Urinalysis for proteinuria will be performed (spot urine sample for protein/creatinine ratio may be used).
11. Changes in concomitant medications / significant non-drug therapies will be recorded (in case of early discontinuation until 30 days after last dose of study drug).
12. Changes in immunosuppressive medication (including study drug dosage) will be recorded (in case of early discontinuation until 30 days after last dose of study drug).
13. Information on rejection episodes, hemodynamic compromise, MACE, hospitalization, infections, and other (S)AEs that occurred since the last visit will be recorded
14. End of Study / End of Treatment information will be obtained.

7.1 Follow-up of Patients after End of Study Treatment

For all patients who were included into this trial, whether discontinued treatment prematurely or completed the entire study, the final examination will be performed 18 months after transplantation (Visit 7 and / or visit 7.1, Month 18).

At a minimum, all patients who discontinue from the study treatment prematurely will be contacted within 30 days following study treatment termination, to follow-up on any safety issues. Documentation of MACE, infections, immunosuppressive medication, and other concomitant medication should be continued for the period of 30 days following the last dose of the per protocol immunosuppressive regimen.

For all patients documentation of SAEs should be continued until 30 days after the patient has stopped study participation (visit 7 or 7.1, Month 18). Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug.

Following discontinuation of the per protocol immunosuppressive regimen, the immunosuppressive therapy will be on the investigator's discretion.

7.2 Information to be collected on Screening failures

If a patient who signed informed consent fails to be **enrolled** into the trial at Month 3 for any reason, the patient's number and the reason for non-enrollment will be entered into the Screening Failure Log.

7.3 Patient demographics / other baseline characteristics

The following demographic data and other baseline characteristics will be recorded:

- **Demography:** date of birth, sex, and ethnic origin
- **Relevant medical history / current medical conditions:**
  Relevant prior diseases and surgeries as well as concomitant diseases will be recorded with date of diagnosis / surgery and information on whether it is an active problem.
  For women of childbearing potential the serum pregnancy test (β-HCG) will be performed locally within 7 days prior to Screening (Month 3 post Tx). Results must be available and negative prior to administration of medication and reported on the CRF.
- **Renal history**
  Any significant prior and current renal diseases (e.g. presence of glomerulonephritis, nephrectomia, etc.) will be recorded with date of diagnosis and information whether it is an active problem).
- **Transplantation information:**
  Donor information
  age, sex, race, viral serology on CMV, EBV, HepC, HbsAg, HIV
  Recipient information
  date of transplantation, duration of cold ischemia time, percentage of panel reactive antibodies (PRA) , viral serology on CMV, EBV, HepC, HbsAg, HIV, end stage disease leading to transplantation
  Initiated immunosuppressive regimen, including induction therapy

7.4 Treatments

Records of all immunosuppressive drugs (Everolimus, Cyclosporin A, Tacrolimus, MPA, corticosteroids) used and dosages administered are to be kept during the whole study. Starting 5 days prior to the Screening visit, all changes to the medication dosing regimen should be recorded in the Dosage Administration Record CRF, along with the reason for change and dates.

The immunosuppressive regimen initiated after transplantation, including information whether and which induction therapy was applied, will be recorded.

Drug accountability for **Everolimus** medication will be noted by the investigator and/or study personnel at each visit using pill counts. This information should be captured in the source document at each visit.

7.5 Efficacy

The following efficacy variables will be obtained and recorded:

- **Endomyocardial biopsy – Rejection episodes / graft loss / re-transplant**
  Per protocol biopsies will be performed at visits 2, 4, 6 and 7 and results of a biopsy that may have been performed at Month 1 post Tx will be recorded retrospectively. Additionally, a biopsy will be performed in any case of suspected rejection. Biopsies will be read and interpreted by local pathologists according to the ISHLT 1990 and/or 2004 diagnosis criteria (Stewart et al, 2005). A copy of the pathology report will be collected and filed in the investigator's folder. The results will be recorded on the Endomyocardial Biopsy CRF at respective visit.

  All suspected rejection episodes must be recorded on the Endomyocardial Biopsy log / Suspected Rejection CRF, with the date rejection was first suspected, whether anti-rejection therapy was administered, whether the acute rejection was confirmed or with final clinical diagnosis specified, and final clinical outcome.

  Biopsy-proven acute rejection

  (ISHLT 1990 grade ≥ 3A resp. ISHLT 2004 grade ≥ 2R)

  The occurrence of a biopsy-proven acute rejection is diagnosed from per-protocol biopsies or from biopsies performed for suspected rejection episodes. Per protocol biopsies will be performed at Visits 2, 4, 6 and 7 / 7.1.

  In all suspected rejection episodes, a graft core biopsy and an echocardiography will be performed within 48 hours, regardless of the initiation of anti-rejection therapy. The results including date of occurrence of first symptoms will be recorded in the Endomyocardial Biopsy log / Suspected Rejection CRF and will be used for the efficacy analysis.

  Rejection episodes will be reported on the Endomyocardial Biopsy log / Suspected Rejection CRF only, and not on the AE CRF. An Endomyocardial Biopsy log / Suspected Rejection CRF will be completed each time a suspected or biopsy-proven acute rejection has occurred. Rejection episodes occurring more than 10 days after the start of the preceding one will be considered as a new rejection episode.

Rejection with hemodynamic compromise

The occurrence of an acute rejection with hemodynamic compromise will be assessed using the Hemodynamic Compromise CRF. Positive inotrope therapy or vasoactive treatment will be recorded on the Prior-/Concomitant medications CRF.

Graft loss / re-transplantation

The allograft will be presumed to be lost on the day the patient is scheduled for re-transplantation. This will be reported on the End of Treatment CRF if medication is discontinued prematurely and Study Completion CRF. Graft loss / re-transplantation are considered a Serious Adverse Event and must be reported on the Serious Adverse Event Case Report Form, which must be faxed to Novartis.

Major Adverse Cardiac Events (MACE)
Major Adverse Cardiac Event will be defined as one of the following:

- any death
- myocardial infarction
- coronary artery bypass grafting

All major adverse cardiac events will be recorded on the CRF and are subject to expedited reporting as specified in section 8.1.

- **Echocardiogram**
  Echocardiograms will be performed as needed for suspected rejection episodes. Results will be recorded on the Echocardiogram CRF.

- **Electrocardiograms (ECG)**
  A 12-lead ECG will be written and documented in the CRF with ventricular rate, PQ interval, QRS duration and QT interval.
  Additionally, the investigator will assess the following:

heart rate:	normal, bradycard, tachycard,
rhythm:	eurhythmia, arrhythmia,
block signs:	S-A Block, AV-Block °I, °II (Wenckebach, Mobitz, Periodic), or °III, Interventricular Block (right bundle-branch, left bundle-branch)

7.6 Safety

Safety assessments will consist of monitoring and recording all infections, AEs and SAEs, the regular monitoring of hematology, blood chemistry, and regular measurement of vital signs.

Infections

All infection episodes must be recorded on the Infection CRF (CMV infections on the CMV Infection CRF); they should not be collected on the AE CRF. Infections should be listed with severity, relationships, sample site, genus and species of microorganism specified, start and end dates, action taken.

CMV infection is defined as seroconversion of a negative patient or isolation of CMV from urine, saliva, blood or any other tissue. Symptomatic or clinically apparent CMV infection should be classified according to the criteria of the Paris CMV workshop (1993) into presumptive and proven CMV disease. Briefly, the diagnosis of presumptive CMV disease requires the demonstration of CMV viremia by any method in addition to fever > 38°C for at least 2 days in the absence of another clinical source, combined with one of the following findings: atypical lymphocytosis > 3%, WBC count < 4,000/mm^3 or platelet count < 100,000/mm^3. The diagnosis of proven CMV disease requires, apart from the presence of signs and/or symptoms of organ involvement, the detection of CMV in the affected organ. Particular attention will be given to clinically apparent CMV infections (presumptive and proven CMV disease).

Adverse events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Study drug includes the investigational drug under evaluation and the comparator drug or placebo that is given during any phase of the trial. Medical conditions / diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. the severity grade (mild, moderate, severe)
2. its relationship to the study drug (Everolimus) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. action taken i.e:
   (a) no action taken;
   (b) study drug dosage adjusted/temporarily interrupted;
   (c) study drug permanently discontinued due to this adverse event;
   (d) concomitant medication taken;
   (e) non-drug therapy given;
   (f) hospitalization/prolonged hospitalization
5. whether it is serious, where a serious adverse event (SAE) is defined as one which:
   - is fatal or life-threatening
   - results in persistent or significant disability/incapacity
   - constitutes a congenital anomaly/birth defect
   - requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:

  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - 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 patient's general condition
  - treatment of acute rejection; acute rejections are considered to be a protocol exempted event. They should not be reported simply because they result in a hospitalization and thus meet the criteria for an SAE.. Acute rejections should be reported as SAEs only if they are unusual in appearance, clinical course and/or are graft threatening
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- is a MACE or a graft loss

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 8.1.

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

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

Physical examination

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

Vital signs

Height will be recorded at Screening visit (Visit 1) only. Vital signs will be recorded at every study visit, and include body temperature, radial pulse rate, systolic and diastolic blood pressure and weight (kg). Blood pressure and pulse rate will be assessed after the patient has rested in the sitting position for at least five minutes; blood pressure should be assessed at the same arm each time of determination.

Laboratory evaluations

The center's local laboratory will be used to analyze the clinical laboratory data during the study.

The following variables will be examined:

Hematology:	hemoglobin, leukocytes (including differential blood count and absolute neutrophil count), red blood cell and platelet count hematokrit (HK)
Blood chemistry:	sodium, potassium, urea, creatinine, glucose (fasting) uric acid, ALAT, ASAT, albumin, total bilirubin, total cholesterol, HDL, LDL, triglycerides, CPK
Viral Serology:	CMV (including pp65 Ag) only at Screening (or up to 6 months prior screening): EBV, Hepatitis B (HbsAg), Hepatitis C, HIV
Frozen Storage:	2 tubes of EDTA blood
Urinanlysis:	protein GFR will be calculated according to the formula given below, Section 7.7

For determination of the drug levels see Section 7.10.

Viral serology

All patients should be tested for EBV, Hepatitis B (HBsAg), Hepatitis C, CMV and HIV prior to study inclusion (earlier tests ≤ 6 months are acceptable). Any patients with a positive Hepatitis B surface antigen or Hepatitis C or HIV will be excluded from study participation. If results are not available at the Screening visit, the patient may be included. If results of a newly initiated assessment at the Screening visit will be positive, the patient will subsequently be dropped from the study and administered the standard care provided by the center.

During the course of the trial, only CMV status (including pp65 Ag) will be assessed.

7.7 Tolerability

Renal safety and tolerability will be the main objective of this trial. The following variables of renal safety and tolerability will be obtained and recorded:

- **Glomerular Filtration Rate (GFR)**
  The glomerular filtration rate (GFR) is the best clinical estimate of renal function in health and disease, and correlates well with the clinical severity of renal function disturbances. Several studies have shown that in patients with progressive renal disease, GFR declines or reciprocal serum creatinine levels elevates linearly over time in a predictable manner.

  The GFR will be calculated via MDRD (primary endpoint) and Cockcroft-Gault-Formula:

  Calculated value of GFR in ml / min - **MDRD formula**

  For men: GFR = 170 x (serum creatinine $^{-0,999}$) x (age$^{-0,176}$) x (urea nitrogen $^{-0,17}$) x (albumin^{0,318})

  For women: GFR = 170 x (serum creatinine $^{-0,999}$) x (age$^{-0,176}$) x (urea nitrogen $^{-0,17}$) x (albumin^{0,318}) x 0.762

  with urea nitrogen = urea / 2.144.

  Calculated value of GFR in ml/min - **Cockcroft-Gault formula**

  For men: GFR= $\frac{(140 - Age) \times Body\ Weight\ [kg]}{72 \times Serum\ Creatinine\ [mg/dl]}$

  For women: GFR= $\frac{0{,}85 \times (140 - Age) \times Body\ Weight\ [kg]}{72 \times Serum\ Creatinine\ [mg/dl]}$

  units: [g/dl] for albumin, [mg/dl] for serum creatinine, [mg/dl] for serum urea

  Furthermore, tolerability of study medication can be assessed from the rate of patients who withdraw prematurely from study medication or in whom study medication had to be converted to another immunosuppressive regimen due to abnormal laboratory results, adverse events, or toxicity.

  All changes to the immunosuppressive medication dosing regimen will be recorded on the Dosage Administration Record CRF, along with the reason for change.

- **Serum Creatinine**
  For the analysis of serum creatinine, venous blood will be drawn and analyzed in the center's local laboratory.
  Besides changes from baseline, the slope of the decline in reciprocal serum creatinine (1 divided by serum creatinine) versus time will be analyzed as an indicator of progressive renal disease (for the creatinine slope, see Gretz 1994; Lacour 1992; Kaplan et al., 2003; Kasiske et al., 2001).

7.8 Resource utilization

Approximately 95% of treatment costs of transplanted patients are related to hospitalization, immunosuppressants and concomitant medication. As information on immunosuppressants, concomitant medication and dialysis is collected traditionally in all transplant clinical studies, the focus of additional resource utilization data collection should be on hospitalization events. Thus, all relevant information about initial hospitalization due to transplantation and hospitalization after transplantation (in the transplant center and outside) will be recorded. The information collected this way includes reason for admission (including admission for adverse events, including infection, for dialysis post transplantation, and for treatment of acute rejection), the dates of admission and discharge, number of days on Intensive Care Units and number of days on a normal ward.

7.9 Health-related Quality of Life

None

7.10 Pharmacokinetics

The actual sample collection times, and the date and time of the previous drug dose (Everolimus, Tacrolimus or Cyclosporin A) will be recorded on CRF using a 24 hour clock.

Cyclosporin/Tacrolimus A whole blood levels will be measured starting at Screening Visit. For patients of the CNI group Cyclosporin A/Tacrolimus blood level will be measured at every study visit, for patients of the CNI-free group Cyclosporin A/ Tacrolimus blood level will be measured until Cyclosporin A or Tacrolimus is removed from the immunosuppressive regimen (Month 6 or 8 post Tx).

Everolimus blood levels will be measured in all patients starting at Screening Visit and at every study visit thereafter (if applicable).

- **Cyclosporin A (CsA) whole blood tests**
  Analysis of the Cyclosporin A whole blood levels will be performed locally at the center. Whole blood level for CsA will be assessed within 5 minutes before the Cyclosporin A administration (C0-h level).

- **Tacrolimus (Tac) whole blood tests**
  Analysis of the Tacrolimus whole blood levels will be performed locally at the center. Whole blood level for Tac will be assessed 5 minutes before the Tacrolimus administration (C0-h level).

- Everolimus **whole blood tests**
  For the analysis of the Everolimus whole blood levels 2 ml of blood should be

drawn in EDTA tubes. The C-0h level will be obtained with blood sampling within 5 minutes prior to medication intake.

7.11 Pharmacogenetics/pharmacogenomics

None.

7.12 Other biomarkers

None.

7.13 Additional Assessments

None

8 Safety monitoring

8.1 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has signed the informed consent form and until 30 days after the patient has stopped **study participation** must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship to study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the local Novartis [redacted]

[redacted]

8.2 Pregnancies

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

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis [redacted]

8.3 Data Monitoring Board

An external and independent Data Safety Monitoring Board (DSMB) will be instituted before study start. The DSMB will review safety-related issues and will be entitled to make recommendations for changes in study conduct. Details on the function of the DSMB will be laid out in a separate DSMB Charter.

9 Data review and database management

9.1 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 patient 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 drug is being stored, dispensed, and accounted for according to specifications. Key trial personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing

demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. Data not requiring a written or electronic record will be defined before study start and will be recorded directly on the CRFs, which will be documented as being the source data. The investigator must also keep a copy of the signed informed consent form.

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 the recording of data that will be used for all primary efficacy and safety 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.

9.2 Data collection

Designated investigator staff must enter the information required by the protocol onto the Novartis CRFs that are printed on 3-part, non-carbon-required paper. Field monitors will review the CRFs for completeness and accuracy and instruct site personnel to make any required corrections or additions. The CRFs are forwarded to Data Management by field monitors or by the investigational site, one copy being retained at the investigational site and one copy being the working copy for the monitor. Once the CRFs have been received by Data Management, their receipt is recorded and forwarded for data entry and data management processes. If CRFs have been sent for data entry by the investigational site directly, Data Management staff has to review the CRFs upon receipt for any serious adverse event.

9.3 Database management and quality control

Data from the CRFs are entered into the study database by Contract Research Organization staff using double data entry with verification upon second entry. Text items (e.g. comments) are entered once and checked manually against the CRF.

Subsequently, the entered data are systematically checked by Data Management staff, using error messages printed from validation programs and database listings. Obvious errors are corrected by Data Management personnel, according the obvious correction document. Other errors or omissions are entered on Data Query Forms, which are returned to the investigational site for resolution. The signed original and resolved Data Query Forms are kept with the CRFs at the investigator site, and a copy is sent Data Management so the resolutions can be entered into the database. Quality control audits of all key safety and efficacy data in the database are made prior to locking the database.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events

will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

At the conclusion of the study, the occurrence of any protocol violations 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 made available for data analysis. Any changes to the database after that time can only be made by joint agreement between the Trial Statistician and the Clinical Trial Leader (both from the German CPO).

10 Statistical methods

10.1 Statistical methods

[redacted] Analyses will be done when all patients have completed the trial at 18 months post Tx (or discontinued prematurely). The following periods will be considered for analyses:

- The primary analysis of renal safety and tolerability concerns the period of randomized treatment between Month 6 (baseline) and Month 18 or the last assessment within this period in the event of a patient's premature discontinuation from the study. If indicated, e.g. for analysis of renal function and type and frequency of adverse events, the period from Month 6 to Month 18 may be portioned into (a) the switch period between Month 6 and Month 9 and (b) the maintenance period between Months 9 and 18 after Tx.
- As a separate study period, the first 6 months between transplantation and Month 6 post Tx will be analyzed with regard to treatment, efficacy, and safety of the immunosuppressive regimen.
- To allow conclusions about the total treatment period of the CNI-based versus the CNI-free treatment regimen including initial treatment and randomized therapy, the total period between transplantation and Month 18 will be analyzed and compared between the two treatment groups. In patients who discontinue prematurely from the study, both the last available information under study treatment as well as an additional assessment at Month 18 will be analyzed.

The group of patients who were not randomized to one of the two treatment groups at Month 6 (Baseline visit) will be handled as a third patient group within exploratory analyses and described with respect to primary and secondary outcome variables and treatment variables for the same periods as described above.

Adverse events will be analyzed separately for the initial 3 months period between Screening and Baseline visit and for the randomized treatment period between Baseline visit (Month 6) and Month 18, but also for the total treatment period.

Significant events like rejection episodes, hemodynamic compromise, and MACE will additionally be analyzed for the period between transplantation and Screening (Month 3 post Tx).

Unless otherwise stated, all statistical tests will be two-sided and use the 0.05 level of statistical significance. All summary statistics will be presented by treatment group. Frequency distributions will be provided for categorical variables and the two treatment groups will be compared with chi^2-tests. Descriptive statistics of mean, standard deviation, minimum, median and maximum will be presented for continuous variables, comparisons of the two treatment groups will be performed with suitable chosen 2-sample tests. Time to event data including rates of affected patients will be assessed by Kaplan-Meier statistics and compared between the two groups with the logrank test.

Data from all centers that participate in this study will be combined.

A detailed description of the statistical evaluation of this study will be provided in a Statistical Analysis Plan which will be finalized prior to closure of the study database.

10.2 Populations for analysis

The enrolled patient population (ENR population) will include all patients who signed an informed consent regardless whether they received study treatment or not.

The Safety Population (SAF population) will consist of all patients who signed an informed consent and who were treated with at least one dose of any immunosuppressive medication after the Screening visit.

Note: The statement that a patient had no adverse events constitutes a safety assessment.

The Randomized Population (RAN) is defined by all patients who were randomized at Baseline visit. This population will include patients who were randomized but not treated with the randomized medication.

The ITT population will consist of all randomized patients who received at least one dose of any immunosuppressive therapy after Baseline Visit (Month 6) and have at least one post-baseline assessment of the primary outcome variable (renal function based on MDRD method). Randomized patients without data on the primary outcome variable will be excluded from this population; their data will be analyzed for the initial treatment period (up to Month 6) and within the RAN and SAF.

Following the intent-to-treat principle, patients will be analyzed according to the treatment group they were assigned to at randomization.

The Per-protocol Population will consist of all ITT patients who did not show major deviations from the protocol procedures that may have an impact on the study outcome and who have completed the treatment phase at Month 18 according to protocol. Criteria that are assumed to have such an impact will be defined before analysis during the Blind Review Meeting.

Besides the two patient groups who were eligible for randomization, a third patient group will be defined in whom a heart transplantation was performed but who did not qualify for randomization at Baseline visit (Month 6). This group will be addressed as "not randomized patients" (NRP) and described with respect to treatment and outcome variables.

10.3 Background and demographic characteristics

Demographic and background information will be summarized for the ENR-, the SAF-, the ITT-, and the PP- Population, using frequency distributions for categorical variables and descriptive statistics of mean, standard deviation, minimum, median and maximum for continuous variables. Background information includes prior medication, past/current medical conditions and transplant history.

Medical history will be coded using MedDRA and will be presented by system organ class, MedDRA preferred term and treatment group. Separate tables will be provided for past medical condition and current medical condition. Prior medication will be coded according to WHO Drug Reference List.

In addition to these variables which were evaluated at Screening (Visit 1, Month 3 post Tx), the course of renal function (GFR) as well as efficacy variables (treated acute rejection, biopsy proven acute rejection of ISHLT 1990 grade ≥ 3A resp. ISHLT 2004 grade ≥ 2R, acute rejection associated with hemodynamic compromise, graft loss / re-transplantation, death) will be determined and properly described for the period between Transplantation and Baseline (Visits 2 - Month 6 post Tx).

The two treatment groups will be compared descriptively with respect to these variables. Further, the NRP group will be described using the same variables.

No formal statistical testing is planned for comparability purposes.

10.4 Study treatments

10.4.1 Study medication

Study medication is Everolimus, RAD001); the other components of the immunosuppressive regimens are considered as concomitant medication.

Duration (days) of Everolimus, study medication application will be summarized. Dosage averages will be calculated including and excluding zero doses for periods of temporary interruption of study medication regardless of whether this was due to safety reasons or patients' non-compliance. Daily Everolimus, dose levels will be summarized with mean, standard deviation, minimum, median, and maximum by time interval. Frequency of dose reduction (including temporary dose interruption) for safety reasons as per protocol guidelines as well as average daily dose will be presented by visit. Reasons for dose adjustments (including temporary dose

interruption) will be presented by frequency distribution. Permanent treatment discontinuations will be analyzed by frequencies.

These analyses will be performed per treatment group, for the ITT- and the PP population and related to the study phases (see section 10.1).

10.4.2 Concomitant therapy

Daily Cyclosporin A and Tacrolimus doses adjusted by the patients' visit-specific body weight, MPA doses, and steroids (expressed in doses equivalent to prednisone) will be summarized by visit and in the same way as the study medication. Data will be presented separately for each treatment group. Induction therapy (Basiliximab or ATG or no induction) received by patient will be summarized by treatment group, for the total (SAF) population, but also for the NRP group.

Duration (days) of treatment with Cyclosporin A, Tacrolimus, MPA, and steroids as well as frequency of Cyclosporin A, Tacrolimus and MPA dose adjustments (including temporary dose interruption) for safety reasons as per protocol guidelines will be determined. Reasons for dose adjustments (including temporary dose interruption) will be presented by frequency distribution. Permanent treatment discontinuations will be analyzed using frequency distribution. All other immunosuppressive therapies will be summarized by ATC (Anatomical, Therapeutic, Chemical) classes.

All analyses for concomitant medication will be presented per treatment group and study phase (see section 10.1).

Corresponding data of the NRP group will be reported in a similar way.

Medications other than those mentioned in this section taken concomitantly with the study medication will be summarized by treatment group and study period through frequency tables. Concomitant medication will be coded and summarized according to the ATC classification system.

10.5 Primary objective

The primary aim of this study is to show superior renal function under the CNI-free regimen compared to the CNI-based regimen with respect to GFR as calculated by MDRD method.

10.5.1 Variable

The primary variable for assessment of renal function is the

- glomerular filtration rate (GFR) at Month 18, as assessed by the MDRD method (recalculated values, see section 7.5).

10.5.2 Statistical hypothesis, model, and method of analysis

According to the recommendation given in the Points to Consider document on "Adjustment for Baseline Covariates" (CPMP, 2003), the null hypothesis H_0 of similar GFR level in both treatment groups

H_0: $\mu_{CNI\text{-}free} = \mu_{CNI\text{-}based}$

will be tested against the two-sided alternative hypothesis of different efficacy (different GFR levels at month 18 after Tx) of the CNI-free regimen compared to the CNI-based regimen

H_1: $\mu_{CNI\text{-}free} \neq \mu_{CNI\text{-}based}$

with an analysis of covariance (ANCOVA) using "treatment" and "center" as factors and "baseline GFR value at Baseline visit 2 (Month 6)" as covariate. Type-I error probability will be set to a two-sided α=0.05. Adjusted means (=LS-means, LS: least square means) will be presented for the treatment contrast of GFR at Month 18 post Tx together with its confidence interval and a two-sided p-value.

The ITT population will be used for the primary analysis. This analysis follows the intention-to-treat principle and thus reflects the actual performance of the investigational drug under practical conditions ("pragmatic approach").

10.5.3 Handling of missing values/censoring/discontinuations with respect to the primary outcome variable

If a patient discontinues from the study prematurely missing data with respect to the target parameter will be substituted by the last recorded value (last observation carried forward, LOCF). The LOCF method will only be applied if a patient has at least one assessment after Baseline, i.e. on Visits Months 8 to 18. Otherwise, the patient will be excluded from efficacy analysis within the ITT population (see section 10.2). Under the assumption that the GFR will remain fairly stable or even worsen in the CNI group but will probably even improve in the CNI-free group, this strategy corresponds to a conservative estimate of the therapy effect within both treatment groups.

Additionally, sensitivity analyses will be performed including the following imputation strategy:

- Missing data for the primary outcome variable will be replaced by the mean of the non-missing values in the same treatment group. Further sensitivity analyses may be specified in the statistical analysis plan.

10.5.4 Supportive analyses

The course of the GFR will be of special interest. Changes from Baseline to each post-baseline measure will be calculated by treatment group for each study visit. In addition, the GFR as recalculated by the Cockcroft-Gault method will be analyzed in the same manner (see secondary objectives).

In addition to quantitative analyses, the frequency distributions of patients with an improved GFR at study month 18 compared to BL (Month 6 post Tx) will be compared between the two regimens.

If patients of the ITT population are switched from the CNI group to the CNI-free group during the study or during follow-up, they will be analyzed in their randomized group. If appropriate, a subgroup analysis will be performed comparing patients of the CNI group with and without switch to CNI-free treatment including a further analysis comparing both subgroups to the randomized CNI-free group. If treatment will be modified in the CNI-free group, they will be analyzed as randomized.

It is planned to evaluate renal function and efficacy variables also at Month 18 in patients who discontinue prematurely (prior to Month 18) from the trial. An additional exploratory analysis will be conducted using the assessments at Month 18.

Additionally to the analyses of data from the interval between BL (Month 6) and Month 18, the primary outcome variable will also be evaluated for the interval between Transplantation (prior to Tx) and Month 18.

Results from these supportive analyses will be interpreted in an explorative manner.

Corresponding data from the NRP group will be described in a similar manner.

10.6 Secondary objectives

10.6.1 Efficacy

The following secondary efficacy variables will be analyzed in an explorative manner:

- Occurrence of treatment failure up to Month 18 defined as composite endpoint of biopsy proven acute rejection of ISHLT 1990 grade ≥ 3A resp. ISHLT 2004 grade ≥ 2R, acute rejection episodes associated with hemodynamic compromise, graft loss / re-transplant, death, loss to follow up (at least one condition must be present).
- Occurrence of MACE and each of its components at Month 18

Additionally to the analyses of data from the interval between BL (Month 6 post Tx) and Month 18, all secondary outcome criteria will also be evaluated for the interval between Month 0 (prior to Tx) and Month 18.

Event data:

Event rates will be estimated using the Kaplan-Meier method to handle patients who discontinue the treatment prior to suffering from an event adequately. The two groups will be compared using the logrank test.

This procedure will be applied for the composite endpoint of treatment failure and each of its components, as well as MACE and each of its components.

Narratives including relevant medical information will be provided for each biopsy proven acute rejection, CAV, graft loss, or death.

Corresponding data from the NRP group will be described in a similar manner.

10.6.2 Safety

Safety variables will be analyzed separately for the period between a) Screening and Baseline, b) for the period between Baseline and Month 9, c) for the period between Baseline and final assessment (Month 18 or date of premature withdrawal from the study), d) as well as for the total treatment period (Screening to Month 18). For the randomized treatment period, analyses will be performed according to the treatment group into which the patients were randomized.

All analyzes of safety parameters will be based on the safety population. Corresponding data from the NRP group will be described similarly for the period between Screening and Baseline visit.

The key safety variables which will be analyzed will be as follows.

- Incidence and severity of infections, in particular clinically apparent CMV
- Incidence and severity of Adverse Events (AEs) and Serious Adverse Events (SAEs)
- Incidence of AEs leading to discontinuation from the study
- Relative frequency of abnormal vital signs measurements and laboratory parameters

The incidence rates for (serious) adverse events and infections will be analyzed by treatment group.

AEs/Infections

Generally, infections data are analyzed together with AE data. In addition, infection data will be analyzed separately.

Data collected by AE CRFs and by Infection CRFs and CMV-CRFs are to be coded with the MedDRA dictionary that gives preferred term and body system information. The incidence of AEs will be summarized by body system, preferred term, severity, and relationship to study drug. All information pertaining to AEs noted during the study will be listed by treatment group and patient, detailing verbatim given by the investigator, the preferred term, the body system, start/end dates, severity and drug-relatedness. The AE onset will also be shown relative (in number of days) to the day of initial dose per study period (within the first 3 months, after Baseline (Month 6)).

In addition to being analyzed similarly as AEs, as described above, the relative frequency of infection by type and micro-organism will be tabulated. AEs occurring 7 or more days after the discontinuation of study medication will not be included in AE/infection summary tables.

Laboratory data

Abnormalities according notable criteria (see Appendix 2) will be identified. The proportions of patients with clinically notable abnormalities according to the notable criteria will be summarized. Shift tables describing changes from status prior transplantation (Month 0) and Baseline based on the expanded normal limits will be

presented for treatment endpoints (study Month 6 and 18) and worst observations during the different study periods (up to Month 6 as well as between Month 6 and Month 18). The worst observation is defined as the highest or lowest measure during the different observations periods whereby high or low are chosen according to the direction of abnormality (e.g. the highest will be chosen for serum creatinine, the lowest for leukocytes). Further, descriptive statistics of change from baseline of all laboratory variables will be presented by visit. A by-patient listing of all laboratory data (with clinically notable abnormalities being flagged) will be generated. Only assessments obtained up to 2 days after the discontinuation of study medication will be considered "on-treatment" and analyzed with relationship to Everolimus.

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 (see Appendix 2). Appropriate incidence rates of clinically notable abnormalities for between-group differences will be provided. Further, descriptive statistics of change from baseline of all vital signs variables will be presented by visit. A by-patient listing of all vital signs (with clinically notable abnormalities being flagged) will be generated. Shift tables describing changes from baseline based on clinically notable criteria will be presented for treatment endpoint (Month 18) and worst on-treatment observations. Only assessments obtained up to 2 days after the discontinuation of study medication will be considered "on-treatment".

10.6.4 Tolerability

In addition to the analysis of the primary outcome variable of renal safety and tolerability, the following will be analyzed:

- Renal function as assessed by Cockcroft-Gault at moth 18 after Tx
- Serum creatinine and creatinine slope (1/serum creatinine versus time) including the treatment period between BL (Month 6) and Month 18

Analyses of renal function as determined by other calculations (serum creatinine, glomerular filtration rate (GFR, Cockcroft-Gault)) will be evaluated in the same manner as described for the primary outcome measure.

In addition to quantitative analyses, the frequency distributions of patients with an improved GFR at study Month 18 compared to BL (Month 6) will be compared between the two regimens.

The creatinine slope (1 / serum creatinine versus time) will be determined from all assessments between Month 6 and Month 18 (both visits included) using a linear regression model. These slopes will be compared with a two-sided Wilcoxon rank-sum test between the treatment groups.

Additionally, tolerability of study medication will be assessed from the rate of patients who withdraw prematurely from study medication or in whom study medication had to be converted to another immunosuppressive regimen due to abnormal laboratory

results, adverse events, or toxicity. A number of reasons are pre-defined in section 7.7 of this protocol. The frequency distribution of these reasons will be presented with absolute and percent values. The most frequent reasons (total n ≥ 5) for discontinuation and/or conversion as well as the total number of patients who are affected by such intolerability of study medication will be compared between the two treatment groups using the exact Fisher test.

10.6.5 Resource utilization

The treatment costs which arise from hospitalization, immunosuppressants, dialysis and concomitant medication will be performed separately by the Health Economics Department of Novartis. Results will be added in an Appendix to the Clinical Study Report.

10.6.6 Health-related Quality of Life

No health-related Quality of Life assessments are planned to be performed in this study.

10.6.7 Pharmacokinetics

Analysis of the Cyclosporin A, Tacrolimus and Everolimus blood levels will be done by treatment group and separately for the treatment phases (up to and after Month 6), the NRP group will be analyzed.

Everolimus

Mean blood level values of Everolimus will be presented in tabular form for each timepoint (visit window) and as mean value over time. Trough values will be tried to be kept in a therapeutic window of 5 – 10 ng/mL during the whole study. The number of patients with deviations from the therapeutic window will be counted (separately for values “below” and “above” therapeutic range) and tabulated per visit and in total.

Patients with any trough level value outside the therapeutic window will be described in detail by narratives reporting also Everolimus dose level and dose adjustments, if applicable.

Cyclosporin A

Mean blood level values of Cyclosporin A will be presented in tabular form for each timepoint and as mean value over time. Blood levels will be tried to be kept in therapeutic windows. The number of patients with deviations from the therapeutic window (see section 6.5.2) will be counted and tabulated per visit and in total.

In the CNI-free group mean blood level values of cyclosporin A will be presented in tabular form for each assessment up to Month 8.

Tacrolimus

Mean blood level values of Cyclosporin A will be presented in tabular form for each timepoint and as mean value over time. Blood levels will be tried to be kept in

therapeutic windows. The number of patients with deviations from the therapeutic window (see section 6.5.2) will be counted and tabulated per visit and in total.

In the CNI-free group mean blood level values of Tacrolimus will be presented in tabular form for each assessment up to Month 8.

10.6.8 Pharmacogenetics/pharmacogenomics

No measurements of pharmacogenetics/pharmacogenomics will be done in this trial.

10.6.9 Biomarkers

No biomarkers will be assessed in this trial.

10.7. Interim analysis

No interim analysis is planned.

10.8 Sample size calculation

The probable difference between the CNI-free - and the CNI-group in the GFR is estimated as δ = 8 ml/min with σ = 16 ml/min. With α=.05 (two sided significance level) and 1-β = 90% (power), n=86 patients per group are required to demonstrate superior efficacy of the CNI-free regimen compared to the CNI-group in the GFR using the t-test [redacted]. To compensate for some uncertainty of the assumptions for sample size calculation, the calculated sample size is increased by $\approx$ 15%. Therefore, a total number of N=200 patients (n=100 per treatment group) will be randomized and treated in both treatment arms after Baseline (Month 6 post Tx).

In order to achieve the planned number of randomized patients as exactly as possible which may be hampered by the delay between inclusion (Screening – Month 3 post Tx) and randomization (Baseline - Month 6 post Tx), the rate of non-randomized patients will be determined when 150 patients will be randomized, and extrapolated to a number of 200 randomized patients. Recruitment will be stopped, when 200 patients + 120% of the extrapolated rate of non-randomized patients will be included at Screening. The further 20% of non-randomized patients are considered as a safety margin to avoid underrecruitment of randomized patients.

According to amendment 4, enrollment into this study will be terminated by 31st December 2015, by that time about 165 patients will have been recruited into this trial. Under the assumptions above, this would lead to a power of 82%. Since this sample size will contain also patients who discontinued the trial/medication early or who had other protocol deviations, the actual power will even be somewhat lower.

Under the assumptions specified in the initial protocol, the study will still have 82% power with the now reduced sample size. That means that the scientific value will not

be compromised with 82% probability. However, even if the study should just fail to reach statistical significance, it will most likely still show the presence (or absence) of a non-significant trend, which would contribute to the body of evidence for this treatment option.

11 Discussion and rationale for study design features

A parallel group design is the most appropriate model to show differences between two treatments. The design includes an initial phase of 3 months during which patients are treated according to center standard outside the trial and an additional 3-months Run in phase with a Cyclosporin A or Tacrolimus based immunosuppressive regimen which is required by clinical needs.

Therapy switch from the CNI-based to the CNI-free regimen after randomization follows experiences from previous clinical trials as well as the recommendations of the second German-Austrian Certican Consensus Conference (Rothenburger et al., 2007b, see section 1 of this protocol).

Blinding of the two study treatments was not reasonable in this trial because dosing of Everolimus,, Tacrolimus and Cyclosporin A has to be based upon trough levels. Therefore the study has to be planned open-label. However, the endpoint of the study is GFR which is an objective outcome variable depending on laboratory measures. An influence of open-label treatment on this primary outcome variable is limited because dosing behavior will mainly be governed by drug trough levels but only in a few expected cases of renal toxicity by the creatinine level.

The randomization visit at Month 6 was scheduled at a time-point after Tx when the adapation of the individual organism to the graft is considered stable, on average of all transplant patients. It is to be expected that the immunological risk at this timepoint is lower, and the benefit of CNI elimination will continue. For this purpose, a CNI-free regimen will be compared with a CNI based immunosuppressive regimen. It is expected, that the CNI-free regimen will result in a superior renal function when compared to the CNI -based regimen, while it is as safe and effective as the CNI-based regimen with regard to occurrence of biopsy proven acute rejection episodes of ISHLT 1990 grade ≥ 3A resp. ISHLT 2004 grade ≥ 2R, acute rejection episodes associated with hemodymamic compromise, graft loss / re-transplant, death, and lost to follow up, as well as of treatment failure (composite endpoint).

A maintenance treatment period of about 9 months under the two regimens, CNI-based versus CNI-free, is considered sufficiently long to explore any differences between both groups in the glomerular filtration rate, which is the primary outcome measure.

In summary, the present study design is adequate for investigating the influence of different immunosuppressive regimens with or without CNI on renal function.

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Appendix 1: Administrative procedures

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 2001/83/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

Responsibilities of the investigator and IRB/IEC/REB

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

Informed consent

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. 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 patient source documents.

The informed consent form that complies with regulatory requirements and is considered appropriate for this study is provided separately. Any changes to the consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB / IEC / REB, and a copy of the approved version must be provided to the Novartis monitor after IRB / IEC / REB approval.

Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB / IEC / REB. Only amendments that are required for patient safety may be implemented prior to IRB / IEC / REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any

immediate action required for the safety of any patient 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 / REB at the study site should be informed within 10 working days.

Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical trial agreement.

Study drug supply and resupply, storage, and tracking

Study drugs 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 designated assistants have access. Upon receipt, the study medication should be stored according to the instructions specified on the drug 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. They will include storage conditions for the drug and the randomization number but no information about the patient.

The investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Drug accountability will be noted by the field monitor during site visits and at the completion of the trial. Patients will be asked to return all unused study drug and packaging at the end of the study or at the time of study drug discontinuation.

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

Appendix 2: Clinically notable laboratory values and vital signs

	Notable criteria	
Laboratory variable	**Standard units**	**SI units**
Liver function and related variables		
SGOT (AST)	≥3 × ULN	≥3 × ULN
SGPT (ALT)	≥3 × ULN	≥3 × ULN
GGT	≥3 × ULN	≥3 × ULN
Bilirubin	≥2.0 mg/dL	≥34.2 μmol/L
Alkaline phosphatase	≥3 × ULN	≥3 × ULN
Albumin	None	None
Total protein	None	None
Renal function, metabolic and electrolyte variables		
Urea	None	None
Creatinine	>30% above baseline	>30% above baseline
Uric acid	M ≥12 mg/dL	M ≥714 μmol/L
	F ≥9 mg/dL	F ≥535 μmol/L
Glucose	<45 mg/dL	<2.5 mmol/L
	>250 mg/dL	>13.9 mmol/L
Cholesterol	≥350 mg/dL	≥9.1 mmol/L
Triglycerides	≥750 mg/dL	≥8.5 mmol/L
CPK (MB)	None	None
Sodium	None	None
Chloride	None	None
Potassium	≤3.0 mEq/L	≤3 mmol/L
	≥6.0 mEq/L	≥6 mmol/L
Magnesium	<0.97 mg/dL	<0.4 mmol/L
	>3.65 mg/dL	>1.5 mmol/L
Calcium	≤6 mg/dL	≤1.5 mmol/L
	≥13 mg/dL	≥3.2 mmol/L
Phosphate	None	None
Amylase	≥2 × ULN	≥2 × ULN
Testosterone*	None	None
LH	None	None
FSH	None	None
Lipase	≥2 × ULN	≥2 × ULN

*male patients

Notable criteria

Laboratory variable	Standard units	SI units
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
Urinalysis		
Albumin (mg/dL)	None	None
Glucose (mg/dL)	None	None
Erythrocytes	None	None
Protein/creatinine	<200 mg/g	<22.7 mg/mmol

Harmonized notable vital signs (and weight)

Vital sign variables	Notable criteria
Pulse (beats/min.)	None
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)
Temperature (°C)	None
Weight (kg)	None

Appendix 3: Possible Cyclosporin A drug interactions

All of the individual drugs cited below are well substantiated to interact with Cyclosporin A. In addition, concomitant non-steroidal anti-inflammatory drugs, particularly in the setting of dehydration, may potentiate renal dysfunction.

A) Drugs that may potentiate renal dysfunction

Antibiotics	Antifungals	Gastrointestinal agents
Gentamicin Tobramycin Vancomycin Trimethoprim with-sulfamethoxazole	Amphotericin B Ketoconazole	Cimetidine Ranitidine
Antineoplastics	**Anti-inflammatory drugs**	**Immunosuppressives**
Melphalan	Azapropazon Diclofenac Naproxen Sulindac	Tacrolimus

B) Drugs that alter Cyclosporin A concentrations

Cyclosporin A is extensively metabolized. Cyclosporin A concentrations may be influenced by drugs that affect microsomal enzymes, particularly cytochrome P-450 III-A. Substances that inhibit this enzyme could decrease metabolism and increase Cyclosporin A concentrations. Substances that are inducers of cytochrome P-450 activity could increase metabolism and decrease Cyclosporin A concentrations. Monitoring of circulating Cyclosporin A concentrations and appropriate **Cyclosporin A** dosage adjustments are essential when these drugs are used concomitantly.

Drugs that increase Cyclosporin A concentrations

Calcium channel blockers	Antifungals	Antibiotics
Diltiazem Nicardipine Verapamil	Ketoconazole Fluconazole Itraconazole	Clarithromycin Erythromycin
Glucocorticoids	**Other drugs**	
	Bromocriptine Danazol	

Grapefruit and grapefruit juice affect Cyclosporin A metabolism, increasing blood concentrations of Cyclosporin A, thus should be avoided. Methylprednisolone, Metoclopramide, Allopurinol may have a small influence on Cyclosporin A metabolism, by slightly increasing blood concentrations of CsA. Thus, if patients are on methylprednisolone, metoclopramide, or allopurinol, the dose should be kept stable throughout the trial.

Drugs that decrease Cyclosporin A concentrations

Antibiotics	Anticonvulsants	Other drugs
Nafcillin Rifampin	Phenobarbital Phenytoin	Octreotide

Rifabutin is known to increase the metabolism of other drugs metabolized by the cytochrome P-450 system. The interaction between rifabutin and Cyclosporin A has not been studied. Care should be exercised when these two drugs are administered concomitantly. Troglitazone, Carbamazepine and Ticlopidine may also decrease CsA concentrations, but to a lesser extent. Thus, if patients are on stable therapy with these drugs, the dose should be kept stable throughout the trial, and patients should be closely monitored throughout the study.

Other drug interactions

Reduced clearance of prednisolone, digoxin and lovastatin and simvastatin has been observed when these drugs are administered with Cyclosporin A. In addition, a decrease in the apparent volume of distribution of digoxin has been reported after Cyclosporin A administration. Severe digitalis toxicity has been seen within days of starting Cyclosporin A in several patients taking digoxin. Cyclosporin A should not be used with potassium-sparing diuretics because hyperkalemia can occur.

During treatment with Cyclosporin A, vaccination may be less effective. The use of live vaccines should be avoided. Myositis has occurred with concomitant lovastatin and simvastatin, frequent gingival hyperplasia with nifedipine, and convulsions with high dose methylprednisolone.

Population screen for co-medications influencing Everolimus

Patients concomitantly receiving erythromycin antibiotics (erythromycin or azithromycin) had an average 20% lower Everolimus CL/F than those not receiving these co-medications. A single patient receiving intraconazole had a 3-fold lower Everolimus CL/F compares with the population average. These observations indicate that potent inhibitors of CYP3A can decrease the clearance of Everolimus and increase its blood levels.

Additional drugs or drug classes explored in the population model for which no influence on Everolimus CL/F was detected were: atorvastatin (n=74 patients), pravastatin (n=41), simvastatin (n=18), gemfibrozil (n=10), quinolone antibiotics (n=124), Bactrim® (n=450), and various calcium-channel blockers (dihydropyridines, n=267, diltiazem, n=22 and verapamil, n=5).

Inducers of CYP3A4 (e.g. rifampin, carbamazepine, phenytoin, and barbiturates have been shown or have the potential to decrease exposure to Everolimus, If these drugs are necessary, Everolimus, doses may have to be increased. Potent inhibitors of

CYP3A4 such as ketoconazole, itraconazole and fluconazole should be avoided while the patient is on study medication. Everolimus has the potential to increase the exposure to terfenadine, astemizole and cisapride; hence these drugs should be avoided. In vitro data suggested that Everolimus may have the potential to interact with quinidine, fluoxetine and paroxetine, and alternative medications should be considered. Since the potential for drug interaction with digoxin has not been evaluated, patients on digoxin should have periodic measurement of digoxin levels.

Appendix 4: Possible Tacrolimus Drug-Drug Interactions

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 Cyclosporin A resulted in additive/synergistic nephrotoxicity. Patients switched from Cyclosporin A to Tacrolimus should receive the first Tacrolimus dose no sooner than 24 hours after the last Cyclosporin A dose.

Dosing may be further delayed in the presence of elevated Cyclosporin A levels.

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**
Diltiazem	clotrimazole	clarithromycin
nicardipine	fluconazole	erythromycin
nifedipine	itraconazole	troleandomycin
verapamil	ketoconazole**	
	voriconazole	
Gastrointestinal Prokinetic Agents	Other Drugs	
Cisapride	bromocriptine	

Metoclopramide	chloramphenicol cimetidine Cyclosporin A 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.

***Drugs that may decrease Tacrolimus blood concentrations**

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

*This table is not all inclusive.

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. Based on a clinical study of 5 liver transplant recipients, co-administration of Tacrolimus with nelfinavir increased blood concentrations of Tacrolimus significantly and, as a result, a reduction in the Tacrolimus dose by an average of 16-fold was needed to maintain mean trough Tacrolimus blood concentrations of 9.7 ng/mL. Thus, frequent monitoring of Tacrolimus blood concentrations and appropriate dosage adjustments are essential when nelfinavir is used concomitantly. 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).

Following co-administration of Tacrolimus and sirolimus (2 or 5 mg/day) in stable renal transplant patients, mean Tacrolimus AUC0-12 and Cmin decreased approximately by 30% relative to Tacrolimus alone. Mean Tacrolimus AUC0-12 and Cmin following co-administration of 1 mg/day of sirolimus decreased approximately 3% and 11%, respectively. The safety and efficacy of Tacrolimus used in combination with sirolimus for the prevention of graft rejection has not been established and is not recommended.

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]

Reference: Prograf package Insert, Revised April 2006.

Appendix 5: Dose Reduction of Everolimus and MPA

Dose reduction or temporary interruption may be performed for MPA or Everolimus. However, Everolimus should be continued on a stable dose level, if possible, and reduced or interrupted only if the symptoms do not respond to the reduction of the MPA dosage.

Implementation of dose reduction will be based on thrombocytopenia, leukopenia, neutropenia, hypercholesterolemia, hypertriglyceridemia, 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 restarting or increasing the dose of study medication back to original levels.

In cases of recurrent infections serum antibody concentration should be measured; if hypogammaglobulinemia presents as persistent and clinically significant, patients should be examined accurately and appropriate actions should be taken; dose reduction or change of immunosuppression should be taken into consideration.

Patients with recurrent pulmonary disorders e.g. cough/dyspnea should as soon as possible be examined accurately for signs of bronchiectasis; dose reduction or change of immunosuppression should be taken into consideration.

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 < 2,500/mm³ dose may be reduced at the discretion of the investigator A second dose reduction may be implemented if the WBC continues to fall

Dose Reduction	**EC-MPS**	**MMF**
Maintenance dose	3 tablets 360 mg b.i.d.	3 capsules 500 mg b.i.d.
Initial dose reduction	2 tablets 360 mg	2 capsules 500 mg b.i.d.
Second dose reduction	1 tablet 360 mg + 1 tablet 180 mg b.i.d..	1 capsules 500 mg + 1 capsule 250 mg b.i.d.

Increase or restart of study medication after a drop in platelets / WBC

Increase dose of study medication following a single dose reduction

After a single dose reduction, full dose of study medications **must** restart if:

- platelet count > 100,000/mm³ (at least 3 days)
- WBC > 3,500/mm³ (at least 3 days)

Increase dose of study medication following a double dose reduction

After a double dose reduction the mid dose of study medications **may** be restarted if:

- platelet count > 75,000/mm³ (at least 3 days)
- WBC > 3,500/mm³ (stable) (at least 3 days)

the full dose of study medications **must** be restarted if

- platelet count > 100,000/mm³ (at least 7 days)
- WBC > 3,500/mm³ (stable) (at least 7 days)

Restart of dose of study medication following an interruption

After an interruption of study medications (due to a decrease in platelets/WBC) study medication **may** be restarted at the lowest dose if:

- platelet count > 50,000/mm³ (at least 3 days)
- WBC > 3,500/mm³ (stable) (at least 3 days)

the mid dose of study medications **may** be restarted if:

- platelet count > 75,000/mm³ (at least 3 days)
- WBC > 3,500/mm³ (stable) (at least 3 days)

the full dose of study medications **must** be restarted if

- platelet count > 100,000/mm³ (at least 7 days)
- WBC > 3,500/mm³ (stable) (at least 7 days)

Absolute neutrophil count cutoff levels

A decrease in absolute neutrophil counts (ANC) to less than 1,000/mm³ should be avoided during the study. The investigator should use his/her discretion to reduce the dose of non-study medication known to be associated with neutropenia or leukopenia (e.g. ganciclovir, trimethoprim-sulfamethoxazole) before considering initiating a reduction in the dose of study medication.

Recommendations for adjusting the dose of study medication in case of a decrease in absolute neutrophil counts are as follows:

ANC < 1,500/mm³:	Consider dose reduction (per investigator discretion)
ANC < 1,000/mm³:	Mandatory interruption of study medication

Restart of study medication after a drop in ANC that required interruption of study medication

ANC > 1,500/mm³ for 7 days:	Restart full dose of study medication

Lipid cutoff levels

Evaluations of plasma cholesterol and/or triglyceride levels can result from a number of drugs commonly used in renal transplantation, including study medication, steroids, Cyclosporin A, and other drugs.

If plasma cholesterol and/or triglyceride levels are found to be elevated, the dosing of all concomitant medication potentially affecting cholesterol and/or triglyceride levels should be re-considered and optimized as appropriate, in addition to providing dietary advice.

If plasma cholesterol and/or triglyceride levels are still found to be elevated and the elevation is confirmed by a second measurement (performed within two weeks under fasting conditions [last meal ≥ 8 hours prior to sampling]) treatment based on the National Cholesterol Education Program Adult Treatment Panel II (NCEP ATP II) guidelines (see Appendix 3) should be instituted. The patient's CHD risk should be assessed as the NCEP ATP II guidelines are based on presence/absence of CHD and number of CHD risk factors.

Treatment of elevated lipids should be maximized prior to dose reduction or interruption of study medication.

Based on the National Cholesterol Education Program (NCEP) guidelines (Appendix 3) the recommendations for treatment of hyperlipidemia prior to reduction/interruption of study medication are as follows:

If Total Cholesterol ≥ **250** mg/dL (6.5 mmol/L) and/or

LDL-C ≥ **160** mg/dL (4.1 mmol/L):

Review Concomitant Medication that may potentially contribute to lipid elevations and provide Dietary Instruction (Registered Dietitian)

If Total Cholesterol still ≥ **250** mg/dL (6.5 mmol/L) and/or

LDL-C still ≥ **160** mg/dL (4.1 mmol/L):

Institute Statin (HMG CoA Reductase Inhibitor, e.g. Lescol®) Therapy Unless Contraindicated

If Total Cholesterol still ≥ **250** mg/dL (6.5 mmol/L) and/or

LDL-C still ≥ **160** mg/dL (4.1 mmol/L):

Optimize Statin Therapy and/or Implement Other Lipid Lowering Therapy

If Total Cholesterol still ≥ **250** mg/dL (6.5 mmol/L) and/or

LDL-C still ≥ **160** mg/dL (4.1 mmol/L) and/or

TG ≥ **600** mg/dL (6.9 mmol/L):

Consider Fibrate Therapy for Treatment of Hypertriglyceridemia

If Total Cholesterol still ≥ **250** mg/dL (6.5 mmol/L) and/or

LDL-C still ≥ **160** mg/dL (4.1 mmol/L) and/or

TG still ≥ **600** mg/dL (6.9 mmol/L):

Consider Dose Reduction / Interruption

Recommendations for adjusting the dose of study medication in case of hypercholesterolemia [Total Cholesterol ≥ 250 mg/dL (6.5 mmol/L) and/or LDL-Cholesterol ≥ 160 mg/dL (4.1 mmol/L)] and / or hypertriglyceridemia [TG ≥ 600 mg/dL (6.9 mmol/L)], after treatment of elevated lipids had been maximized, are as follows:

Total Cholesterol and/or **Triglycerides**

= 250 – 750 mg/dL = 6.5 – 19.4 mmol/L	= 600 – 1000 mg/dL = 6.9 – 11.4 mmol/L	Dose reduction should be considered
>750 mg/dL > 19.4 mmol/L	> 1000 mg/dL > 11.4 mmol/L	Study medication should be Interrupted

NB: If a patient is restarting the dose of study medication, the investigator my use his/her discretion with regard to the adjusted dose of study medication, i.e., they are not required to increase doses back to full dose regardless of the platelet or WBC levels, the ANC levels, and/or the cholesterol or triglyceride levels.

Handling of Gastrointestinal Problems

In case of gastrointestinal problems that are caused by the treatment with MPA or Everolimus the first step should be to divide the total daily dose in 3 to 4 single dosages. In case of persisting gastrointestinal complaints, the MPA dosage should be reduced in steps of 360 mg/day until the event resolves.

In the event of gastrointestinal problems that are caused by any other reason (e.g. infections) the medication dosage of MPA and Everolimus should be maintained. Other appropriate actions should be taken based on the investigators' experience and discretion.

Appendix 6: National Cholesterol Education Program Guidelines[1]

Total cholesterol	
Under 200 mg/dL	Desirable
200 – 239 mg/dL	Borderline-high
240 mg/dL and over	High
HDL cholesterol	
Under 35 mg/dL	Low

Treatment based on LDL cholesterol

Diet Therapy	*Initiation Level*	*LDL Goal*
Without CHD and with fewer than 2 risk factors*	160 mg/dL or over	Under 160 mg/dL
Without CHD and with 2 or more risk factors*	130 mg/dL or over	Under 130 mg/dL
With CHD	Over 100 mg/dl	100 mg/dL or under
Drug Treatment	*Initiation Level*	*LDL Goal*
Without CHD and with fewer than 2 risk factors*	190 mg/dL or over	Under 160 mg/dL
Without CHD and with 2 or more risk factors*	160 mg/dL or over	Under 130 mg/dL
With CHD	Over 130 mg/dl	100 mg/dL or under

***CHD Risk Factors:**

Positive

- Age: Men ≥ 45 yrs
  Women ≥ 55 yrs or premature menopause without estrogen replacement therapy
- Family history of premature CHD (definite myocardial infarction or sudden death before 55 yrs of age in father or other male first-degree relative, of before 65 yrs of age in mother or other female first-degree relative)
- Current cigarette smoking
- Hypertension (Blood pressure ≥ 140/90 mmHg [confirmed by measurements on several occasions] or taking antihypertensive medication)
- HDL Cholesterol < 35 mg/dL (0.6 mmol/L)
  (confirmed by measurements on several occasions)
- Diabetes mellitus

Negative:

[1] Data from Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Summary of the second report of the National Cholesterol in Adults [Adult Treatment Panel II] JAMA 269[23]:3015-3023, 1993

- HDL Cholesterol ≥ 60 mg/dL (1.6 mmol/L)
  (confirmed by measurements on several occasions)

Appendix 7: ISHLT Standardized Cardiac Biopsy Grading

Acute Cellular Rejection

2004		**1990**	
Grade 0R[a]	No rejection	Grade 0	No rejection
Grade 1R, mild	Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage	Grade 1, mild	
		A-Focal	Focal perivascular and/or interstitial infiltrate without myocyte damage
		B-Diffuse	Diffuse infiltrate without myocyte damage
		Grade 2, moderate (focal)	One focus of infiltrate with associated myocyte damage
Grade 2R, moderate	Two or more foci of infiltrate with associated myocyte damage	Grade 3, moderate	
		A-Focal	Multifocal infiltrate with myocyte damage
Grade 3R, severe	Diffuse infiltrate with multifocal myocyte damage ± edema, ± hemorrhage ± vasculitis	B-Diffuse	Diffuse infiltrate with myocyte damage
		Grade 4, severe	Diffuse polymorphous infiltrate with extensive myocyte damage ± edema, ± hemorrhage + vasculitis

[a] Where “R” denotes revised grade to avoid confusion with 1990 scheme.

The presence or absence of acute antibody-mediated rejection (AMR) may be recorded as AMR 0 or AMR 1, as required (see below)

Nonrejection Biopsy Findings

2004	1990
Ischemic injury	Ischemic injury
Early – up to 6 weeks post-transplant	A = up to 3 weeks post-transplant
Late – related to allograft coronary disease	B = late ischemia
Quilty effect	Quilty effect
	A = no myocyte encroachment
	B = with myocyte encroachment
Infection	Infection
Lymphoproliferative disorder	Lymphoproliferative disorder

Recommendations for Acute Antibody-Mediated Rejection (AMR)

2004		1990
AMR 0	Negative for acute antibody-mediated rejection No histologic or immunopathologic features of AMR	
AMR 1	Positive for AMR Histologic features of AMR Positive immunofluorescence or immunoperoxidase staining for AMR (positive CD68, C4d)	Humoral rejection (positive immunofluorescence, vasculitis or severe edema in absence of cellular infiltrate) recorded as additional required information

(Lit: Stewart S et al., 2005)