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Clinical Development

RAD001/Everolimus/Certican®

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

Statistical Analysis Plan (SAP)

Author:	███████████████████
Document type:	SAP Documentation
Document status:	Final 1.0
Release date:	02-JUN-2017
Number of pages:	25

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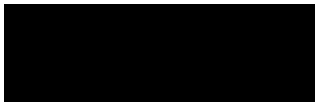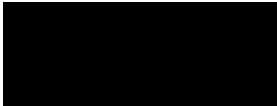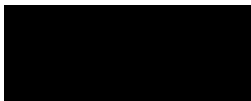
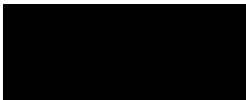Signature   Date

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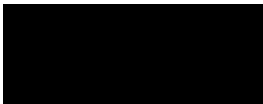
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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
02-Jun-2017	Prior to DB lock	Creation of final version	N/A - First version	NA

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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
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DSMB	Drug Safety Monitoring Board
EBV	Epstein Barr virus
ECG	Electrocardiogram
ENR	Enrolled Patient Population
EC-MPS	Enteric Coated Mycophenolate Sodium (Myfortic®)
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, Certican®
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

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

1 Introduction

This Statistical Analysis Plan describes the implementation of the statistical analysis planned in the protocol.

1.1 Study design

This was a prospective, multi-center, randomized, controlled, parallel group, open label study in heart transplant recipients. Enrollment was terminated at 31st December 2015 with a protocol amendment. At that time 162 de novo heart transplant patients have been randomized to the two treatment groups at Baseline visit (Month 6 post Tx). The patients were recruited from 9 transplant centers in Germany.

During the first three months post Tx the patients may have been treated according to center standards. Latest after study inclusion (Month 3 post Tx ±2 weeks), the patients received 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 was confirmed by additional in- and exclusion criteria were randomized and hence allocated to one of the two treatment groups in a 1:1 ratio in the following way:

A randomization list was produced 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 was 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 was specified in a separate document which was withhold from the study centers. The randomization list was kept sealed in a secure location.

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

Randomization of individual patients was performed centrally by a CRO. Allocation of a patient to one of the two treatment groups was performed in the following steps.

1. Information about patient enrollment (Screening Visit – Month 3 post Tx): Study sites informed the randomization department of the CRO about each patient inclusion via fax.

2. Randomization (Baseline Visit – Month 6 post Tx): At day of randomization, the site provided the information of eligible patient to the CRO by fax. The CRO randomization department allocated the patient the next free consecutive randomization number allocated to the site. Randomization number and allocated treatment (according to the randomization list) were provided to the site by fax.

Patients then either received an immunosuppressive regimen consisting of a CNI (Tacrolimus or Cyclosporin A) with Everolimus with corticosteroids or were switched to the CNI-free regimen in the following way:

Starting the day following the Month 6 assessment, Cyclosporin A was reduced to ≤75 ng/mL (according to C0 level) or Tacrolimus was 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 was added to the patient´s immunosuppressive regimen. Consequently, patients received a transitional immunosuppressive regimen of Cyclosporin A or Tacrolimus and Everolimus and MPA or MMF until complete switch to the CNI-free regimen was achieved at 9 months post Tx.

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

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

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

Obligatory biopsies were obtained at Month 6, 9, 12, 18. Facultatively biospsies may have been obtained at every study visit.

Statistical analysis and report writing was performed when all patients had completed Month 18 after Tx assessment.

The primary analysis of renal safety and tolerability concerned 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.

No interim analysis was conducted.

1.2   Study objectives and endpoints

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 of the protocol)

2   Statistical methods

2.1   Data analysis general information

All statistical analyses were performed ███████████████████████████████ ██████████████████████████████ Analysis was carried out using the SAS (Statistial Analysis System) software, version 9.2, 2009, SAS Institute Inc., Cary, North Carolina, USA.

Analyses were done when all patients had completed the trial at 18 months post Tx (or discontinued prematurely).

The following periods were 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 was 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 initial 3 months period between Screening and Baseline visit (**run-in period**) was analyzed with regard to treatment, efficacy, and safety of the immunosuppressive regimen.

In patients who discontinued prematurely from the study, the last available information under study treatmentwas analyzed.

Adverse events were analyzed separately for the initial 3 months period between Screening and Baseline visit (**Run-in period**) and for the randomized treatment period between Baseline visit (Month 6) and Month 18.

Significant events like rejection episodes, hemodynamic compromise, and MACE were additionally analyzed for the period between transplantation and Screening (Month 3 post Tx) (**Pre-screening period**).

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

Data from all centers that participated in this study were combined and the factor center was included in the analysis of the primary endpoint.

2.1.1   General definitions

Study drug:

The term "Study drug" refers to any drug administered to the patient as part of the required study procedures.

Certican®/ Everolimus was investigationsal drug. Sandimmun®Optoral/Cyclosporin A, Prograf®/Tacrolimus and MPAs (Myfortic®/EC-MPS or CellCept®/MMF) were considered as study drug as well. Corticosteroids were handled in the same way as concomitant medication.

Date of first administration of study drug:

"Date of first administration of study drug" is defined as the first intake of study medication which should start within 5 days preceding the Screening visit and be documented on the Everolimus therapies CRF.

Baseline:

"Baseline" in the sense of "baseline value" means all values collected at Baseline visit at month 6 or, if not available, the corresponding value collected at Screening visit.

Last contact:

Last date a contact with the patient is documented, e.g. date of study visit, telephone call, letter, etc.

2.2   Analysis sets

The **Enrolled Patient Population (ENR)** includes all patients who signed an informed consent regardless whether they received study treatment or not.

The **Safety Population (SAF)** consists 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 also include patients who were randomized but not treated with the randomized medication.

The **Full Analysis Set (FAS)** consists 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 (PP)** consists of all FAS 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 period at Month 18 according to protocol. Criteria that are assumed to have such an impact were defined before analysis during the Blind Review Meeting and are documented in the Appendix, section 5.6 Rule of exclusion criteria of analysis sets.

For the period before Baseline visit (Month 6) the enrolled patient population was divided by randomization status into randomized patients and not randomized patients.

2.2.1   Subgroup of interest

2.3   Patient disposition, demographics and other baseline characteristics

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

Medical history was coded using MedDRA and was presented by system organ class, MedDRA preferred term and treatment group. Separate tables were provided for past medical condition and current medical condition. Prior medication was 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 $\geq$ 3A resp. ISHLT 2004 grade $\geq$ 2R, acute rejection associated with hemodynamic compromise, graft loss / re-transplantation, death) were determined and properly described for the run-in period between Screening (Visit 1, Month 3 post Tx) and Baseline (Visits 2, Month 6 post Tx).

The two treatment groups were compared descriptively with respect to these variables.

No formal statistical testing was conducted for comparability purposes.

2.3.1   Patient disposition

Patient disposition was summarized for all patients by absolute and relative frequencies of patients completing the study phases screening, randomization, treatment and study completion. Reasons for discontinuation of screening, treatment and study were shown by

treatment for all patients (screening) resp. the Randomized Set (treatment and study). The number of patients per analysis set was summarized by treatment.

Protocol violations were reported descriptively by treatment and a listing was generated for each treatment for all screened patients.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Duration (days) of Everolimus application were summarized. Dose interruptions, i.e. days with dose of 0 mg were considered for calculation of duration. Daily Everolimus dose levels were summarized with mean, standard deviation, minimum, median, and maximum by visit. Dosage averages were 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. Assignment of the DAR records to the visits were calculated based on the visit dates. Reasons for dose adjustments (including temporary dose interruption) were presented by frequency distribution. These frequencies of dose reduction (including temporary dose interruption) for safety reasons as per protocol guidelines were presented by study period. Permanent treatment discontinuations were analyzed by frequencies.

These analyses were performed per treatment group, for the SAF population and related to the study periods in the randomized treatment period (see section 2.1 Data analysis general information). For the run-in period, duration and mean daily dose were summarized for the ENR population displaying both, randomized versus not randomized patients as well as the inial treatment groups CNI+MPA versus CNI+ Everolimus

Daily Cyclosporin A and Tacrolimus doses adjusted by the patients' visit-specific body weight and MPA doses were summarized by visit and in the same way as Everolimus. Data were presented separately for each treatment group. Induction therapy (Basiliximab or ATG or no induction) received by patient was summarized by treatment group, for the SAF population. The distribution of the specific CNI medications was summarized by treatment 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 were determined. Reasons for dose adjustments (including temporary dose interruption) were presented by frequency distribution. Permanent treatment discontinuations were analyzed using frequency distribution. All other immunosuppressive therapies were summarized by ATC (Anatomical, Therapeutic, Chemical) classes.

All analyses were presented per treatment group and study period (see 2.1 Data analysis general information).

2.4.2   Prior, concomitant and post therapies

Medications other than those mentioned in section 2.4.1 taken concomitantly with the study medication were summarized by treatment group and study period through frequency tables. Concomitant medication was coded and summarized according to the ATC classification system.

2.5   Analysis of the primary objective

2.5.1   Primary endpoint

The primary aim of this study was 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 (cGFR/MDRD).

The primary variable for assessment of renal function was the

- glomerular filtration rate (GFR) at Month 18, as assessed by the MDRD method (recalculated values, see Appendix, section 5.1.2 Calculated GFR.

2.5.2   Statistical hypothesis, model, and method of analysis

The null hypothesis H_0 of similar GFR level in both treatment groups

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

was 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 was set to a two-sided $\alpha=0.05$. Adjusted means (=LS-means, LS: least square means) were presented for the treatment contrast of GFR at Month 18 post Tx together with its confidence interval and a two-sided p-value.

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

2.5.3   Handling of missing values/censoring/discontinuations

If a patient discontinued from the study prematurely missing data with respect to the target parameter were substituted by the last recorded value (last observation carried forward, LOCF). The LOCF method was only applied if a patient had at least one assessment after Baseline, i.e. on Visits Months 8 to 18. Otherwise, the patient was excluded from efficacy analysis within the FAS population. Prematurely performed month 18 visits were shifted to the closest visit following the date of last observation.

Patients of the FAS population who switched from the CNI group to the CNI-free group during the study or during follow-up, were analyzed in their randomized group.

Additionally, sensitivity analysis was performed with a repeated measurement analysis.

2.5.4   Supportive analyses

The primary analysis was once more performed with the PP set (as observerd analysis, AOA)

The course of the GFR was of special interest. Changes from Baseline to each post-baseline measure were calculated by treatment group for each study visit.

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) was compared between the two regimens. For group comparison, a Fisher's exact test was calculated.

Additionally to the analyses of data from the interval between BL (Month 6) and Month 18, the primary outcome variable was also evaluated for the interval between Screening (Month 3) and Baseline (Month 6).

In addition to the LOCF method described above, missing values were handeled with an adapted LOCF method (LOCF-2), where the last recorded value under the initially given treatment after randomization was used for substitution of the missing data.

Results from these supportive analyses were interpreted in an explorative manner.

2.6   Analysis of secondary efficacy objective(s)

2.6.1   Secondary endpoints

The following secondary efficacy variables were 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 $\geq$ 3A resp. ISHLT 2004 grade $\geq$ 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

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

- Renal function as assessed by Cockcroft-Gault at month 12 and 18 after Tx

- Serum creatinine and reciprocal creatinine slope (1/serum creatinine versus time) including the treatment period between BL (Month 6) and Month 18

2.6.2   Statistical hypothesis, model, and method of analysis

Event data:

Event rates were estimated using the Kaplan-Meier method to handle patients who discontinue the treatment prior to suffering from an event adequately. Time to event was defined as the time from date of randomization to the first documented date of the event. The two groups were compared using the log-rank test.

This procedure was 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 were provided for each biopsy proven acute rejection, graft loss, or death.

Tolerability:

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

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

Additionally, tolerability of study medication was 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. The frequency distribution of these reasons was presented with absolute and percent values. The most frequent reasons (total n $\geq$ 5) for discontinuation and/or conversion as well as the total number of patients who are affected by such intolerability of study medication were compared between the two treatment groups using the exact Fisher test.

2.6.3   Handling of missing values/censoring/discontinuations

Missing values were imputed with the last observation carried forward (LOCF) method described at section 2.5.3.

2.7   Safety analyses

2.7.1   Adverse events (AEs)

Safety variables were analyzed separately

- for the period between Screening and Baseline (run-in period)

- for the period between Baseline and Month 9 (switch period)

- for the period between Month 9 and Month 18 (maintenance period)

- for the period between Baseline and final assessment (Month 18 or date of premature withdrawal from the study) (randomized treatment period),.

For the randomized treatment period, analyses of treatment emergent adverse events were performed according to the treatment group into which the patients were randomized.

All analyses of safety parameters were based on the safety population. For the period between Screening and Baseline visit summaries of all adverse events were displayed for the ENR population by randomization status, i.e. randomized versus not randomized patients.

The key safety variables which were analyzed are 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 were analyzed by treatment group.

AEs/Infections:

Generally, infections data were analyzed together with AE data. In addition, infection data were analyzed separately.

Data collected by AE CRFs and by Infection CRFs and CMV-CRFs were coded with the MedDRA dictionary that gives preferred term and body system information. The incidence of AEs were summarized by body system, preferred term, severity, and relationship to study drug. All information pertaining to AEs noted during the study were 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 was also 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 was tabulated. AEs occurring 30 or more days after the discontinuation of study medication were not included in AE/infection summary tables.

2.7.1.1   Adverse events of special interest / grouping of AEs

No adverse events of special interest were defined.

2.7.2   Deaths

Treatment deaths were summarized together with serious treatment emergent adverse events and other significant treatment emergent advese events by treatment group for the Safety Set (SAF).

Furthermore, deaths were analyzed as composite part of the secondary endpoints treatment failure and major adverse cardiac events for the Full Analysis Set (FAS).

2.7.3   Laboratory data

Abnormalities according notable criteria (see Appendix 2 of study protocol) were identified. The proportions of patients with clinically notable abnormalities according to the notable criteria were summarized. Shift tables describing changes from status prior transplantation (Month 0) and Baseline based on the expanded normal limits were 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 was defined as the highest or lowest measure during the different observations periods whereby

high or low were 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 were presented by visit. A by-patient listing of all laboratory data (with clinically notable abnormalities being flagged) was generated. Only assessments obtained up to 2 days after the discontinuation of study medication were considered "on-treatment" and analyzed with relationship to Everolimus.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

Any clinically significant abnormalities were presented as past/current medical condition.

2.7.4.2 Vital signs

Vital signs variables included measurements of oral body temperature, systolic and diastolic blood pressures, pulse and body weight. Vital signs were examined for abnormal values and change from Baseline according to pre-specified clinically notable criteria (see Appendix 2 of study protocol). Appropriate incidence rates of clinically notable abnormalities for between-group differences were provided. Further, descriptive statistics of change from baseline of all vital signs variables were presented by visit. A by-patient listing of all vital signs (with clinically notable abnormalities being flagged) was generated. Shift tables describing changes from baseline based on clinically notable criteria were presented for treatment endpoint (Month 18) and worst on-treatment observations. Only assessments obtained up to 2 days after the discontinuation of study medication were considered "on-treatment".

2.8 Pharmacokinetic endpoints

Analysis of the Cyclosporin A, Tacrolimus and Everolimus blood levels were done by treatment group and separately for the treatment periods (after Month 6).

Everolimus:

Mean blood level values of Everolimus were presented in tabular form for each timepoint (visit window) and as mean value over time. The number of patients with deviations from the therapeutic window (see section 5.1.4 Target therapeutic ranges) were 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 were described in detail by narratives reporting also Everolimus dose level and dose adjustments, if applicable.

Cyclosporin A:

Mean blood level values of Cyclosporin A were presented in tabular form for each timepoint and as mean value over time. Blood levels were tried to be kept in therapeutic windows. The number of patients with deviations from the therapeutic window (see section 5.1.4 Target therapeutic ranges) were counted and tabulated per visit and in total.

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

Tacrolimus:

Mean blood level values of Tacrolimus were presented in tabular form for each timepoint and as mean value over time. Blood levels were tried to be kept in therapeutic windows. The number of patients with deviations from the therapeutic window (see section 5.1.4 Target therapeutic ranges) were counted and tabulated per visit and in total.

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

2.9   PD and PK/PD analyses

Pharmacogenetics/pharmacogenomics were not assessed in this trial.

2.10   Patient-reported outcomes

No health-related Quality of Life assessment was performed in this study.

2.11   Biomarkers

No biomarkers were assessed in this trial.

2.12   Other Exploratory analyses

No additional exploratory analyses were performed.

2.13   Interim analysis

No interim analysis was conducted.

3   Sample size calculation

The probable difference between the CNI-free - and the CNI-group in the GFR was 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 were required to demonstrate superior efficacy of the CNI-free regimen compared to the CNI-group in the GFR using the t-test ███████████ ██████████████. To compensate for some uncertainty of the assumptions for sample size calculation, the calculated sample size was increased by ≈ 15%. Therefore, a total number of N=200 patients (n=100 per treatment group) were initially planned to be randomized and treated in both treatment arms after Baseline (Month 6 post Tx).

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

4   Change to protocol specified analyses

Missing data for the primary outcome variable were dealt with the LOCF method according to protocol, but instead of an additional replacement with the mean of the non-missing values, the LOCF2 method (as described in section 2.5.4) as well as repeated measures analysis (see section 2.5.3) were used.

Not randomized patients were considered for the run-in period but not for the randomized treatment period.

5   Appendix

5.1   Definitions

5.1.1   Study periods

The following study periods were used for analysis:

- Pre-screening period: Tx – V1/M3/Screening

- Run-in period: V1/M3/Screening – V2/M6/Baseline

- Randomized treatment period: V2/M6/Baseline – V7/M18/EOS

    - Swith period: V2/M6/Baseline – V4/M9

    - Maintenance period: V4/M9 – V7/M18/EOS

In the event of a patient's premature discontinuation, the respective period was defined till the last assessment within this period.

For patients who discontinue prematurely from the study, ~~both~~, the last available information under study treatment was analyzed.

5.1.2   Calculated GFR

MDRD formula

$$cGFR \; [ml/min] = 170 \; \times serum \; creatinie[mg/dl]^{-0.999} \times age[years]^{-0.176} \times urea \; nitrogen[mg/dl]^{-0,17} \times albumin[g/dl]^{0.318} \times C$$

with C=1 for men and C=0.762 for women
and *urea nitrogen* = urea/2.144

Cockcroft-Gault formula

$$cGFR \; [ml/min] = \frac{D \; \times (140 - age[years]) \times Body \; Weight \; [kg]}{72 \; \times Serum \; Creatinine \; [mg/dl]}$$

with D=1 for men and D=0.85 for women

Age[years]: calculated as ("Visit date" [days] – "Date of birth" [days]) / 365.25

Age, *Body Weight* and all serum variables were taken from the respective visit. Missing values of *Body Weigth* were imputed by carrying forward the last known observation, if *Body Weigth* was missing at Screening (V1/M3), the first non-missing observation was carried backward.

5.1.3   Objectives

Steroids

- Source: Other Immunosuppressive Therapies

- Occurrence: "Immunosuppressive therapy" WHO ATC codes H02 and L04

Treatment failure

Treatment failure was defined as a composite endpoint of biopsy proven acute rejection of ISHLT 1990 grade $\geq$3A (ISHLT 2004 grade $\geq$2R), acute rejection episodes associated with hemodynamic compromise, graft loss / re-transplant, death, loss to follow up (at least one condition must be present).

Biopsy proven acute rejection

- Source : Endomyocardial biopsy CRF at respective visit

- Occurrence: "ISHLT grade / 1990" in ("Grade 3A", "Grade 3B", "Grade 4") AND/OR "ISHLT grade / 2004" in ("Grade 2R moderate", "Grade 3R severe")

- Date of event: "Date of biopsy"

Acute rejection episodes associated with hemodynamic compromise

- Source: Endomyocardial biopsy CRF at respective visit

- Occurrence: "Is hemodynamic compromise present?" = 1 ("Yes")

- Date of event: "Date of biopsy"

Graft loss

- Source: Hospitalization CRF

- Occurrence: "Primary reason for hospitalization" = 20 ("Graft loss")

- Date of event: "Date of admission"

Loss to follow-up

- Source: Study completion CRF

- Occurrence: "Primary reason for premature discontinuation" = 8 ("Lost to follow-up")

- Date of event: "Last known date subject took study drug"

MACE

Major Adverse Cardiac Evets (MACE) were defined as one of the following: any death, myocardial infarction, coronary artery bypass grafting

Prior to Screening, MACE are documented on the Relevant medical history CRF, section "Major Adverse Cariac Events". After start of study drug, MACE are documented on the Adverse Event CRF.

Death

- Source: Study completion CRF
- Occurrence: "Primary reason for premature discontinuation" = 10 ("Death")
- Date of event: "Date of death"

Myocardial infarction

- Source: Adverse Events CRF
- Occurrence: "Advese event" MedDRA PT in (10000891, 10028596, 10066592, 10049768) AND/OR "Mark if AE meets definition of MACE"=1 (ticked)
- Date of event: "Start date"

Coronary artery bypass grafting

- Source: Adverse Events CRF
- Occurrence: "Advese event" MedDRA PT = 10011077 AND/OR "Mark if AE meets definition of MACE"=1 (ticked)
- Date of event: "Start date"

Specific adverse events

Adverse Events leading to permanent discontinuation of study drug

- Source: Adverse Events CRF / Infections CRF/CMV CRF
- Occurrence: "Action taken" = 2 ("Study drug permanently discontinued due to this adverse event/infection")

Infections

- Source: Adverse Events CRF / Infections CRF/CMV CRF
- Occurence: Infections are all treatment emergent adverse events with MedDRA SOC = 10021881 (Infections and infestations) or events verified as infections after medical review (not necessarily coded as "Infections and infestations").

5.1.4   Target therapeutic ranges

Everolimus

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

Cyclosphorin A

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

From Month 3 up to Month 6: 100 – 200 ng/mL. After Month 6: 50 – 150 ng/mL.

In the CNI-free group the Cyclosporin A will be reduced to a dose resulting in a C0 level of $\leq$ 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.

Tacrolimus

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

From Month 3 up to Month 6: 5-10 ng/mL. After Month 6: 3-8 ng/mL.

In the CNI-free group the Tacrolimus will be reduced to a dose resulting in a C0 level of $\leq$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.

5.2   Imputation rules

5.2.1   Study drug

In case of missing or partial start date, the start date should be shifted to earliest possible date, but not earlier than the Screening visit. Missing or partial end dates should be shifted as far back as possible but not later than the last known date subject took study drug (from Study Completion CRF).

5.2.2   AE date imputation

In case of missing or partial start date or end date of an AE, the start date should be shifted to the earliest possible date, but not earlier than the first intake of study drug while the end date should be shifted as far back as possible.

5.2.3   Concomitant medication date imputation

In case of missing or partial start date or end date of a concomitant medication, the start date should be shifted to the earliest possible date, but not earlier than the first intake of study drug while the end date should be shifted as far back as possible.

5.2.3.1   Prior therapies date imputation

In case of missing or partial start date or end date of a prior therapy, the dates should be shifted to the earliest possible date, but not earlier than the first intake of study.

5.2.3.2   Post therapies date imputation

In case of missing or partial start date or end date of a post therapy, the start date should be shifted to the earliest possible date, but not earlier than the first intake of study drug while the end date should be shifted as far back as possible.

5.2.3.3   Other imputations

5.3   AEs coding/grading

5.4   Laboratory parameters derivations

Clinically notable laboratory values and vital signs are defined in chapter 12, Appendix 2 of the study protocol.

5.5   Statistical models

5.5.1   Primary analysis

5.5.2   Key secondary analysis

5.6   Rule of exclusion criteria of analysis sets

The rules for subject classification in the analysis sets are defined in the VAP Module 3 "CRAD001ADE14_Module 3_ Protocol Deviations_Final1.1_31-Mai-2017.doc" and the DRM protocol "Protocol_DRM_20170522.docx".

6   Reference

Not applicable