

Clinical Development

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

## **RAP Module 3 – Detailed Statistical Methodology**

### **Amendment 5**

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### Document History – Changes compared to the previous version of RAP module 3

Date	Changes
25-Jan-2016	<ul style="list-style-type: none"><li>• For multiple renal function assessments within a visit window, guidelines given in section 1.1 were insisted to be followed, i.e., the closest value to the planned visit instead of the average will be taken for imputation.</li><li>• Type of induction was identified as the first intake of rATG or basiliximab by Day 1 post-transplant.</li></ul>
16-Feb-2016	<ul style="list-style-type: none"><li>• Modified the 12-month analysis cut-off day: Month 12 Visit + 2 Weeks;</li><li>• Modified the definition of NODM NMQ; The terms 'pre-transplantation/ prior to or at randomization' replaced with 'prior to or at baseline' and post-transplantation/ post-randomization to 'post-baseline'</li></ul>
26-Feb-2016	<ul style="list-style-type: none"><li>• Inserted PD IDs for major PDs</li></ul>
10-Nov-2016	<ul style="list-style-type: none"><li>• Re-organized the sections to match the new SAP template</li><li>• <b><u>The following analyses were removed:</u></b><ul style="list-style-type: none"><li>• Risk analysis for the primary endpoint</li><li>• Subgroup analysis for other secondary efficacy endpoints, except for tBPAR and eGFR&lt;50 at 12 months</li><li>• Per protocol analysis for secondary and other secondary points</li><li>• Imputation methods using LOCF and penalty-based adjustment</li></ul></li><li>• <b><u>The following details were added:</u></b><ul style="list-style-type: none"><li>• Compliance set population was added</li><li>• Analysis of "study treatment"</li><li>• Definition of MACE</li><li>• The population and imputation methods were added for different analysis</li><li>• Analysis method for imputed datasets</li><li>• SAS codes for multiple imputation, and back-to-control imputation were added</li><li>• Disposition summary, prior- and concomitant medication were added</li><li>• Definition of initial CNI stratum and CNI switch</li><li>• Definition of MPA compliance</li></ul></li><li>• <b><u>The following revisions were made:</u></b><ul style="list-style-type: none"><li>• Definition of on-treatment period for AE summary: to be consistent with the whole program, 7-days is used</li><li>• The list of (co)variates in different models was changed and harmonized</li><li>• The imputation of concomitant medication start day</li><li>• The visit window table</li></ul></li><li>• Changed the imputation rule for incomplete AE/CM start/end dates</li><li>• Revised the definition of last contact day</li><li>• Revised the covariates for the multiple imputation (removed M1 eGFR)</li></ul>



Date	Changes
20-Feb-2017	<ul style="list-style-type: none"><li>• Clarified the definition of compliance</li><li>• [REDACTED]</li><li>• Revised the liver function criteria</li><li>• Added that prednisone and equivalent was not used during study as major deviation for PP</li><li>• Added the table of selection criteria for FAS and SAF</li><li>• Specified HLA mismatch as categorical variable (<math>\leq 3</math> or <math>&gt; 3</math>) in statistical models</li><li>• Specified Kenward-Roger method for denominator degrees of freedom in mixed effect model. Used "Study Day" instead of "subject" in the random statement.</li><li>• Added dummy code for mixed effect model</li><li>• Defined treatment-emergent AE</li><li>• Added program specific safety risk events</li><li>• Added safety events for clinical trial safety disclosure</li><li>• Added notable lab abnormalities in the list of newly occurring abnormality criteria</li><li>• Updated the visit windows</li><li>• Added details for multiple imputation and the control-based imputation</li><li>• Changed Month 1 to Week 4. Changed "subject" to "patient"</li></ul>
27-Feb-2018	<ul style="list-style-type: none"><li>• Added discontinuation reasons hierarchy when several study drugs are affected</li><li>• In laboratory assessments, for multiple observations in the same visit window, the worst case is selected</li><li>• The last disposition date will be defined as the latest date in the database (across all visit dates itself, all visit related assessment dates, other assessment dates, event dates (start and end), medication dates).</li></ul>

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## 1 Introduction

This document presents detailed Statistical Analysis Plan (SAP) of study CRAD001A2433 entitled “A 24 month, multicenter, randomized, open-label safety and efficacy study of concentration-controlled everolimus with reduced calcineurin inhibitor vs mycophenolate with standard calcineurin inhibitor in de novo renal transplantation- Advancing renal TRANSplant eFficacy and safety Outcomes with an eveRolimus-based regiMen (TRANSFORM)”. This document covers futility, 12-month and 24-month analyses. Notable examples of analyses only to be performed at Month 12 (and not Month 24) include the non-inferiority analyses for the primary endpoint (tBPAR or eGFR(MDRD4) < 50 ml/min/1.73m<sup>2</sup>) and the key secondary endpoint (tBPAR, graft loss or death), the superiority analysis for the primary endpoint, and the analysis for compliant patients.

## 2 Statistical Methods

Twelve-month and 24-month data will be analyzed by Novartis according to the data analysis section 9 of the study protocol which is available in [Appendix 16.1.1 of the CSR](#), unless otherwise indicated. Important information is given in the following sections and details are provided. The futility analysis is described in [Section 2.12.1](#), and will be performed by the CRO of Quanticate.

All statistical analyses, tables and data listings will be produced using SAS® statistical software, Version 9.4 (or higher) for Unix.

### 2.1 Data Analysis General Information

The cut-off day is defined as the latest study day before and up to which data will be used in the analysis on an individual patient level. The cut-off date for 12-month analysis will be the day of Month 12 Visit (specifically, Date of Discontinuation/Study Phase Completion as recorded on the Month 12 Disposition eCRF) + 2 Weeks, but no later than Day 450 (upper limit of Month 12 analysis window). For the 24-month analysis, there will be no cut-off day. All data in the clinical database will be used for the analyses.

Data listings will include all data collected up to the cut-off date for the 12-month analysis, or all data recorded in the database for the 24-month analysis.

For summary tables and figures, the following rules will be applied unless otherwise indicated:

- Categorical data will be summarized by frequencies and percentages. Continuous data will be summarized by mean, median, standard deviation, minimum and maximum and the number of non-missing data points.
- All AE/Infection, notable events, CMV information, EBV information and other events of interest will be summarized based on all collected events with onset on or after the first day of study medication up to the cut-off date or seven days after last dose of study medication. For SAE/infection and death, all events will be summarized.
- All lab or vital sign tables will include data up to the cut-off date or two days after last dose of study medication (on-treatment analysis);

- Efficacy and renal function analyses will be primarily based on all available data including those after study medication discontinuation; as a sensitivity analysis they will include only data up to two days after last dose of study medication (on-treatment analysis). Patients will be censored for the time to event analyses if they do not have an event. For on-treatment analysis, the censoring day is two days after discontinuation of study medication or the last contact day, whichever is earlier; for analysis regardless of on-treatment or off-treatment, the censoring day is the last contact day.
- For post-baseline continuous values, for a given patient, if multiple numeric measurements for a given variable are reported within the same visit window (see the definition for visit windows in [Section 4.1](#)), the following rule will be applied:
  - For quantitative measures including EVR/CsA/TAC trough levels, the closest value to the planned visit (baseline visit: date of transplant; other visits: midpoint of visit window) is taken (if tie, the last will be used).
  - For qualitative (categorical) assessment, the worst value of all records observed in the visit window will be used. An event defined on a quantitative measure is also a qualitative (categorical) assessment. For example, ALT >3x ULN; the highest (worst) value is compared to the ULN.

Details about the definition of efficacy and safety events, data handling conventions including the ‘re-aligned’ visit windows, imputation of missing dates, and other details can be found in the [Section 4](#).

## 2.1.1 General Definition

### 2.1.1.1 Study Day

The date of randomization is defined as **Day 1**.

A study day is defined as the number of days since the randomization and for a particular date it is calculated as follows:

Study day = Assessment date – randomization date + 1.

Day 1 is the reference point for separating pre- and post-randomization. For assessments performed before Day 1, the calculation is as follows:

Study day = Assessment date – randomization date.

### 2.1.1.2 Date of Last Dose

In general a study regimen stops if the combination is not given anymore, i.e. the date of last dose of study regimen is the earliest ‘date of last dose’ among the study drugs contained in the study regimen.

However, for the investigational regimen containing everolimus, the date of last dose of study regimen is the date of the last intake of the investigational drug everolimus. This is a conservative approach in that any events occurring while still taking everolimus will be considered on-treatment events, even if the complete regimen is no longer being administered.



### 2.1.1.3 Last Contact Day

The last contact day for the 12-month analyses will be determined by screening the 12-month database and taking the maximum of any dates found post-randomization. If the maximum date is after the cut-off date for the 12-month analysis, use the cut-off day as the last contact day for the 12-month analysis.

The last contact day for the 24 months analyses corresponds to the last recorded date in the database (across all visit dates itself, all visit related assessment dates, other assessment dates, event dates (start and end), medication dates). It should be prior to or on the day of study completion and therefore dates of events which occur after study completion will not be considered.

### 2.1.1.4 Baseline

The baseline value is the last non-missing value prior to the randomization.

The baseline body weight should be taken as the last non-missing weight prior to randomization. It is anticipated that in some cases, *baseline body weight* may be missing. In such cases, when used to derive other variable (i.e. dose per body weight), *baseline body weight* will be taken from the next available visit on the *Vital signs* form. However, in summary statistics of vital signs data, missing baseline body weights will be treated as missing. The exact algorithm to derive *baseline body weight* is as follows: it is the *last* assessment of any evaluations done up to the date of randomization; if there is no such assessment, it will be the *first* assessment taken after the date of randomization.

The baseline height will be derived in a similar way as the baseline body weight. Subsequently, BMI will be calculated.

### 2.1.1.5 On-Treatment

An *on-treatment* observation will be any assessment obtained on and after Day 1 but no later than two days after the discontinuation of randomized study medication. However, for AE/Infection, notable events, CMV information, EBV information and other events of interest, events occurring up to seven days (inclusive) after discontinuation of study medication are considered “*on-treatment*”.

## 2.2 Analysis Sets

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

The **compliance set** (CS) consists of all patients in the FAS who are compliant for both CNI and investigational drug (EVR/MPA). Compliance is defined in [Section 2.4.2](#).

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

- Patient received multiple solid organ or tissue transplants (PD ID: EXCL04)
- Renal cold ischemia time > 30 hr (PD ID: INCL04)
- Patient received kidney from a non-heart beating donor (PD ID: INCL06)
- Patient Stratified incorrectly (PD ID: TRT08)
- Patient randomized but did not receive study drug (EVR or MPA) (PD ID: TRT01)
- Patient received treatment other than what they were randomized to (PD ID: TRT07)
- Induction agent other than basiliximab or rATG used (PD ID: TRT05)
- Patient did not receive any basiliximab or rATG for induction use (PD ID: TRT06)
- Prohibited Concomitant Medication used (PD ID: COMD03)
- Prednisone or equivalent was not used during the study (PD ID: TRT14)

The **safety set (SAF)** consists of all patients who received at least one dose of study drug. Patients will be analyzed according to their actual treatment regimen and according to the actual stratum they initially belong to. All safety analyses will be performed on the SAF.

Patients who did not sign the study main informed consent form will be excluded from any analysis sets (FAS, PPS, CS, and SAF). If a patient was mis-randomized due to documented (IVRS) administrative error (eligibility criteria), but received study drug, this patient will belong to both FAS and SAF. [Table 2-1](#) illustrates the selection of patients for the FAS and SAF.

**Table 2-1 Selection of patients for the full-analysis set and the safety set**

IC	TX	RND	Mis-RND	RX	Dataset(s)
No	Y/N	Y/N	Y/N	Y/N	Exclusion
Yes	No	No	No	No	Screening failure
Yes	Yes	No	No	No	Randomization failure
Yes	Yes	Yes	No	Y/N	FAS
Yes	Yes	Yes	Yes	Yes	FAS
Yes	Y/N	Y/N	Y/N	Yes	SAF
Yes	No	Yes	Yes	No	Exclusion
Yes	Yes	Yes	Yes	No	Exclusion
Yes	No	Yes	No	No	Exclusion

IC=informed consent, Tx=transplantation, RND=randomization, Rx=study treatment

### 2.2.1 Subgroup of Interest

The following demographic/baseline characteristics are defined at the study level as subgroups for specified analyses:

- Recipient characteristics:
  - Age group: <60 vs ≥60 yr
  - Gender
  - Race: Caucasian, Black, Asian and All other races
  - Region: US, EU, Asia, Australia, Latin America, and Middle East

- DGF (delayed graft function)
- BMI <30 and  $\geq 30$
- Donor/transplant characteristics:
  - Age group: <60 vs  $\geq 60$  yr
  - Gender
  - Cold ischemia time: < 20 vs  $\geq 20$  hr
  - End stage disease leading to transplant (Glomerular disease, Diabetes mellitus and All other diseases)
  - Donor type (living donor, standard criteria and expanded criteria deceased donor): donor type will be derived based on Kidney Donor Background Information eCRF, and not the randomization stratification from IRT.
  - HLA mismatches:  $\leq 3$  vs  $> 3$
- CNI (tacrolimus vs. cyclosporine)
- Induction (basiliximab vs. rATG):
  - Basiliximab: preferred term: BASILIXIMAB; drug code/ID: 10892631
  - rATG: preferred term: ANTITHYMOCYTE IMMUNOGLOBULIN, or ANTITHYMOCYTE IMMUNOGLOBULIN (RABBIT); drug code/ID: 10878131 or 10878151

As early use of rATG can be for delayed graft function, type of induction will be identified as the first intake of rATG or basiliximab by Day 1 post-transplant.

## 2.3 Patient Disposition, Demographics and Baseline Characteristics

### 2.3.1 Patient Disposition

Patient disposition will be summarized in terms of the number and percentage of patients who complete the screening, prematurely discontinued from study medication and from study (by primary reasons). When there are multiple reasons for discontinuation associated to study drugs and CNI that happened the same day, the primary reason will be the one related to, by order of priority, Everolimus, Tacrolimus, MPA and Cyclosporine. The number of patients in the different analysis sets, incidence of protocol deviations, and incidence of major protocol deviations and other deviation criteria leading to exclusion from per-protocol set will be summarized by treatment group. Listings of screen failure and study completion with primary reasons for premature discontinuation of the randomized study treatment will also be provided.

In addition, the following listings will be presented:

- Screen failure
- Study completion status
- Protocol Deviations (PDs)
- Major protocol deviations and other deviation criteria leading to exclusion from per-protocol set
- Patients excluded from any analysis sets

### 2.3.2 Patient Demographics and Baseline Characteristics

Demographic and background information will be summarized based on the FAS population.

Incidence rates of diabetes at baseline (see the definition in [Section 2.8.3.3](#)) and delayed graft function will be also summarized.

Delayed graft function is defined when any of the following criteria are met within 21 days (end day of Week 2 visit window) after transplant:

- AE eCRF page: MedDRA lower level term includes words: “graft dysfunction” or “graft function delayed”; verbatim contains “delayed graft function” or “DGF”.
- Kidney Allograft Rejection eCRF page: “Primary reason rejection was suspected” = Delayed or slow recovery of graft function post-revascularization” or “Primary clinical diagnosis” = “delayed graft function”.

### 2.3.3 Medical History

Relevant medical history/current medical conditions will be summarized by primary system organ class, preferred term, and treatment group. Frequencies and percentages of patients in the FAS in each treatment group will be presented.

## 2.4 Treatments

The following descriptive analyses will be performed on the SAF by treatment group and total, unless otherwise stated.

### 2.4.1 Study Treatment

#### Duration of Exposure

Duration of exposure to study medication for SAF patients with a specified end date (date of last dose of study medication), i.e. for patients who permanently discontinued from study treatment or patients who completed the study:

Duration of exposure = (Date of last dose of study medication – Date of first dose of study medication + 1)

Duration of exposure to study medication for SAF patients without a specified end date:

Duration of exposure = (Date of Month 12 study cut-off date – Date of first dose of study medication + 1)

Note that duration of exposure includes periods of temporary interruption of study medication.

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

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

### Average Daily Doses and Body Weight-Adjusted Average Daily Doses

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

### Dose Changes and Interruptions

The number and percentage of patients with dose interruptions/adjustments will be summarized by reason for change and by the number of adjustments (any, one, two, three, more than three).

### Switching CNIs

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

### Trough Levels of Study Drugs

Everolimus, cyclosporine and tacrolimus trough levels (in ng/mL) will be summarized at each visit window using descriptive statistics, and the incidence rates of patients below, within or above the trough level target ranges at each visit will be presented for patients on treatment at that visit. The target ranges for CsA and TAC trough levels are provided in [Table 2-1](#). The target range for everolimus trough levels is 3-8 ng/mL throughout the study.

Box plots of everolimus, cyclosporine and tacrolimus trough levels will be presented by visit for each treatment group. The target trough level ranges will be shown in the plots.

**Table 2-2 CNI trough level target ranges**

Study Visit	Tacrolimus target ranges		Cyclosporine target ranges	
	EVR arm	MPA arm	EVR arm	MPA arm
Day 1 ≤ Month 2	4-7 ng/mL	8-12 ng/mL	100-150 ng/mL	200-300 ng/mL
Month 3 ≤ Month 6	2-5 ng/mL	6-10 ng/mL	50-100 ng/mL	150-200 ng/mL
Month 7 ≤ Month 24	2-4 ng/mL	5-8 ng/mL	25-50 ng/mL	100-200 ng/mL

## 2.4.2 Compliance

### 2.4.2.1 Compliance for MPA

For each day, a patient is compliant to MPA as long as this patient takes MPA (non-compliant when MPA was off). If a patient is compliant for at least 70% of days on study, then this is a compliant patient.

### 2.4.2.2 Compliance for CNI/EVR:

To evaluate patient compliance for CNI/EVR, CNI/EVR trough levels will be imputed (see [Section 4.2.2](#) for details) for each day from the date of the first dose of the respective study drug (CNI/EVR) to the maximum study drug on-treatment date, which is defined as the minimum of (the date of the last study drug dose plus two days or the last contact day). For each day, patient compliance will be assessed by comparing the imputed trough level with the corresponding

target trough level range. If a patient was compliant for at least 70% of days on study, then this is a compliant patient.

### 2.4.3 Prior/Concomitant Medication

Medications will be identified using the NovDTD including Anatomical Therapeutic Chemical (ATC) code. Prior medications are defined as drugs taken prior to the first dose of randomized study medication regardless of whether they continue thereafter. Any medication given at least once between the date of the first dose and the last dose of randomized study medication will be defined as concomitant medication, including those started before randomization and continued into the treatment period. Any medication started after the discontinuation of randomized study medication will not be considered as concomitant medication. Prior or concomitant medication will be identified based on recorded or imputed start and end dates. Rules for imputing incomplete (start and end) dates are described in [Section 4.2.4](#).

Prior and concomitant medications will be summarized by treatment group and total in separate tables for SAF. Medications will be presented in alphabetical order, by ATC codes and grouped by *anatomical main group* (the 1<sup>st</sup> level of the ATC codes). Tables will show the overall number and percentage of patients receiving at least one drug within a particular ATC code and at least one drug in a particular anatomical main group.

#### 2.4.3.1 Steroids

Steroids will be displayed using prednisone equivalent body weight adjusted doses. The doses displayed in the following table are considered equivalent. To determine prednisone equivalent doses, doses will be multiplied by the conversion factor shown in [Table 2-2](#). To adjust the dose, the body weight measured closest to the start of a steroid dose will be used (from vital signs eCRF).

**Table 2-3 Steroids conversion factors**

WHO drug code	Preferred Term Corticosteroid	Equivalent Dose [mg]	Conversion Factor
000447xx	Prednisone	5	1
000162xx	Prednisolone	5	1
000496xx	Methylprednisolone	4	1.25
012428xx	Meprednisone	4	1.25
001867xx	Prednylidene	40/7	0.875
000319xx	Triamcinolone	4	1.25
000146xx	Cortisone	25	0.2
000286xx	Hydrocortisone	20	0.25
002131xx	Fludrocortisone	2	2.5
000085xx	Betamethasone	0.75	20/3
000664xx	Paramethasone	2	2.5
000160xx	Dexamethasone	0.75	20/3
008827xx	Deflazacort	6	5/6
006445xx	Cloprednol	3	5/3

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

### 2.4.3.2 Immunosuppressive Therapies

All immunosuppressive medications will be summarized by ATC code, WHO preferred term and treatment group as follows:

- Concomitant other than study medication (cyclosporine, everolimus, tacrolimus & MPA)
- Taken after early discontinuation of randomized study medication

### 2.4.3.3 Lipid-Lowering Drugs

Any medication with ATC code C10A will be considered lipid-lowering drugs. Lipid-lowering agents will be grouped by ATC code and summarized by WHO preferred terms. For any of these medications, the number of patients (and percentage) receiving at least one dose *concomitantly* with randomized study medication will be displayed; this will not include any drugs started after the discontinuation of study medication.

## 2.5 Analysis of Primary Objective

### 2.5.1 Primary Endpoint

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

### 2.5.2 Statistical Model, Hypothesis, and Method of Analysis

The primary analysis will be performed on the Full Analysis Set following the intent-to-treat principle.

#### Testing of CNI effects:

Based on FAS without imputation, treatment by CNI interaction for the composite endpoint of tBPAR or eGFR (MDRD4) < 50 mL/min/1.73m<sup>2</sup> will be assessed using a logistic regression model including covariates/factors for treatment, CNI, region, interaction of treatment and CNI, interaction of treatment and region, donor type, HLA mismatch ( $\leq 3$  vs  $> 3$ ), induction therapy, recipient gender, recipient age, donor age, DGF, and eGFR (MDRD4) at Month 1. In the model, recipient and donor age will be treated as continuous variables. If the interaction is not significant at the level of 0.10, i.e. the effects of treatment are similar for each CNI, then the primary analysis will be based on the pooled CNIs, i.e. everolimus plus reduced CNI (EVR+rCNI) vs. MPA plus standard CNI (MPA+sCNI). If this test shows significantly different event rates for tacrolimus vs. cyclosporine, then testing will be performed for the 2 CNIs separately, with the tacrolimus subgroup being considered primary [REDACTED]

#### Testing strategy to control type I error:

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

- a. Non-inferiority of EVR+rCNI vs. MPA+sCNI will be evaluated based on the primary endpoint of tBPAR or eGFR (MDRD4)  $< 50 \text{ mL/min/1.73m}^2$  at Month 12 using a 10% non-inferiority margin (see [Section 2.5.2.1](#)).
- b. Non-inferiority of EVR+rCNI vs. MPA+sCNI will be evaluated with a 10% non-inferiority margin for the key secondary endpoint of tBPAR, graft loss or death at Month 12 (see [Section 2.6.2](#)).
- c. Superiority of EVR+rCNI to MPA+sCNI will be evaluated based on the primary endpoint of tBPAR or eGFR (MDRD4)  $< 50 \text{ mL/min/1.73m}^2$  at Month 12 (see [Section 2.5.2.2](#)).

The above hierarchical fixed hypothesis testing procedure will not inflate overall Type I error rate. Therefore, each hypothesis will be tested at the one-sided 0.025 significance level and no multiplicity adjustment is needed. For these statistical tests, one-sided p-values will be presented in the analysis outputs.

### 2.5.2.1 Non-Inferiority of Everolimus Plus Reduced CNI to MPA Plus Standard CNI

#### The null hypothesis:

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

#### The alternative hypothesis:

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

The proportion of patients meeting the primary endpoint of tBPAR or eGFR (MDRD4)  $< 50 \text{ mL/min/1.73m}^2$  at Month 12 will be compared using a confidence interval approach.

Multiple imputation will be used as the primary method for handling missing data (see [Section 2.5.3](#) and [Section 4.2.1.1](#) for detail). The analysis first creates multiple (100) imputations of missing eGFR (MDRD4) values under a missing at random (MAR) assumption, resulting in multiple (100) imputed datasets. The imputation model assumes a multivariate normal model for the eGFR (MDRD4) measurements. This model will be estimated separately within each treatment stratum. Together with the tBPAR data, the binary composite endpoint of tBPAR or eGFR (MDRD4)  $< 50 \text{ mL/min/1.73m}^2$  at Month 12 post-transplantation will be derived.

To the resulting 100 imputed datasets, the proportion of patients meeting the primary endpoint of tBPAR or eGFR (MDRD4)  $< 50 \text{ mL/min/1.73m}^2$  at Month 12 will be estimated, yielding 100 sets of parameter estimates and associated covariance matrices. The analysis results are then combined according to Rubin's rules to derive overall estimates and confidence intervals that adequately reflect missing data uncertainty as well as associated p-values (see [Section 4.7.1](#) for sample analysis codes). The everolimus plus reduced CNI arm will be claimed to have a



non-inferior incidence of tBPAR or eGFR (MDRD4)  $< 50$  mL/min/1.73m<sup>2</sup> compared to the MPA plus standard CNI arm if the upper limit of the 95% CI is below 10%.

### 2.5.2.2 Superiority of Everolimus Plus Reduced CNI to MPA Plus Standard CNI

#### The null hypothesis:

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

#### The alternative hypothesis:

H<sub>A3</sub>:  $R_{\text{EVR+tCNI}} - R_{\text{MPA+sCNI}} < 0$ : the proportion of patients experiencing tBPAR or eGFR (MDRD4)  $< 50$  mL/min/1.73m<sup>2</sup> at 12 months in the everolimus plus reduced CNI (R<sub>EVR+tCNI</sub>) arm is less than that in the MPA plus standard CNI arm (R<sub>MPA+sCNI</sub>) arm.

Following the aforementioned hierarchical fixed hypothesis testing procedure, the hypothesis H<sub>03</sub> for superiority of EVR plus reduced CNI to MPA plus standard CNI will be evaluated only if non-inferiority of EVR plus reduced CNI vs. MPA plus standard CNI is achieved for the primary endpoint (rejecting the hypothesis H<sub>01</sub>) and the key secondary endpoint of tBPAR, graft loss or death at Month 12 (rejecting the hypothesis H<sub>02</sub>, see [Section 2.6.2](#)). The everolimus plus reduced CNI arm will be claimed to be superior to the MPA plus standard CNI arm with respect to composite endpoint of tBPAR or eGFR (MDRD4)  $< 50$  mL/min/1.73m<sup>2</sup> at 12 months if the upper limit of the 95% CI estimated in [Section 2.5.2.1](#) is less than 0.

### 2.5.3 Handling of Missing Values/Censoring/Discontinuations

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

For the component of eGFR  $< 50$  mL/min/1.73m<sup>2</sup>, a value for missing eGFR as a continuous variable will be imputed first (see [Section 4.2.1.1](#) for the main imputation), then dichotomized it to derive this endpoint. As allograft biopsy data will be collected on an as needed basis due to the nature of kidney transplant studies, no particular rule for missing biopsy will be applied.

### 2.5.4 Supportive Analyses

#### 2.5.4.1 Analysis on Treatment Compliant Patients

The analysis outlined for the primary endpoint in [Section 2.5.2](#) will be repeated using Compliant Set.

#### 2.5.4.2 Analysis on Per-Protocol Set

The analysis outlined for the primary endpoint in [Section 2.5.2](#) will be repeated using the Per-Protocol Set.

### 2.5.4.3 Subgroup Analysis

Subgroup analyses will be done for the primary composite endpoint of tBPAR or eGFR (MDRD4) < 50 mL/min/1.73m<sup>2</sup> at 12 months for the subgroups defined in [Section 2.2.1](#). Subgroup analyses will use similar methods described in [Section 2.5.2.1](#).

### 2.5.4.4 Analyses with Other Imputations for Missing eGFR (MDRD4) at Month 12

In addition to the main imputation, additional imputation method assuming missing not at random (MNAR) as provided in [Section 4.2.1.2](#) will be used to impute missing 12-month eGFR value to define the primary variable – composite endpoint of tBPAR or eGFR (MDRD4) < 50 mL/min/1.73m<sup>2</sup>. With these imputations, non-inferiority and superiority analyses described in [Section 2.5.2](#) will be repeated.

## 2.6 Analysis of Key Secondary Objective

### 2.6.1 Key Secondary Endpoints

The key secondary endpoint is the binary composite efficacy failure of tBPAR, graft loss or death at Month 12 post-transplantation.

### 2.6.2 Statistical Model, Hypothesis, and Method of Analysis

For the key secondary objective regarding the composite efficacy failure of tBPAR, graft loss or death, the following hypotheses will be evaluated ( $\alpha=0.025$ , one-sided) only if non-inferiority of EVR plus reduced CNI vs. MPA plus standard CNI is achieved for the primary endpoint (rejecting the hypothesis  $H_{01}$ ), and will be based on the Full Analysis Set:

**The null hypothesis:**

$H_{02}$ :  $REVR_{+CNI} - R_{MPA+sCNI} \geq 0.10$  (non-inferiority margin): the difference in Kaplan-Meier event rate of the composite efficacy failure of tBPAR, graft loss or death at 12 months between the everolimus plus reduced CNI ( $REVR_{+CNI}$ ) and the MPA plus standard CNI arm ( $R_{MPA+sCNI}$ ) is at least 10%.

**The alternative hypothesis:**

$H_{A2}$ :  $REVR_{+CNI} - R_{MPA+sCNI} < 0.10$  (non-inferiority margin): the difference in Kaplan-Meier event rate of the composite efficacy failure of tBPAR, graft loss or death at 12 months between the everolimus plus reduced CNI ( $REVR_{+CNI}$ ) and the MPA plus standard CNI arm ( $R_{MPA+sCNI}$ ) is less than 10%.

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

A Kaplan-Meier table and plot will be produced. The differences between the two KM curves, corresponding to the two treatment arms, will be tested pair-wise using the log-rank test. In

these analyses, patients with event-free will be censored with the censoring time as defined as the Last Contact Day.

### **2.6.3 Handling of Missing Values/Censoring/Discontinuations**

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

### **2.6.4 Supportive Analyses**

As supportive analyses, this non-inferiority analysis will be repeated using the Per-Protocol Set. Based on FAS, Kaplan-Meier event rates at Month 12 will be summarized for the subgroups defined in [Section 2.2.1](#).

## **2.7 Analysis of Other Secondary Objective**

### **2.7.1 Other Secondary Endpoints**

Other secondary efficacy variables to be considered are as follows:

1. Composite endpoint of tBPAR or eGFR (MDRD4)  $< 50$  mL/min/1.73m<sup>2</sup> at Month 24
2. Composite endpoint of tBPAR excluding grade IA rejections or eGFR (MDRD4)  $< 50$  mL/min/1.73m<sup>2</sup> at Months 12 and 24
3. Composite efficacy failure of tBPAR, graft loss, or death at Month 24
4. Composite efficacy failure of tBPAR, graft loss, death, or loss to follow-up at Month 12 and 24
5. Components of composite efficacy failure as well as BPAR, AR, tAR at Month 12 and Month 24
  - a. AR
  - b. tAR
  - c. BPAR
  - d. tBPAR
  - e. tBPAR excluding grade IA rejections;
  - f. Humoral rejection
  - g. Graft loss
  - h. Death.
6. Composite endpoint of tBPAR, graft loss, death or eGFR  $< 50$  mL/min/1.73m<sup>2</sup> at Months 12 and 24
7. Composite endpoint of graft loss or death at Month 12 and Month 24
8. Composite endpoint of BPAR, graft loss or death at Month 12 and Month 24
9. eGFR (MDRD4)  $< 50$  mL/min/1.73m<sup>2</sup> at Month 12 and Month 24

10. Renal function (eGFR by MDRD4, CKD-EPI and Cystatin C-based formulae) at Month 12 and Month 24
11. Renal function change from Week 4 to Month 12 and Month 24
12. Evolution of renal function (eGFR by MDRD4) from Week 4 to Month 12 and Month 24 (slope analyses).

## 2.7.2 Statistical Model, Hypothesis, and Method of Analysis

### 2.7.2.1 Endpoints with eGFR (MDRD4) < 50 mL/min/1.73m<sup>2</sup> as a Component

Similar analysis method used for primary endpoint ([Section 2.5.2.1](#)) will be performed for the endpoint of eGFR (MDRD4) < 50 mL/min/1.73m<sup>2</sup> and the composite endpoints with eGFR (MDRD4) < 50 mL/min/1.73m<sup>2</sup> as a component based on the FAS. Difference between the event rates, and the corresponding 95% confidence interval and p-value for equality test will be provided. The multiple imputation presented in [Section 4.2.1.1](#) will be applied for missing eGFR (MDRD4) values.

- eGFR (MDRD4) < 50 mL/min/1.73m<sup>2</sup> at Months 12 and 24
- composite endpoint of tBPAR or eGFR (MDRD4) < 50 mL/min/1.73m<sup>2</sup> at Month 24
- composite endpoint of tBPAR excluding grade IA rejections or eGFR (MDRD4) < 50 mL/min/1.73m<sup>2</sup> at Months 12 and 24
- composite endpoint of tBPAR, graft loss, death or eGFR (MDRD4) < 50 mL/min/1.73m<sup>2</sup> at Months 12 and 24

In addition, the composite endpoint of tBPAR or eGFR (MDRD4) < 50 mL/min/1.73m<sup>2</sup> at Month 24 will be analyzed in similar manner based on compliant set population. The endpoint of eGFR (MDRD4) < 50 mL/min/1.73m<sup>2</sup> at Month 12 will be summarized on the FAS for the subgroups defined in [Section 2.2.1](#).

### 2.7.2.2 Endpoints without eGFR (MDRD4) < 50 mL/min/1.73m<sup>2</sup> as a Component

Based on FAS, for the composite efficacy failure (tBPAR, graft loss or death) at Month 24 and the composite endpoint of BPAR, graft loss or death at Month 12 and Month 24, Kaplan-Meier event rates will be estimated and compared between the everolimus plus reduced CNI and the MPA plus standard CNI arm. Similarly Kaplan-Meier event rates will be estimated and compared for AR, tAR, BPAR, tBPAR, tBPAR excluding grade IA rejections, AMR, graft loss, death, the composite endpoint of graft loss or death, and composite endpoint of tBPAR, graft loss, death, or loss to follow-up at Months 12 and 24. Kaplan-Meier event rate difference, 95% confidence interval and p-value for equality test will be provided. To assess time-to-event occurrence, Kaplan-Meier tables and plots will be produced with a log-rank test p-value for the above variables.

In addition, severity of tBPAR will be tabulated by treatment. The endpoint of tBPAR at Month 12 will be summarized on the FAS for the subgroups defined in [Section 2.2.1](#)

Forest plots of event rate differences for **all** efficacy endpoints specified in [Section 2.7.2](#) will be produced on the FAS.

## 2.7.3 Analysis of Renal Function Endpoints

Formulas for computing GFR endpoints can be found in [Section 4.5](#).

### 2.7.3.1 eGFR by CKD-EPI and Cystatin C-based Formulae

The renal function (eGFR by CKD-EPI and Cystatin C-based formulae) analyses will be based on on-treatment analysis without imputation. Renal function and change from Week 4 will be summarized by visit with descriptive statistics. A two-sided t-test will be performed to compare the two treatment groups at each visit. A plot of mean and 95% CI of eGFR by visit will be provided.

### 2.7.3.2 eGFR by MDRD4

The eGFR by MDRD4 analyses will be based on FAS with multiple imputation used as the primary method for the handling of missing data. Renal function and change from Week 4 will be summarized by visit with descriptive statistics. A two-sided t-test will be performed to compare the two treatment groups at each visit. A plot of mean and 95% CI of eGFR (MDRD4) by visit will be provided. These will be repeated for on-treatment renal function analyses.

In addition, if different CNI effect is shown from the logistic regression, eGFR(MDRD4) and change in eGFR(MDRD4) from Week 4 by visit will be summarized for the subgroups of CNI (CsA and TAC).

The proportion of patients by eGFR(MDRD4) range (<30, 30-<45, 45-<60, ≥60 mL/min/1.73m<sup>2</sup>) will be summarized by visit.

For eGFR(MDRD4) at Month 12 and Month 24, analysis of covariance (ANCOVA) will be performed with covariates/factors of treatment, CNI, region, interaction of treatment and CNI, interaction of treatment and region, donor type, HLA mismatch (≤3 vs >3), induction therapy, recipient gender, recipient age, donor age, DGF, and eGFR (MDRD4) at Month 1. In the model, recipient and donor age will be treated as continuous variables. The missing Month 12 or Month 24 values will be imputed using the primary multiple imputation method.

The evolution of renal function (eGFR by MDRD4) will be evaluated via a mixed effect model with intercept and study day as random effects and using covariates/factors treatment, study day, CNI, region, interaction of treatment and study day, interaction of treatment and CNI, interaction of treatment and region, donor type, HLA mismatch (≤3 vs >3), induction therapy, recipient gender, recipient age, donor age, DGF, and eGFR (MDRD4) at Month 1. In the model, study day, recipient and donor age, and eGFR (MDRD4) at Week 4 will be treated as continuous variables. Unstructured variance-covariance can be assumed, and the eGFR (MDRD4) data at Week 4 and onward will be used. The denominator degrees of freedom will be calculated using the Kenward-Roger method. No imputation will be applied for missing data. Based on the mixed effect model, the treatment groups will be compared, slope of renal function evolution for each treatment group will be assessed, and eGFR(MDRD4) value at Month 12/24 will be estimated.

See dummy SAS codes below.

```
proc mixed method=ml;
  class trt CNI region donor HLA induction gender_r DGF usubjid;
```

```
model eGFR= trt day CNI region trt* day trt*CNI trt*region donor HLA
induction gender_r age_d age_r DGF eGFR_1 / ddfm=kr;
random intercept day / patient=usubjid type=UN;
run;
```

## 2.8 Safety Evaluation

Safety variables to be assessed include discontinuation from study, discontinuation from treatment, AE/infection, SAE, notable events, laboratory tests, and vital signs. All safety analyses will be done on the safety set.

### 2.8.1 AEs Including Infections

Generally, infection data are analyzed together with AE data. In addition, infection data will be analyzed separately. Micro-organism will be additionally coded with NovORG dictionary. AEs and infections here refer to treatment-emergent events (on-treatment analysis by including data up to 7 days after the discontinuation of study drug). Treatment-emergent adverse events are defined as adverse events or infections that started after the first dose of randomized study medication or events present prior to the first dose of randomized study medication but that increased in severity. Selected variables will be analyzed using all available data including data assessed beyond study treatment discontinuation: SAEs and deaths.

In all summaries about incidence rates of AEs/Infections, if a patient had multiple occurrences of an AE, the patient will be counted only once in the corresponding AE category. If a patient had multiple adverse events within a system organ class, he or she will be counted only once for that class. If a patient had multiple severity ratings for an AE, he or she will only be counted under the maximum rating.

The following AEs/infections will be analyzed by system organ class and preferred term:

- Any events (AEs/infections)
- Frequent events ( $\geq 10\%$  in any treatment group)
- Events requiring study drug dose adjustment or temporary interruption
- Events leading to premature discontinuation of study drug
- Events suspected to be study drug related
- Events requiring study drug dose adjustment or temporary interruption or leading to premature discontinuation of study drug
- Events by maximum severity
- Serious events (SAEs/serious infections)
- Serious events suspected to be study drug related
- Death

Subgroup analyses will be done for AEs and SAEs including infections for the following subgroups:

- CNI (tacrolimus vs. cyclosporine)
- Region: US, EU, Asia, Australia, Latin America, and Middle East

Summaries by standard MedDRA query (SMQ) level (level 1 to 4, SMQ - narrow search) and preferred term will be produced for AEs and SAEs including infections, with relative risks and their 95% confidence intervals displayed.

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

The MedDRA version used for reporting the study will be indicated as a footnote in the outputs.

## Infections

The derivation of the infection type (viral, bacterial, fungal, and others) is based on the coded microorganism. Microorganisms are coded with NovORG (Novartis Organism Dictionary). The codes in NovORG are text strings of seven characters, L-*abcde*, where *a, b, c, d*, and *e* may be numbers or letters, e.g., L-1E601 (for *enterococcus faecalis*), L-24801 (for *staphylococcus aureus*) and L-43131 (for *candida albicans*). The 3<sup>rd</sup> character, *a*, will be used to determine infection type defined in [Table 2-3](#).

**Table 2-4 Novartis Organism Dictionary Categories for Infections**

<b>NovORG Code</b>	<b>Infection Type</b>
L-1bcde, L-2bcde	Bacterial
L-3bcde	Viral
L-4bcde	Fungal
L-xbcde, where x ≠ 1,2,3,4.	Other
Infections may not have been cultured or may have been recorded on the Adverse Events eCRF, for all such events the organism type is unknown	Unknown

In addition to summarizing infections together with AEs, the infections will be also tabulated by infection type (viral, bacterial, fungal, and others) and micro-organism of infections.

### 2.8.2 Safety Events of Interest

Safety events of interest, such as risks defined in the Safety Profiling Plan, Risk Management Plan or events of interest regarding signal detection or routine analysis are defined in the Program Case Retrieval Sheet (CRS) that is stored in CREDI at the path Cabinets/CREDI Projects/R/RAD001A/Integrated Medical Safety.

The following safety events of interest will be summarized with the number and percentage of patients experiencing the events, together with risk ratios (RRs) and 95% CIs. The version of the Case Retrieval Sheet used for the analyses will be described in a footnote. This includes MedDRA version and NMQ (Novartis MedDRA Queries) dictionary date.

- Anemia: Haematopoietic erythropenia (SMQ, broad search)



- Gastrointestinal ulcers: Gastrointestinal ulceration (SMQ, narrow search)  
This is a sub-SMQ under "Gastrointestinal perforation, ulceration, haemorrhage or obstruction (SMQ – narrow search)"
- Interstitial lung disease (CRS)
- Hyperlipidemia (CRS)
- Major cardiovascular events: Ischaemic heart disease and Cardiac failure (SMQ narrow search)
- Malignancy (CRS)
- NODM (See [Section 2.8.3.3](#))
- Peripheral edema (CRS)
- Proteinuria (associated chronic kidney disease) (CRS)
- Pleural effusion: MedDRA preferred term "Pleural effusion"
- Renal failure, excluding proteinuria (CRS)
- Stomatitis/mouth ulceration (CRS)
- Thrombocytopenia: Haematopoietic thrombocytopenia (SMQ, narrow search)
- Thrombotic and thromboembolic events: Embolic and thrombotic events (SMQ)
- Thrombotic microangiopathy (CRS)
- Wound healing events/disorders or complications: See [Section 4.4.1](#).

### 2.8.3 Program Specific Safety Risk Events

The following program specific safety risk events as defined in the Program CRS will be summarized with the number and percentage of patients experiencing the events, together with risk ratios (RRs) and 95% CIs.

- Angioedema
- Chronic allograft nephropathy
- Edema (including peripheral edema)
- Everolimus and calcineurin inhibitor (CNI) induced renal dysfunction
- Exposure in pregnancy/breast-feeding women
- Hyperlipidemia
- Impaired male fertility
- Infections
- Infections (Polyomavirus infection)
- Interstitial lung disease
- Leukopenia and pancytopenia
- Malignancy
- New onset diabetes mellitus (NODM)
- Proteinuria (AE based definition)
- Proteinuria (lab based definition)
- Renal graft thrombosis
- Stomatitis and Mouth ulceration
- Teratogenicity



- Thrombotic microangiopathies (TMA)
- Venous thrombosis
- Wound-healing complications

## 2.8.4 Other Safety Events

### 2.8.4.1 CMV

The incidence of CMV infection within each treatment group will be tabulated by donor versus recipient CMV serology pattern. Other CMV infection-related information including CMV syndrome, CMV disease with organ involvement will be tabulated by treatment group.

Additionally, CMV infection, syndrome and disease will be analyzed by donor/recipient CMV serology status pre-transplantation and CMV prophylaxis. Within each CMV serology status, the Cochran Mantel Haenszel test will be used to examine differences between the treatment arms adjusting for the presence/absence of CMV prophylaxis. CMV prophylaxis is defined as the use of antiviral drugs specified in [Table 2-4](#) within 14 days of transplantation that are taken consecutively for 30 days or more.

**Table 2-5 CMV prophylaxis**

ATC code	Drug code	WHO preferred term
J05AB	00587301	aciclovir
J05AB	00587302	aciclovir sodium
J05AB	00784201	ganciclovir
J05AB	00784202	ganciclovir sodium
J05AB	01226201	famciclovir
J05AB	01269701	valaciclovir
J05AB	01269702	valaciclovir hydrochloride
J05AB	01319501	penciclovir
J05AB	01542201	valganciclovir
J05AB	01542202	valganciclovir hydrochloride
J05AD	00731301	foscarnet
J06BB	00849701	immunoglobulin cytomegalovirus

### 2.8.4.2 BKV

The incidence of BKV infection will be tabulated for each treatment group:

- Any BKV infection
- BKV infection with a urinary or serological sign
- Clinical or laboratory indicated BKV infection
- BKV infection with an organ involvement (histological evidence)

### 2.8.4.3 New Onset Diabetes

A patient is identified as not having diabetes at baseline if all of the following conditions are met:

- Diabetes was not reported as a medical history in Relevant medical history panel (MedDRA preferred term containing diabetic or diabetes);
- No prior diabetic medication with ATC level 2 code “A10” taken prior to baseline.
- Glucose (random) < 11 mmol/L (200 mg/dl), or fasting glucose measurements < 7 mmol/L (126 mg/dl) at the time of transplantation;

For patients who do not have diabetes at baseline, new onset of diabetes will be identified if any of the following conditions are met:

- Diabetes is reported as an adverse event (MedDRA preferred term containing diabetic or diabetes) with a date of onset (AE start date) post-baseline.
- Any concomitant medication with ATC level 2 code “A10” used in diabetes, if administered for more than 2 consecutive weeks post-baseline.
- Fasting glucose measurements  $\geq 7$  mmol/L (126 mg/dl) post-baseline on two separate occasions, or glucose (random)  $\geq 11$  mmol/l (200 mg/dl) on two separate occasions.

The date of onset will be the earliest date when any of the above conditions is met. Depending on the onset date, a patient will be identified as having DM prior to baseline if the date is prior to or at baseline, and a patient will be identified as have DM post-baseline if the date is after baseline.

In addition, new onset diabetes will be identified with a second definition below:

New onset diabetes, defined in patients who were not diabetic at baseline, will be identified from the NODM NMQ in patients where diabetes is recorded as reason for a medication given post-baseline lasting for 30 days or more (Medications will be identified by searching ATC level 2 code of A10).

Notes: The NODM NMQ includes all PTs with root ”diab” included in the NODM SMQ plus the PT “Hyperglycaemic hyperosmolar nonketotic syndrome” which includes the LLT “Diabetic hyperosmolar non-ketoacidosis”. In more descriptive terms, this would mean that the NODM NMQ will include two sets of Preferred Terms (PTs) as follows:

All PTs with root ”diab” included in the NODM SMQ

PTs of “Hyperglycaemic hyperosmolar nonketotic syndrome” with LLT as “Diabetic hyperosmolar non-ketoacidosis”.

The expansions for the acronyms are as follows: NODM= New-Onset Diabetes Mellitus, NMQ = Novartis MedDRA Queries, SMQ =Standard MedDRA query, LLT =Lowest Level Term, PT = Preferred Term.

### 2.8.4.4 Notable Events

Notable events include death, non-fatal SAEs (including infections and rejections reported as SAE) and AEs (including infections and rejections) leading to discontinuation from the study treatment.

#### 2.8.4.5 Vital Signs

Vital signs variables include measurements of oral body temperature, systolic and diastolic blood pressures, pulse and body weight. Vital signs will be examined for abnormal values and change from baseline according to pre-specified clinically notable criteria. Appropriate incidence rates of clinically notable abnormalities (see [Section 4.6.2](#)) will be provided. Further, descriptive statistics of all vital signs variables as well as the changes from baseline will be presented by visit. A by-patient listing of all vital signs (with clinically notable abnormalities being flagged) will be generated.

#### 2.8.4.6 Laboratory Data

Descriptive statistics (mean, standard deviation, minimum, median and maximum) of quantitative laboratory variables, including change from Baseline, will be generated by visit for laboratory parameters. Categorical levels of urinary protein/creatinine ratio (<30, 30 - <500, 500 - <1000, 1000 - <3000, ≥3000 mg/g) will additionally summarized by visit. When there will be multiple observations in the same visit, the worst case will be selected for this visit.

Laboratory results recorded as >n or <n (above or below detection limit) will be either converted to n (if above detection limit) or set to one-half n (if below detection limit) for the purposes of summary statistics (e.g. if <0.2 was reported 0.1 will be used for the analyses). Original raw results will be listed.

Abnormalities according to the clinical notable criteria (see [Section 4.6.1](#)) will be identified and tabulated for each applicable lab parameter. Lipids levels are categorized based on the following criteria per American Heart Association ([Adult treatment panel III 2002](#)). A by-patient listing of individual patient laboratory data will be generated; values outside of clinical notable will be flagged.

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

- Borderline high: 130 – <160 mg/dL
- High: 160 – <190 mg/dL
- Very high:  $\geq 190$  mg/dL
- Total cholesterol /HDL ratio level is defined as
  - Normal: <5
  - High:  $\geq 5$  but  $\leq 7$
  - Very High:  $>7$

Newly occurring abnormalities since baseline will be summarized by treatment for the clinical notable laboratory abnormalities and the following abnormality criteria (AST or SGOT; ALT or SGPT; TBL: total bilirubin; ALP: serum alkaline phosphatase).

- ALT  $> 3 \times$  ULN
- ALT  $> 5 \times$  ULN
- ALT  $> 8 \times$  ULN
- ALT  $> 10 \times$  ULN
- ALT  $> 20 \times$  ULN
- ALT or AST  $> 3 \times$  ULN
- ALT or AST  $> 5 \times$  ULN
- ALT or AST  $> 8 \times$  ULN
- ALT or AST  $> 10 \times$  ULN
- ALT or AST  $> 20 \times$  ULN
- ALT or AST  $> 3 \times$  ULN & TBL  $> 1.5 \times$  ULN
- ALT or AST  $> 3 \times$  ULN & TBL  $> 2 \times$  ULN
- ALT or AST  $> 5 \times$  ULN & TBL  $> 2 \times$  ULN
- ALT or AST  $> 8 \times$  ULN & TBL  $> 2 \times$  ULN
- ALT or AST  $> 10 \times$  ULN & TBL  $> 2 \times$  ULN
- ALT or AST  $> 20 \times$  ULN & TBL  $> 2 \times$  ULN
- ALP  $> 1.5 \times$  ULN
- ALP  $> 2 \times$  ULN
- ALP  $> 3 \times$  ULN
- ALP  $> 5 \times$  ULN
- TBL  $> 1 \times$  ULN
- TBL  $> 1.5 \times$  ULN
- TBL  $> 2 \times$  ULN
- TBL  $> 3 \times$  ULN
- ALP  $> 3 \times$  ULN & TBL  $> 2 \times$  ULN
- ALT or AST  $> 3 \times$  ULN & TBL  $> 2 \times$  ULN & ALP  $< 2 \times$  ULN

### **2.8.5 Safety Events for Clinical Trial Safety Disclosure**

For the legal requirements of ClinicalTrials.gov and EudraCT, at the end of the study, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 5% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

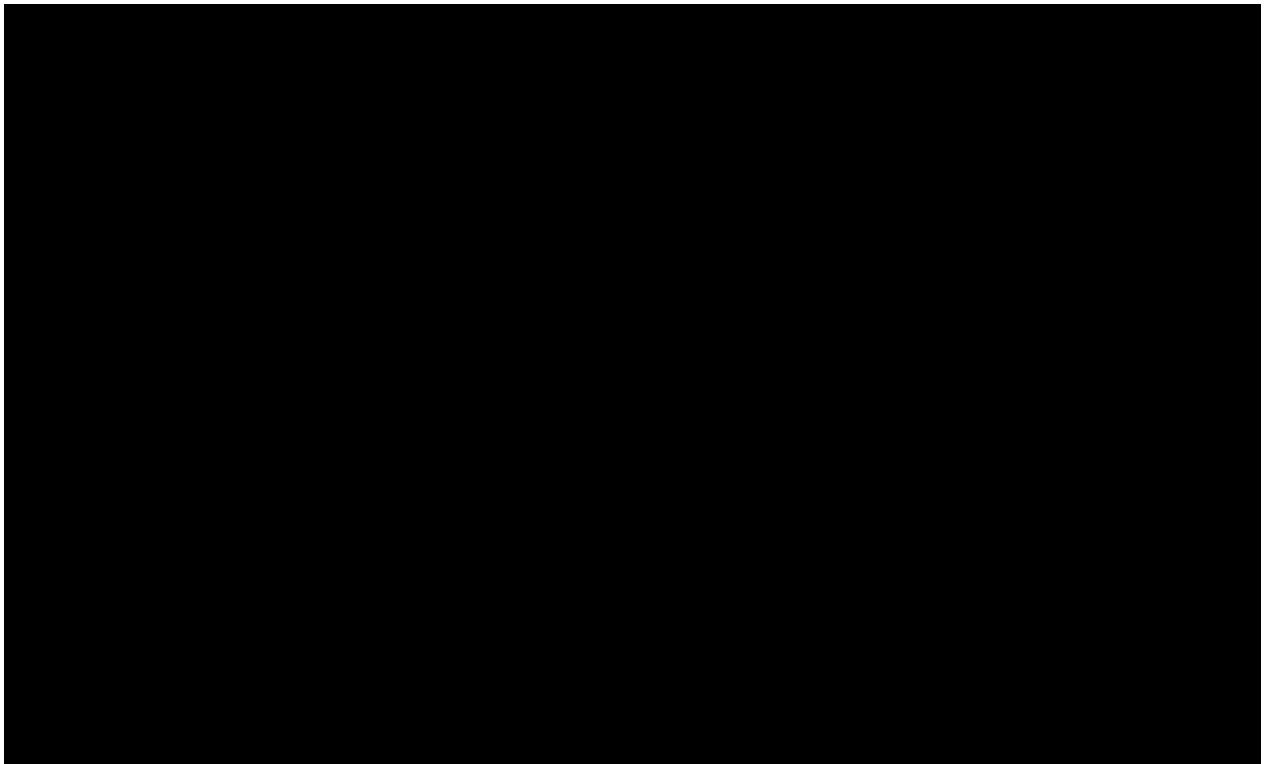
- a single occurrence will be counted if there is  $\leq 1$  day gap between the end date of the preceding AE and the start date of the consecutive AE;
- more than one occurrence will be counted if there is  $> 1$  day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a  $\leq 1$  day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

- The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

### **2.9 Pharmacokinetic (PK)/Pharmacodynamic (PD)/PK-PD/Biomarkers Evaluations**

Not applicable.



## 2.12 Interim Analyses

A futility analysis will be performed when approximately 30% of patients have completed 6 months on the study. The futility analysis described in Section 1.4.1 will be based on the study target population, which consists of 6-month completers and remaining about 70% patients to be enrolled.

The futility analysis outlined in this document is not designed to constitute a binding measure.

All analyses will be provided by the CRO independent team to the Futility Review Board. This list of analyses can be amended at the request of the Futility Review Board. Details of the analyses will be specified in the futility analysis RAPs

### 2.12.1 Futility Analysis

Although the primary study endpoint (the composite of tBPAR or eGFR (MDRD4)  $< 50$  ml/min/1.73m<sup>2</sup>) is at Month 12, the futility analysis will be based on the endpoint at 6 months. In kidney transplant trials, typically most tBPAR events (e.g. 80% in A2309 study) occur within the first 6 months, and eGFR at Months 6 and 12 are very similar (e.g. in A2309 study, the mean eGFR was 57.2 at Month 6 vs. 56.3 at Month 12 in the everolimus 1.5 mg group). Therefore, it is expected that the 6-month endpoint will be a good predictor of the 12-month endpoint.

The futility of the non-inferiority for the primary endpoint will be assessed via conditional power together with 95% prediction interval. Conditional power is the probability of rejecting the following null hypothesis given the observed data from the futility analysis patients (6-month completers) and assumptions on the data from future patients. In conjunction with the conditional power, a prediction interval will be calculated to estimate the potential treatment effect and its associated precision (See the calculations of the conditional power and prediction interval in [Section 2.12.3](#)).

$H_{01}$ :  $R_{EVR+tCNI} - R_{MPA+sCNI} \geq 0.10$  (non-inferiority margin): the difference in proportion of patients experiencing tBPAR or eGFR (MDRD4)  $< 50$  mL/min/1.73m<sup>2</sup> at 6 months between the everolimus plus reduced CNI ( $R_{EVR+tCNI}$ ) and the MPA plus standard CNI arm ( $R_{MPA+sCNI}$ ) is at least 10%, vs.

$H_{A1}$ :  $R_{EVR+tCNI} - R_{MPA+sCNI} < 0.10$  (non-inferiority margin): The difference in proportion of patients experiencing tBPAR or eGFR (MDRD4)  $< 50$  mL/min/1.73m<sup>2</sup> at 6 months between the everolimus plus reduced CNI ( $R_{EVR+tCNI}$ ) and the MPA plus standard CNI arm ( $R_{MPA+sCNI}$ ) is less than 10%.

For the futility analysis, the incidence rate of the composite endpoint of tBPAR or eGFR (MDRD4)  $< 50$  ml/min/1.73m<sup>2</sup> will be assessed for each arm for the **6-month completers**. The 6-month completers are defined as follows:

- ~30% of the total randomized patients who have reached Month 6 or discontinued from study early (note: For those patients who were beyond Month 6 in the study, tBPAR up to Month 12 and eGFR (MDRD4) at Month 12 will be used instead if they are available at the time of the futility analysis).
- Patients who have not reached Month 6 yet, but have experienced a tBPAR, graft loss or death event.

For the 6-month completers, it is expected that there will be some patients who drop out from the study prior to Month 6 or miss Month 6 assessments. Missing Month 6 eGFR (MDRD4) will be imputed via the following approach, then the eGFR(MDRD4) value will be dichotomized to derive the component of eGFR (MDRD4) < 50 mL/min/1.73m<sup>2</sup>.

- Under the assumption of missing not at random (MNAR), patients who lost their grafts will be assigned a value of zero.
- Otherwise, under the assumption of missing at random (MAR), patients who had missing values including those who died with a functioning graft will have a Month 6 eGFR imputed using **multiple imputation** method based on the longitudinal eGFR data at all available time points up to Month 6 and covariates of randomization strata (donor type and CNI), HLA mismatches ( $\leq 3$  vs  $> 3$ ) and induction.

For the remaining 70% of the patients, expected 6-month failure rates will be assumed using the following scenario:

- Same incidence rates as observed from the 30% futility analysis patients (6-month completers)

For completeness, an assessment of non-inferiority (with NI margin = 10%) for the key secondary endpoint of tBPAR, graft loss or death at Month 6, as well as superiority for the primary endpoint of tBPAR or eGFR (MDRD4) < 50 ml/min/1.73m<sup>2</sup> at Month 6 will be provided using the same approach (i.e. conditional power together with prediction interval) and the assumption for the remaining 70% of patients.

The futility analysis described above assumes the data from tacrolimus [REDACTED]. The Independent Review Board may assess the poolability based on the unblinded futility analysis data and request additional analysis in the tacrolimus subgroup if this is indeed needed.

### Non-Binding Futility Stopping Rule

Based on futility characteristics simulations, the futility stopping rule is developed, which is based on the conditional power for the non-inferiority of the composite endpoint of tBPAR or eGFR (MDRD4) < 50 ml/min/1.73m<sup>2</sup>. Recommendation to stop the trial due to futility can be considered if the calculated conditional power is  $\leq 2\%$  based on the scenario described in [Section 2.12.1](#).

### 2.12.2 Other Analyses

In addition to the futility analysis described in the previous section, the following analyses will be performed for the **6-month completers with data up to Month 6**.

#### Demographic and background information:

- Summary of demographics and transplant background information by treatment

**Disposition:**

- Summary table and listing of patient disposition at Month 6: ongoing study/study treatment, completed study/study treatment, and premature discontinuations of study/study treatment with reasons by treatment
- Summary of patient disposition at Month 6 by treatment and **randomization strata** (CNI: CsA vs TAC, and donor type: living vs standard criteria vs expanded criteria deceased donor)
- KM plot of premature discontinuation of study medication

**Study medication:**

- Summaries of average daily doses of study drug (everolimus and MPA) as well as CNI (cyclosporine and tacrolimus)
- Summaries of number (percent) of patients with EVR/CNI trough levels within/below/above target ranges
- Box-plots of EVR/CNI trough levels with target ranges displayed

**Efficacy (up to Month 6):**

- Summary of raw incidence rate (n and %) for the following events by treatment as well as by treatment and randomization strata
  - composite of treated biopsy proven acute rejection (tBPAR) or  $GFR < 50 \text{ mL/min/1.73m}^2$
  - composite of tBPAR, graft loss, death or  $GFR < 50 \text{ mL/min/1.73m}^2$
  - $GFR < 50 \text{ mL/min/1.73m}^2$
- Summary of Kaplan-Meier incidence rate for the following events by treatment as well as by treatment and **randomization strata**:
  - composite of tBPAR, graft loss or death
  - composite of graft loss or death
  - individual endpoints of death, graft loss, tBPAR, BPAR, tAR, AR
- Kaplan-Meier plot for:
  - Composite endpoint of tBPAR, graft loss or death
  - tBPAR
  - Graft loss/death
- Forest plot of efficacy events

Exceptions for Month 6 incidence rate: For those patients who were beyond Month 6 in the study, tBPAR up to Month 12 and eGFR (MDRD4) at Month 12 will be used instead if they are available at the time of the futility analysis.

**Renal function:**

- Summaries of estimated GFR (MDRD4) and serum creatinine by visit, as well as by visit and randomization strata



- Summaries of the changes from Week 4 for estimated GFR (MDRD4) and serum creatinine by visit
- Plot of mean and 95% CI for estimated GFR (MDRD4) by visit
- Incidence of patients with estimated GFR(MDRD4) in specified categories (<30; 30-<45; 45-<60; 60-<90; >90 ; <50 mL/min/1.73m<sup>2</sup>) by visit (Week 4 and onward visits)

#### AE/SAE

Summary by primary SOC & PT for the followings:

- Frequent events ( $\geq 10\%$  in any treatment group) regardless of study drug relationship
- Serious events regardless of study drug relationship by primary SOC & PT, and additionally by **randomization strata**
- Infections regardless of study drug relationship by type of infection & specific micro-organism
- Events suspected to be related to study drug
- Events leading to study drug discontinuation by primary SOC & PT, and additionally by **randomization strata**
- Primary cause of death/graft loss

Note: infections should be included as part of AEs.

#### Laboratory

- Summary of lipids (total cholesterol and triglycerides) by visit
- Summary of Hematology (haemoglobin, platelets and total WBC) by visit

The transplant background information, efficacy and GFR analyses will also be performed for the full analysis set with all data available at the time of the futility analysis (e.g. including data prior to Month 6 for patients recently enrolled or data beyond Month 6 for patients who have been in the study over 6 months). AEs/infections leading to study drug discontinuation and SAEs/serious infections will be analyzed for the safety analysis set with all data available at the time of the futility analysis.

Listings for efficacy events and GFR will be provided for the full analysis set, and listings for everolimus and CNI trough levels and AEs will be provided for the safety analysis set.

### 2.12.3 Calculation of Prediction Interval and Conditional Power

#### 2.12.3.1 Predicted Event and Event Rate

Let  $N$  be planned sample size per treatment group ( $N=1020$ ),  $n_i$  be the number of patients for the futility analysis (6-month completers) for the treatment group  $i$  (e.g.  $i$  for EVR and MPA),  $x_i$  be the observed events in the  $n_i$  patients in the treatment  $i$ , and  $p_{f,i}$  is assumed event rate in the future patients in the treatment  $i$ , the predicted (expected) events for the treatment  $i$  will be calculated as follows:

$$e_i = x_i + (N - n_i)p_{f,i}$$

The predicted event rate for the treatment  $i$  will be

$$p_i = e_i/N$$

### 2.12.3.2 Prediction Interval

Predicted difference in event rate between the two groups will be

$$p_{EVR} - p_{MPA} = e_{EVR}/N - e_{MPA}/N$$

Prediction interval for the difference will be (Evans, Li and Wei, 2007)

$$(p_{EVR} - p_{MPA}) \pm Z_{0.975} SE_{full}$$

$$\text{where } SE_{full} = \text{SQRT}[p_{EVR}(1 - p_{EVR})/N + p_{MPA}(1 - p_{MPA})/N]$$

### 2.12.3.3 Conditional Power

The predicted difference of  $p_{EVR} - p_{MPA}$  approximately follows a Normal distribution, test statistic  $Z$  can be constructed as

$$Z = (p_{EVR} - p_{MPA} - \delta) / SE_{full}$$

where  $\delta$  is margin ( $\delta = 0.10$  corresponding to  $H_{01}$  and  $H_{03}$  for non-inferiority analyses, and  $\delta = 0$  corresponding to  $H_{03}$  for superiority analysis).

Assuming  $y_i$  be number of events to be obtained in the future patients in the treatment  $i$ , let

$\bar{x}_i = \frac{x_i}{n_i}$  and  $\bar{y}_i = \frac{y_i}{N - n_i}$  be observed event rate in the  $n_i$  patients for the futility analysis and

estimated event rate in the future patients respectively in the treatment  $i$ , the  $Z$  constructed above can be decomposed to

$$\begin{aligned} Z &= (p_{EVR} - p_{MPA} - \delta) / SE_{full} \\ &= \left[ \frac{n_{EVR} \bar{x}_{EVR} + (N - n_{EVR}) \bar{y}_{EVR}}{N} - \frac{n_{MPA} \bar{x}_{MPA} + (N - n_{MPA}) \bar{y}_{MPA}}{N} - \delta \right] / SE_{full} \\ &= \left[ \frac{n_{EVR} (\bar{x}_{EVR} - p_{f,EVR}) + (N - n_{EVR}) (\bar{y}_{EVR} - p_{f,EVR})}{N} - \frac{n_{MPA} (\bar{x}_{MPA} - p_{f,MPA}) + (N - n_{MPA}) (\bar{y}_{MPA} - p_{f,MPA})}{N} + (p_{f,EVR} - p_{f,MPA}) - \delta \right] / SE_{full} \\ &= \left\{ \frac{(N - n_{EVR}) (\bar{y}_{EVR} - p_{f,EVR})}{N} - \frac{(N - n_{MPA}) (\bar{y}_{MPA} - p_{f,MPA})}{N} + \left[ \frac{n_{EVR} (\bar{x}_{EVR} - p_{f,EVR})}{N} - \frac{n_{MPA} (\bar{x}_{MPA} - p_{f,MPA})}{N} \right] + (p_{f,EVR} - p_{f,MPA}) - \delta \right\} / SE_{full} \end{aligned}$$

To reject the null hypothesis,  $Z$  should be  $< -Z_{0.975}$ , namely

$$\frac{(N - n_{EVR}) (\bar{y}_{EVR} - p_{f,EVR})}{N} - \frac{(N - n_{MPA}) (\bar{y}_{MPA} - p_{f,MPA})}{N} < -Z_{0.975} SE_{full} + \delta - (p_{f,EVR} - p_{f,MPA}) - \left[ \frac{n_{EVR} (\bar{x}_{EVR} - p_{f,EVR})}{N} - \frac{n_{MPA} (\bar{x}_{MPA} - p_{f,MPA})}{N} \right]$$

$$\text{Let } A = -Z_{0.975} SE_{full} + \delta - (p_{f,EVR} - p_{f,MPA}) - \left[ \frac{n_{EVR} (\bar{x}_{EVR} - p_{f,EVR})}{N} - \frac{n_{MPA} (\bar{x}_{MPA} - p_{f,MPA})}{N} \right]$$

Then to reject the null hypothesis, we need

$$\frac{(N - n_{EVR}) (\bar{y}_{EVR} - p_{f,EVR})}{N} - \frac{(N - n_{MPA}) (\bar{y}_{MPA} - p_{f,MPA})}{N} < A$$

Therefore, conditional power will be calculated as follows

$$\Pr\left(\frac{(N-n_{EVR})(\overline{y}_{EVR}-p_{f,EVR})}{N}-\frac{(N-n_{MPA})(\overline{y}_{MPA}-p_{f,MPA})}{N}<A\right)$$

The variance of  $\frac{(N-n_{EVR})(\overline{y}_{EVR}-p_{f,EVR})}{N}$  is

$$\frac{p_{f,EVR}(1-p_{f,EVR})\left(\frac{N-n_{EVR}}{N}\right)^2}{N-n_{EVR}}=\frac{(N-n_{EVR})p_{f,EVR}(1-p_{f,EVR})}{N^2}=B_{EVR}$$

Similarly, the variance of  $\frac{(N-n_{MPA})(\overline{y}_{MPA}-p_{f,MPA})}{N}$  is

$$\frac{p_{f,MPA}(1-p_{f,MPA})\left(\frac{N-n_{MPA}}{N}\right)^2}{N-n_{MPA}}=\frac{(N-n_{MPA})p_{f,MPA}(1-p_{f,MPA})}{N^2}=B_{MPA}$$

The conditional power is

$$\begin{aligned} &\Pr\left(\frac{(N-n_{EVR})(\overline{y}_{EVR}-p_{f,EVR})}{N}-\frac{(N-n_{MPA})(\overline{y}_{MPA}-p_{f,MPA})}{N}<A\right) \\ &= \Pr\left(\frac{\frac{(N-n_{EVR})(\overline{y}_{EVR}-p_{f,EVR})}{N}-\frac{(N-n_{MPA})(\overline{y}_{MPA}-p_{f,MPA})}{N}}{\sqrt{B_{EVR}+B_{MPA}}}<\frac{A}{\sqrt{B_{EVR}+B_{MPA}}}\right) \\ &= \Phi\left(\frac{A}{\sqrt{B_{EVR}+B_{MPA}}}\right) \end{aligned}$$

This calculation is adapted from (Chow and Chang, 2007).

For this futility analysis, the predicted event rate and conditional power for the key secondary endpoint of tBPAR, graft loss or death will be calculated based on raw event rate rather than using KM method.

### 3 Determination of Sample Size

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

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

The calculations are based on the following assumptions:

- 80% of patients are randomized to tacrolimus, 20% of patients are randomized to cyclosporine

- 20% and 30% patients are excluded from the PP population at Months 12 and 24 respectively
- For non-inferiority, the event rate in each arm is 50%, based on study results from RAD001A2309 and [Ekberg 2007](#), and the non-inferiority margin for the primary composite endpoint is 10%.
- For the evaluation of superiority, the event rate in the MPA + sCNI arm is 50%.

## 4 Appendix

### 4.1 Visit-Windows

*Visit-windows* will be used to summarize the data by visit and are defined in terms of weeks and months; these will be based on the study schedule of evaluation and comprised a set of days “around” the nominal visits. Visit-windows are non-overlapping; all together they cover the entire study period, e.g., the visit-window *Month 2* comprises study days 45 to 90, i.e., it has the nominal visit Month 2 as “center” and includes the 15 days preceding study day 60 and 30 days thereafter. Generally, visit-windows are not symmetrical around the nominal visit day.

As patients do not necessarily have their examinations at the exact scheduled time, it might be misleading if all data with the same nominal visit number are lumped together for a by-visit analysis. Thus, all data (including reported unscheduled assessments) are “re-aligned” according to the window schema given below. Note that the visit windows defined in the protocol are used to guide investigators whereas the ‘re-aligned’ visit windows in [Table 4-1](#) (simply called visit windows in the following) will be used for the analyses.

**Table 4-1 Visit Windows**

Re-aligned Visit	Visit window	Relative to randomization date		
		Start day of Visit window	Midpoint	End day of Visit window
1	Screening/Baseline	Inform Consent		randomization
2	Day 4	1 (post-randomization)	4	5
3	Week 1	6	7	10
4	Week 2	11	14	21
5	Week 4	22	28	44
6	Month 2	45	60	90
7	Month 4	91	120	150
8	Month 6	151	180	225
9	Month 9	226	270	315
10	Month 12	316	360	450
11	Month 18	451	540	630
12	Month 24	631	720	810

Re-aligned Visit	Visit window	Relative to randomization date		
		Start day of Visit window	Midpoint	End day of Visit window
13	Month 12 Treatment Endpoint (TEP)	1		450
14	Month 12 Study Endpoint (SEP)	1		450
15	Month 24 TEP	1		810
16	Month 24 SEP	1		810

## 4.2 Missing Data Handling

### 4.2.1 Missing GFR Data Imputation

#### 4.2.1.1 Main Imputation

The following is the main imputation method for handling missing eGFR data at Month 12. A similar imputation rule can be applied for missing eGFR at Month 24. These imputations will be applied to the primary analyses for the composite endpoint of tBPAR or eGFR < 50 mL/min/1.73m<sup>2</sup>, as well as for eGFR alone. For the component of eGFR < 50 mL/min/1.73m<sup>2</sup>, a value for missing eGFR as a continuous variable will be imputed first, then it will be dichotomized in order to derive this endpoint.

- Under the assumption of missing not at random (MNAR), patients who lost their grafts will be assigned a value of zero for their missing eGFR at the visits on and after graft loss;
- Multiple imputation: Otherwise, under the assumption of missing at random (MAR), patients who had missing values including those who died with a functioning graft will have a 12-month eGFR imputed using multiple imputation method based on the covariates/factors CNI, region, donor type, HLA mismatch ( $\leq 3$  vs  $> 3$ ), induction therapy, recipient gender, recipient age, donor age, and DGF, and all eGFR (MDRD4) data collected at the visit windows during the analysis period of interest. In the multiple imputation, recipient age, donor age and eGFR (MDRD4) data will be treated as continuous variables. To help preserve the relationship between outcome and covariates within each treatment, a separate model will be run for each treatment. This will also help ensure that the imputation model does not make stronger assumptions on data relations than the analysis model.

To ensure that results can be replicated, the data should be sorted by patient number before running the model (the data should be in horizontal format with one row per patient). If there are multiple renal function assessments within a visit window, guidelines given in [Section 2.1](#) will be followed, i.e., the closest value to the planned visit (midpoint of visit window for post-baseline visits) will be taken (if tie, the last will be used) for imputation. In addition, the seed used in the multiple imputation will be 2433.

See dummy SAS codes below.

```
proc mi data=DATAIN out=DATAOUT nimpute=100 seed=2433;
  by treatment;
  class CNI region donor HLA induction gender_r DGF;
```

```
fcs reg (/details);  
var CNI region donor HLA induction gender_r age_r age_d DGF GFR_vis1  
GFR_VIS2 ... GFR_VISm;  
run;
```

#### 4.2.1.2 Imputation for Sensitivity Analyses

For sensitivity analyses for the composite endpoint of tBPAR or eGFR < 50 mL/min/1.73m<sup>2</sup> as well as for eGFR alone, the following imputation method will be used to impute missing eGFR values at Month 12. Similar imputation rules can be applied to missing GFR at Month 24. Patients who lost their grafts will be assigned a value of zero for their missing eGFR at the visits on and after graft loss. Otherwise, patient who had missing value including those who died with a functioning graft will have a 12-month eGFR imputed using the control-based imputation under the assumption of missing not at random (MNAR). Missing eGFR values in EVR + rCNI arm will be imputed based on the data from the control arm (MPA + sCNI) as everolimus patients would switch to control (standard care) or control-like medication after they discontinue everolimus.

The imputation will be based on CNI, region, donor type, HLA mismatch ( $\leq 3$  vs  $> 3$ ), induction therapy, recipient gender, recipient age, donor age, DGF, and eGFR (MDRD4) at Week 4 as covariates/factors, and all eGFR (MDRD4) data collected at the visit windows during the analysis period of interest. In the multiple imputation, recipient age, donor age and eGFR (MDRD4) data will be treated as continuous variables.

See dummy SAS codes as below:

```
proc mi data= seed=2433 nimpute=100 out=mi_out;  
class treatment CNI region donor HLA induction gender_r DGF;  
fcs reg (/details);  
mnar model (GFR_VIS1 GFR_VIS2 ... GFR_VISm / modelobs = (treatment="MPA"));  
var CNI region donor HLA induction gender_r age_r age_d DGF GFR_VIS1  
GFR_VIS2 ... GFR_VISm;  
run;
```

To ensure that results can be replicated, the data should be sorted by patient number before running the model (the data should be in horizontal format with one row per patient). patientIf there are multiple renal function assessments within a visit window, guidelines given in [Section 2.1](#) will be followed. In addition, the seed used in the multiple imputation will be 2433.

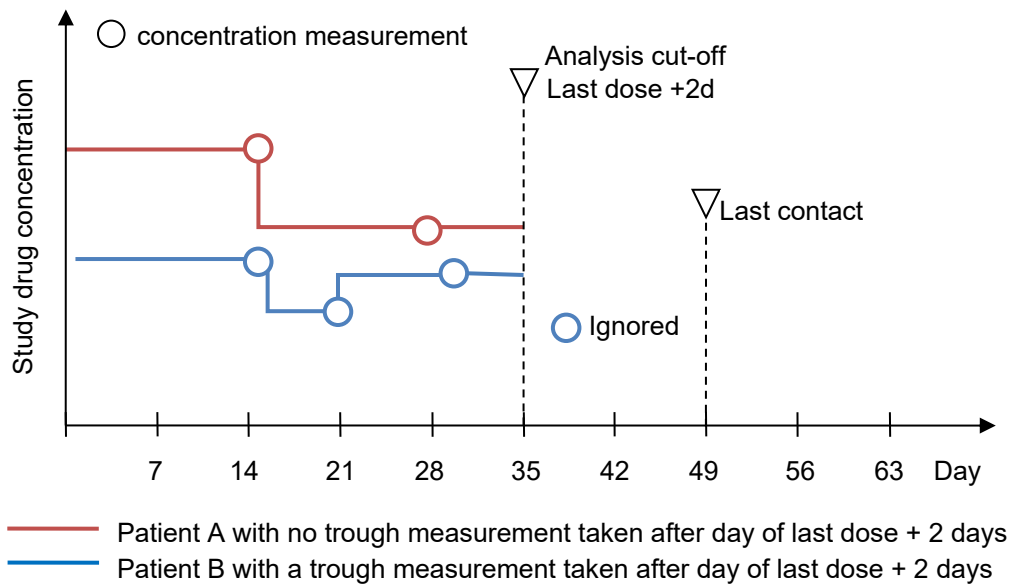
#### 4.2.2 CNI/EVR Trough Level Imputation

The exact time-varying trough concentration is not known. Imputation is required to estimate the time-varying concentration from the available trough concentration and dose records. The imputation method is essentially a backward imputation with a forward component (see illustration in [Figure 4-1](#))

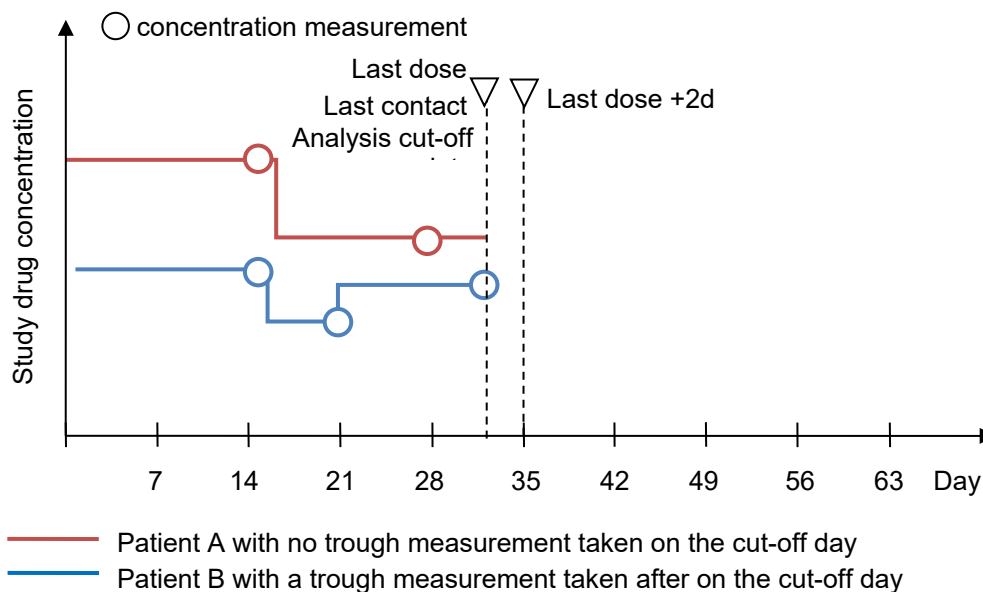
1. For each patient, the maximum study drug on-treatment date will be created as the analysis cut-off date.
2. Trough concentrations after the analysis cut-off date will be ignored.
3. For patients without the study drug trough concentration at the cut-off date, the last observation will be carried forward to the cut-off date, so all patients will have study drug trough concentrations at the cut-off date (carry-forward imputation).

4. Assuming that a patient had concentration measurements on Days  $x$  and  $y$  ( $x < y$ ), the concentration on Day  $x+1$  to  $y-1$  is assumed to be that of Day  $y$ . The first available trough level will be carried backward to the day of the first dose of respective study drug. Therefore each day from the day of the first dose of respective study drug to the cut-off date will have a trough concentration (carry-backward imputation). The rationale for this imputation is that a concentration measurement may trigger a change in dose, so a measured concentration is more representative of the past than of the future.

**Figure 4-1 Imputation rule for concentration data: 2 hypothetical patients**



(a) Last contact day is after the last dose day + 2 days



- (b) Last contact day is the same day as the last dose day (patient discontinued the study and the study drug on the same day)

#### 4.2.3 LOCF for Laboratory and Vital Sign Data

Summary statistics by visit window for laboratory (including renal) and vital sign variables using two different conventions of the last observation carried forward (LOCF) method.

- LOCF using last on-treatment value (treatment endpoint = TEP)
- LOCF using last available value (study endpoint = SEP)

The *month x treatment endpoint* (of a certain variable, e.g., systolic blood pressure) is defined as the last available non-missing *on-treatment* observation (7-day rule) in the study period Day 1 to Day  $z$ , where  $z$  is the last day of the Month  $x$  visit window (for the  $x$  Month analysis). For example,  $z = 195$  is the last day of the Month 6 visit window. Therefore the *Month 6 treatment endpoint* for systolic blood pressure in a patient discontinuing study medication on Day 179 and reporting systolic blood pressures of 155, 190 and 165 mmHg on study Days 149, 180, and 189, respectively, would be 190 mmHg. This imputation is denoted as “TEP” in the visit window column of summary statistics tables.

The *month x study endpoint* (of a certain variable, e.g., systolic blood pressure) is defined as the last available non-missing observation in the study period Day 1 to Day  $z$ , where  $z$  is the last day of the Month  $x$  visit window (for the  $x$  Month analysis). This imputation is denoted as “SEP” in the visit window column of summary statistics tables.

In contrast to the *Month x treatment endpoint*, the *Month x study endpoint* may be an assessment obtained a long time after premature discontinuation of study treatment.



The *month x treatment endpoint* and *month x study endpoint* will be defined for Month 12 and Month 24 and labeled as Month X TEP and Month X SEP (e.g. Month 12 TEP and Month 12 SEP) in the analysis outputs. For the 24-month analysis, only Month 24 TEP and Month 24 SEP will be presented.

#### 4.2.4 Imputation of Incomplete Dates

Although not the rule, partially or completely missing dates occur. Known dates with this issue are the start date on the Medical History eCRF page, start and end dates on the Concomitant Medications eCRF page or Surgical and Medical Procedures eCRF page, and occasionally, start and end dates on the Adverse Event eCRF.

Any date incompletely reported is split into its day, month, and year components. In SAS, a numeric date variable can only be defined if all three date components are known; incomplete dates are to be handled as text strings (character-type variables); as such, they could not be easily processed. An imputation rule for incomplete dates will be performed.

##### 4.2.4.1 Incomplete Start Date for Adverse Events and Concomitant Medication

This algorithm is expressed in the Variable Source Derivation column as #IMPUTA $EV(event)$  where *event* is the partial start date of the adverse event.

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

Note, if the imputed AE (or CM) start is after AE (or CM) end date, then set AE (or CM) start equal to AE (or CM) end date.

	Day	Month	Year
Partial Adverse Event (or Concomitant Medication) Start Date	Not used	MON	YYYY
Treatment Start Date (TRTSDT)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	NC	NC	NC	NC
YYYY < TRTY	(D)	(C)	(C)	(C)
YYYY = TRTY	(B)	(C)	(A)	(A)

YYYY > TRTY	(E)	(A)	(A)	(A)
----------------	-----	-----	-----	-----

The following table is the legend to the logic matrix.

Relationship	
<b>Before Treatment Start</b>	Partial date indicates AE (or CM) start date <b>prior</b> to Treatment Start Date
<b>After Treatment Start</b>	Partial date indicates AE (or CM) start date <b>after</b> Treatment Start Date
<b>Uncertain</b>	Partial date <b>insufficient to determine</b> relationship of AE (or CM) start date to Treatment Start Date
Imputation Calculation	
<b>NC / Blank Uncertain</b>	No convention
<b>(A) After Treatment Start or Uncertain</b>	MAX( 01MONYYYY, TRTSDT+1 )
<b>(B) Uncertain</b>	TRTSDT+1
<b>(C) Before Treatment Start</b>	15MONYYYY
<b>(D) Before Treatment Start</b>	01JULYYYY
<b>(E) After Treatment Start</b>	01JANYYYY

#### 4.2.4.2 Incomplete End Date for Adverse Events

Missing AE end dates will not be imputed.

#### 4.2.4.3 Incomplete End Date for Concomitant Medication

The following table explains the notation used in the logic matrix. Please note that **missing end dates** will not be imputed.

	Day	Month	Year
<b>Partial Conmed. end Date</b>	Not used	MON	YYYY
<b>Last Contact Date (LASTDT)</b>	Not used	LSTM	LSTY

MON MISSING	MON < LSTM	MON = LSTM	MON > LSTM
-------------	------------	------------	------------

YYYY MISSING	NC	NC	NC	NC
YYYY < LSTY	(C)	(A)	(A)	(A)
YYYY = LSTY	(B)	(A)	(B)	(A)
YYYY > LSTY	(C)	(A)	(A)	(A)

Relationship	
Before Last contact date	Partial date indicates CM end date <b>prior</b> to Last Contact Date
After Last contact date	Partial date indicates CM end date <b>after</b> Last Contact Date
Uncertain	Partial date <b>insufficient to determine</b> relationship of CM end date to Last Contact Date
Imputation Calculation	
NC / Blank Uncertain	No convention
(A) Before/After Last contact date	Last day MONYYYY
(B) Uncertain	LASTDT
(C) Before/After Last contact date	31DECYYYY

At the Month-12 analysis, if the above logic is applied and the imputed end date is after the month 12 cut-off date, then the imputed end date is replaced with the month 12 cut-off date.

#### 4.2.4.4 Medical History

Start dates on the Medical History eCRF page are rather frequently incomplete. No dates will be imputed. Incomplete dates (if any) will be listed.

### 4.3 Definition/Derivation of Efficacy Variables

All efficacy endpoints regarding biopsy described below will be identified from local pathologists' evaluation of all biopsy readings. All acute rejections are recorded in the clinical database on the Kidney allograft rejection and Kidney allograft biopsy eCRFs.

#### 4.3.1 Antibody-Mediated (Humoral) Rejection (AMR)

A rejection is considered as an AMR if:

- Acute antibody mediated rejection = "Yes" from kidney allograft biopsy eCRF page

Date of rejection will be “date rejection was first suspected” on the Kidney allograft rejection eCRF, or if missing, the first available date of the biopsy of the particular rejection episode on the Kidney allograft biopsy eCRF page.

#### 4.3.2 Acute Rejection (AR)

A rejection is considered an AR if:

- Primary clinical diagnosis = “Acute rejection” or “Acute and chronic rejection” from Kidney allograft rejection eCRF page; **OR**
- Antibody-mediated rejection (see above); **OR**
- Acute T-Cell mediated rejection = “Yes” from Kidney allograft biopsy eCRF page.

Date of AR will be “date rejection was first suspected” on the Kidney allograft rejection eCRF, or if missing, the first available date of the biopsy of the particular rejection episode on the Kidney allograft biopsy eCRF page.

#### 4.3.3 Treated Acute Rejection (tAR)

A rejection is considered a tAR if:

- Acute rejection (see above); **AND**
- Was anti-rejection therapy administered? = “yes” from Kidney allograft rejection eCRF

Date of tAR will be the date of the corresponding AR (note: tAR is a subset of AR).

#### 4.3.4 Biopsy-Proven Acute Rejection (BPAR)

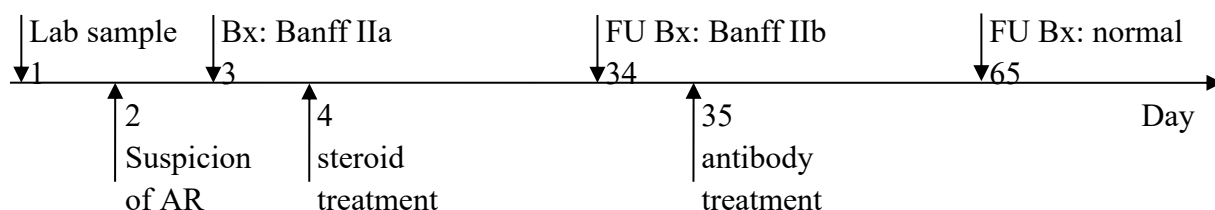
A rejection is considered a BPAR if:

- Primary clinical diagnosis = “Acute rejection” or “Acute and chronic rejection” from Kidney allograft rejection eCRF page; **AND**
- Acute T-Cell mediated rejection = “Yes” or Acute antibody mediated rejection = “Yes” from Kidney allograft biopsy eCRF page.

Date of BPAR will be “date rejection was first suspected” on the Kidney allograft rejection eCRF, or if missing, the first available date of the biopsy of the particular rejection episode on the Kidney allograft biopsy eCRF page (note: BPAR is a subset of AR).

The BPAR episode can be classified into rejection types: t-cell mediated, antibody mediated, or any combination of those (see an illustration in [Figure 4-2](#)).

**Figure 4-2 Example of a rejection episode**



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

A rejection is considered a tBPAR if:

- Biopsy-proven acute rejection (BPAR) (see above) *and*
- Was anti-rejection therapy administered? = “yes” from Kidney allograft rejection eCRF page

Date of tBPAR will be the date of the corresponding BPAR (note: tBPAR is a subset of BPAR, and it is also a subset of tAR).

#### **4.3.6 Antibody Treated Biopsy-Proven Acute Rejection**

A rejection is considered an antibody treated BPAR if:

- Biopsy-proven acute rejection (BPAR) (see above) *and*
- Was antibody treatment administered? = “yes” from Kidney allograft rejection eCRF page

Date of antibody treated BPAR will be the date of the corresponding BPAR (note: antibody treated is a subset of BPAR)

#### **4.3.7 Death**

Death will be recorded at Death eCRF. The date of event will be recorded at this *eCRF* as well.

#### **4.3.8 Graft Loss**

Graft loss will be recorded at Graft Loss eCRF. The date of graft loss will be recorded at this *eCRF* as well.

#### **4.3.9 Loss to Follow-Up**

Patients lost to follow-up for the composite efficacy failure (tBPAR, graft loss or death) for the 12-month analysis are defined as those who meet the following two conditions:

- Last contact day is < Day 316 (start day of the Month 12 visit window);
- Did not experience any efficacy event (of tBPAR, graft loss or death) up to the last contact day for the 12-month analysis.

Patients lost to follow-up for the composite efficacy failure (tBPAR, graft loss or death) for the 24-month analysis are defined as those who meet the following two conditions:

- Last contact day is < Day 631 (start day of the Month 24 visit window);
- Did not experience any efficacy event (of tBPAR, graft loss or death) up to the last contact day for the 24-month analysis

The date of lost to follow-up is the date of last study contact for the respective analysis (12 or 24-month analysis).

### 4.3.10 Composite Efficacy Failure

Several composite endpoints are defined as primary or secondary efficacy variables. The date of efficacy failure is calculated as the earliest available date among the individual components of the composite endpoint.

For the composite endpoints and each individual endpoint, if the date of the event is not available, then the event will be included in listings and the simple proportion efficacy tables, but excluded from survival analysis.

## 4.4 Definition/Derivation of Safety Variables

### 4.4.1 MedDRA Preferred Terms or SMQs to Be Used to Define The Events of Interest

The events of interest will be defined using MedDRA preferred terms or SMQs as follows.

- Wound healing events/disorders or complications

MedDRA Preferred term
<i>Abdominal wound dehiscence</i>
<i>Culture wound positive</i>
<i>Debridement</i>
<i>Fungating wound</i>
<i>Incision site abscess</i>
<i>Incision site blister</i>
<i>Incision site cellulitis</i>
<i>Incision site complication</i>
<i>Incision site erythema</i>
<i>Incision site haematoma</i>
<i>Incision site haemorrhage</i>
<i>Incision site infection</i>
<i>Incision site oedema</i>
<i>Incision site pain</i>
<i>Incision site pruritus</i>
<i>Incisional drainage</i>
<i>Inflammation of wound</i>
<i>Post procedural cellulitis</i>
<i>Post procedural infection</i>
<i>Postoperative stitch sinus</i>

*Postoperative wound complication*

*Postoperative wound infection*

*Promotion of wound healing*

*Stitch abscess*

*Suture related complication*

*Suture rupture*

*Wound abscess*

*Wound complication*

*Wound contamination*

*Wound decomposition*

*Wound dehiscence*

*Wound drainage*

*Wound evisceration*

*Wound haemorrhage*

*Wound infection*

*Wound infection bacterial*

*Wound infection fungal*

*Wound infection helminthic*

*Wound infection pseudomonas*

*Wound infection staphylococcal*

*Wound infection viral*

*Wound necrosis*

*Wound secretion*

*Wound sepsis*

*Wound treatment*

High level term

*Healing abnormal NEC*

Following preferred terms under the high level term “*Healing abnormal NEC*” will also be searched:

*Excessive granulation tissue*

*Impaired healing*

## 4.5 Renal Variables

### 4.5.1 eGFR Using MDRD 4

Estimated GFR using the MDRD formula is based on serum creatinine, age, race and gender. The MDRD formula is:

$$\text{eGFR-MDRD4 [mL/min/1.73m}^2] = 186.3 * (C^{-1.154}) * (A^{-0.203}) * G * R;$$

where C is the serum concentration of creatinine (mg/dL), A is age (years), G=0.742 when gender is female or G=1 if gender is male, and R=1.21 when race is black or R=1 otherwise.

### 4.5.2 eGFR Using Hoek Formula on Cystatin C

Estimated GFR using the Hoek formula based on Cystatin C:

$$\text{eGFR-Hoek [mL/min/1.73m}^2] = -4.32 + 80.35 * 1/C;$$

where C = Cystatin C in mg/L.

### 4.5.3 eGFR Using CKD EPI Formula

$$\text{eGFR-CKDEPI [mL/min/1.73m}^2] = 141 * \min(C/\kappa, 1)^\alpha * \max(C/\kappa, 1)^{-1.209} * 0.993^{\text{Age}} * 1.018 \text{ [if female]} * 1.159 \text{ [if black];}$$

Where C is serum creatinine (mg/dL),  $\kappa$  is 0.7 for females and 0.9 for males,  $\alpha$  is -0.329 for females and -0.411 for males, min indicates the minimum of C/ $\kappa$  or 1, and max indicates the maximum of C/ $\kappa$  or 1.

## 4.6 Clinically Notable Laboratory and Vital Signs Abnormality Criteria/Levels

### 4.6.1 Clinically notable laboratory abnormality criteria/levels

Laboratory variable	Standard units	SI units
<b>Liver function and related variables</b>		
SGOT (ASAT)	$\geq 3 \times \text{ULN}$	$\geq 3 \times \text{ULN}$
SGPT (ALAT)	$\geq 3 \times \text{ULN}$	$\geq 3 \times \text{ULN}$
Bilirubin	$\geq 3 \times \text{ULN}$	$\geq 3 \times \text{ULN}$
<b>Renal function, metabolic and electrolyte variables</b>		
Urea	$\geq 5 \times \text{ULN}$	$\geq 5 \times \text{ULN}$
Uric acid	M $\geq 12 \text{ mg/dL}$ F $\geq 9 \text{ mg/dL}$	M $\geq 714 \mu\text{mol/L}$ F $\geq 535 \mu\text{mol/L}$
Glucose	$< 45 \text{ mg/dL}$ $> 250 \text{ mg/dL}$	$< 2.5 \text{ mmol/L}$ $> 13.9 \text{ mmol/L}$
CK (MB)	None	None
Potassium	$\leq 3.0 \text{ mEq/L}$	$\leq 3 \text{ mmol/L}$



	≥6.0 mEq/L	≥6 mmol/L
Calcium	≤6 mg/dL	≤1.5 mmol/L
	≥13 mg/dL	≥3.2 mmol/L
<b>Hematology variables</b>		
Hemoglobin	<7 g/dL	<4.39 mmol/L
Platelets (thrombocytes)	<50 k/mm <sup>3</sup>	<50 × 10 <sup>9</sup> /L
	≥700 k/mm <sup>3</sup>	≥700 × 10 <sup>9</sup> /L
Leukocytes (WBCs)	≤2.0 k/mm <sup>3</sup>	≤ 2.0 × 10 <sup>9</sup> /L
	≥16 k/mm <sup>3</sup>	≥16 × 10 <sup>9</sup> /L
<b>Hematology variables: differential</b>		
Granulocytes (poly, neutrophils)	≤1,000/mm <sup>3</sup>	≤1 × 10 <sup>9</sup> /L
Eosinophils	≥12%	≥12%
Lymphocytes	≤1,000/mm <sup>3</sup>	≤1 × 10 <sup>9</sup> /L

#### 4.6.2 Clinically notable vital signs abnormality criteria/levels

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

### 4.7 Statistical Models

#### 4.7.1 Dummy Codes for Estimating Event Rate, Event Rate Difference and Respective 95% CI as Well as No-Difference Testing for The Composite Endpoint of tBPAR or eGFR < 50 mL/min/1.73m<sup>2</sup>

As described in [Section 4.2.1](#), multiple imputation, and control-based imputation will be applied to the primary and sensitivity analyses for the composite endpoint of tBPAR or eGFR < 50 mL/min/1.73m<sup>2</sup>. For the component of eGFR < 50 mL/min/1.73m<sup>2</sup>, a value for missing eGFR as a continuous variable will be imputed first, then dichotomized it to derive this endpoint.

To estimate event rate, event rate difference and respective 95% CI as well as no-difference testing for tBPAR or eGFR < 50 mL/min/1.73m<sup>2</sup>, the following dummy SAS codes can be adapted:

```

*** Use multiple imputation, or control-based imputation method to impute a value for
missing eGFR as a continuous variable;
*** Dichotomized imputed eGFR to derive the endpoint of eGFR < 50 mL/min/1.73m2;
*** Derive the composite endpoint of tBPAR or eGFR < 50 mL/min/1.73m2;
*** Assume the dataset imp_data contains the variable EVENT (event=1 if composite
endpoint of tBPAR or eGFR < 50 mL/min/1.73m2 occurred; =0 otherwise) for each of
of the imputations;

```

```

PROC sort data=imp_data;
  by _imputation_;

```

```
run;

ods output RiskDiffCol2=diff;
proc freq data=imp_data;
  by _imputation_;
  tables trt*event/riskdiff;
run;

*** diff dataset contains the following:

Obs    _Imputation_    Row          Risk          ASE
-----
1       1                Row 1         0.3623        0.0289
2       1                Row 2         0.4729        0.0300
3       1                Total         0.4177        0.0210
4       1                Difference    -0.1106       0.0417
5       2                Row 1         0.3732        0.0291
6       2                Row 2         0.4874        0.0300
7       2                Total         0.4304        0.0211
8       2                Difference    -0.1142       0.0418
... ..

*** Event rate and 95% CI in Treatment1;
proc mianalyze data=diff(where=(row='Row 1'));
  modeleffects risk;
  stderr ASE;
run;

*** Event rate and 95% CI in Treatment2;
proc mianalyze data=diff(where=(row='Row 2'));
  modeleffects risk;
  stderr ASE;
run;

*** Difference in event rate and 95% CI for 'Treatment1 -
Treatment2';
*** P-value for the no-difference test;
proc mianalyze data=diff(where=(row='Difference'));
  modeleffects risk;
  stderr ASE;
run;
```

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