Statistical Analysis Plan for

Official Title of Study

EVALUATION OF THE BENEFITS AND RISKS IN MAINTENANCE RENAL TRANSPLANT RECIPIENTS FOLLOWING CONVERSION TO NULOJIX® (BELATACEPT)-BASED IMMUNOSUPPRESSION

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STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

EVALUATION OF THE BENEFITS AND RISKS IN MAINTENANCE RENAL TRANSPLANT RECIPIENTS FOLLOWING CONVERSION TO NULOJIX® (BELATACEPT)-BASED IMMUNOSUPPRESSION

PROTOCOL(S) IM103116

VERSION # 3.0

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2 STUDY DESCRIPTION

2.1 Study Design

This is a randomized, open-label, active-controlled, parallel-group study. Approximately 440 subjects on CNI-based regimens will be randomized in a 1:1 ratio to treatment with either belatacept or continued treatment with their established CNI. All subjects will also receive a background maintenance immunosuppressive regimen of mycophenolate mofetil (MMF) or enteric-coated mycophenolate sodium (EC-MPS)/ mycophenolic acid (MPA), with adjunctive, daily corticosteroids, according to their immunosuppressive regimen at the time of enrollment.

Enrollment will be monitored, and if necessary restricted, to ensure that no more than approximately 25% of patients are receiving CsA at the time of enrollment. In addition, participation by patients receiving the maintenance immunosuppressive combination of tacrolimus with mycophenolate sodium will be limited to no more than approximately 1/3 of all subjects.

Eligible patients must have stable renal function for 12 weeks prior to Enrollment, as defined in Section 3.2 of the protocol.

Subjects will be stratified by site and screening cGFR (defined as the most recent cGFR between Day -42 and Day 1 prior to randomization). Subjects will be stratified by screening cGFR in an approximately 1:2 ratio to the following sub-groups: ≥ 30 to < 45mL/min/1.73m^2 or ≥ 45 to 75mL/min/1.73m^2.

Subjects randomized to belatacept will receive 5mg/kg as an intravenous (IV) infusion on Days 1, 15, 29, 43, and 57, and then every 28 days thereafter. The CNI dose will be tapered to 40% - 60% of the baseline dose by Day 15, 20% - 30% of the baseline dose by Day 22, and will be discontinued by Day 29 (refer to protocol section 4.4 for the protocol allowed visit window around these Days).

Subjects randomized to continue their CNI-based regimen will receive doses targeted to achieve 12-hour trough serum concentrations (C0 levels) of 50 - 250ng/mL (CsA) or 4 - 11ng/mL (TAC). (Refer in the protocol to Figure 3.1.2-1 and Table 3.1.2-1 & Table 3.1.2-2).

2.2 Treatment Assignment

Subjects will be randomized in a 1:1 fashion to receive belatacept or to continue to receive their previous CNI (CsA or TAC). Randomization between these 2 treatment arms will be stratified by site and screening cGFR (≥ 30 to < 45mL/min/1.73m^2 or ≥ 45 to 75mL/min/1.73m^2). The stratification by screening cGFR will be in a 1:2 ratio. Within each stratum, a subject will be randomly assigned to one of the two treatment arms to receive belatacept or to continue to receive CNI, at a 1:1 ratio to ensure equitable distribution across treatment groups.

Randomization numbers will be assigned in the order in which subjects qualify for treatment, not in the order of study enrollment. A randomization schedule will be generated and kept by BMS.

At the time of enrollment, immediately after written informed consent is obtained and before performing any study-related procedures, each subject will be assigned a unique sequential 5-digit subject number beginning with 70001, 70002, 70003, etc. by the interactive voice response system (IVRS) for identification throughout the study. This subject number must not be reused for any other participant in the study. The physician/coordinator must contact IVRS to enroll each subject into a centralized database at the time of signing consent. SAE reporting

for all subjects will begin at the time of enrollment, immediately after written informed consent is obtained.

The subject may be randomized once all entry criteria (inclusion and exclusion) have been met. The physician/coordinator must contact IVRS to randomize each subject into a centralized database.

2.3 Blinding and Unblinding

This is an open-label study.

2.4 Protocol Amendments

The protocol has 7 amendments issued. The Table 1 below summarizes the main purposes of these amendments. See amendments for further details.

Table 1: Protocol Amendments

Amendment #	Protocol Amendments
Amendment #1	Modification to the inclusion/exclusion criteria. [redacted] Inclusion of Clinical criteria for suspicion of PTLD and procedures for monitoring. Update to list of Abbreviations. Minor edits and clarifications throughout the protocol, including table numbering.
Amendment #2	To remove the chest X-ray required at screening (or within 6 months of screening for patients who consent to participate in Germany.
Amendment #3	Modification to the inclusion/exclusion criteria. [redacted] Modification to the Renal Biopsy Requirements. Clarification of Live Vaccines for subjects. Addition of re-testing for screening creatinine labs. Minor edits and clarifications throughout the protocol, including table numbering.
Amendment #4	To incorporate post study access to therapy (PSA) as required by the MOH in Argentina and Colombia for patients with serious disease and will apply to all subjects enrolled in Argentina and Colombia.
Amendment #5	Modification to the inclusion/exclusion criteria. Modification to the MDRD formula, the definition of stable renal function and stable immunosuppression regimen. Addition of re-screening subjects. Extension of screening period. Decrease the frequency of body weight measurements. Minor edits and clarifications throughout the protocol
Amendment #6	Incorporate changes requested by the French MOH to protocol IM103-116 that will apply to all subjects enrolled in France. Addition of contraception requirements for MMF and EC-MPS/MPA and Appendix 04 with additional information regarding avoidance of pregnancy and contraception during treatment with MMF and EC-MPS/MPA.
Amendment #7	Modification to decrease target enrollment from 600 to 400 randomized subjects. The clarification of wording for the following: the CSPAR endpoint for consistency throughout the protocol; the requirement for daily dosing of maintenance corticosteroids throughout study participation; to indicate that protocol-specified tacrolimus through levels being locally determined for patient management will also be captured in the clinical database; the timing for determination of post-belatacept infusion vital signs. Limitation of study participation by

Table 1: Protocol Amendments

Amendment #	Protocol Amendments
	patients enrolled while receiving maintenance immunosuppression with tacrolimus plus mycophenolate sodium to approximately one-third (1/3) of all subjects. Provide a proviso to allow rescreening of patients who were screen failure earlier in the study. Update the definition of menopause; Correction of typographical errors and minor edits grammatical inconsistencies throughout the protocol.

3 OBJECTIVES

3.1 Primary

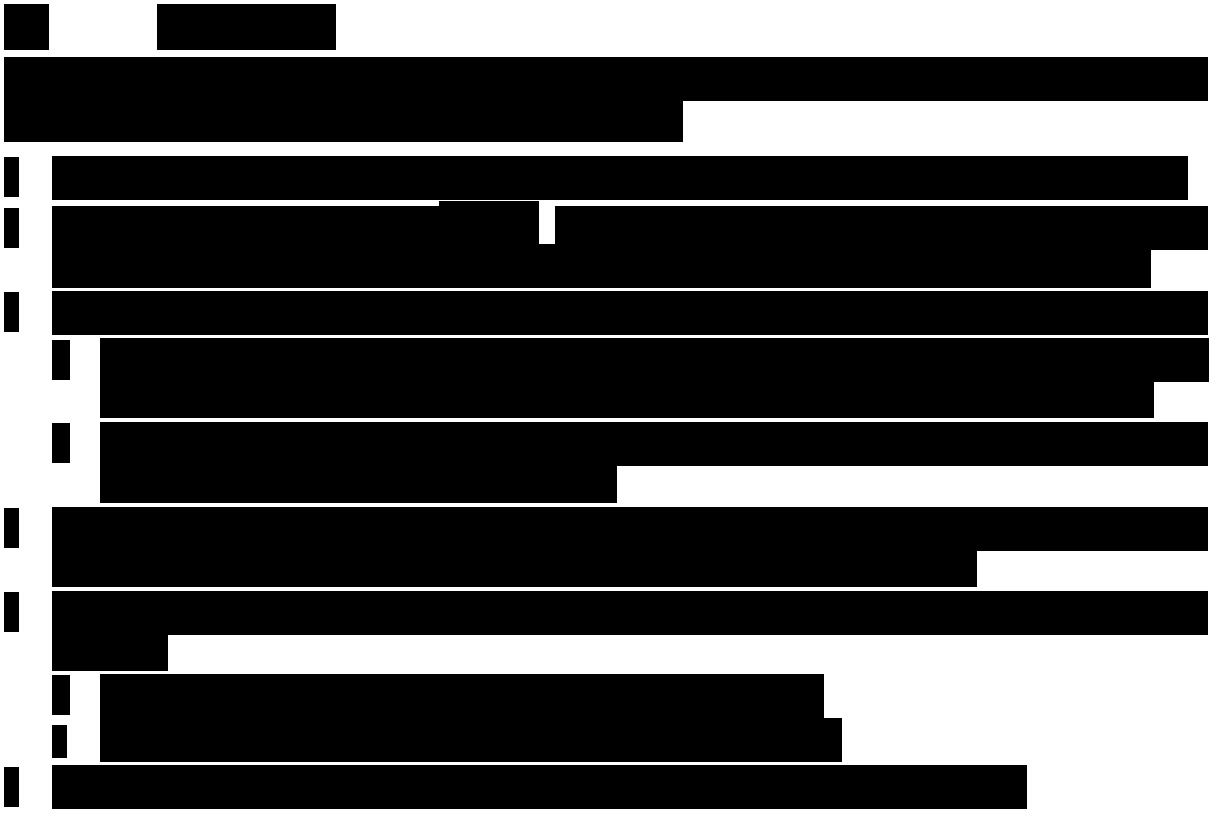
To evaluate patient and functional graft survival in maintenance renal transplant recipients (6 - 60 months post-transplantation) converted from CNI to belatacept-based immunosuppression as compared to those continuing CNI based immunosuppression at 24 months post-randomization.

3.2 Secondary

To evaluate the effect of conversion from CNI to belatacept on the following:

- Composite of patient and functional graft survival at 12 months post-randomization
- The incidence and severity of clinically suspected, biopsy proven acute rejection (AR) at 12 and 24 months post-randomization
- Renal function as assessed by:
  - Mean change in cGFR (4-variable MDRD equation) from baseline (defined as the most recent measurement prior to the first dose of study drug on Day 1) to 12 and 24 months post-randomization (% and absolute)
  - Slopes of cGFR and 1/serum creatinine respectively from baseline as well as from Months 3 to 12 and 3 to 24 post-randomization
  - Proportion of subjects with > 5% and > 10% improvement over baseline in cGFR at 12 and 24 months post-randomization
  - Urine protein/creatinine ratio (UPCR) at baseline, 3, 6, 12, and 24 months post-randomization
- Mean change in systolic and diastolic blood pressure and intensity of the anti-hypertensive treatment regimen (defined as the total number of anti-hypertensive medications used to control hypertension) from baseline to 12 and 24 months post-randomization
- Proportion of subjects with donor specific antibodies (DSA) at Baseline/ Day 1, and Months 12 and 24 post-randomization

- Evaluation of symptom occurrence and symptom distress measured with the Modified Transplant Symptom Occurrence and Symptom Distress Scale-59R (MTSOSD-59R) at baseline, Week 6, and Months 3, 6, and 12 post- randomization
- Safety and tolerability of a belatacept in a conversion setting



4 ENDPOINTS

4.1 Primary Endpoint(s)

Proportion of subjects who survive with a functional graft at 24 months post-randomization

4.2 Secondary Endpoint(s)

- Patient and Functional Graft Survival
  - Proportion of subjects who survive with a functional graft at 12 months post-randomization
- Acute Rejection
  - The incidence and severity of clinically suspected, biopsy proven acute rejection (AR) at 12 and 24 months post-randomization

- Renal Function
  - Mean change from baseline cGFR as calculated by the 4-variable MDRD equation) to 12 and 24 months post-randomization (% change and absolute change).
  - Mean cGFR by study visit, as calculated by the 4-variable MDRD equation.
  - Slopes of cGFR and 1/serum creatinine, respectively, as plotted from baseline as well as from Month 3, to Month 12 and Month 24 post-randomization
  - Proportion of subjects with > 5% and >10% improvement over baseline cGFR, at 12 and 24 months post-randomization
  - Urine protein/ creatinine ratio (UPCR) at baseline, 3, 6, 12 and 24 months post-randomization
- Hypertension
  - Mean change in systolic and diastolic blood pressure and intensity of the anti-hypertensive treatment regimen (defined as the total number of antihypertensive medications used to control hypertension) from baseline to 12 and 24 months post-randomization
- Donor Specific Antibodies (DSA)
  - Proportion of subjects with donor specific antibodies (DSA) at Baseline/Day 1, and Months 12 and 24 post-randomization
- The frequency of symptom occurrence and symptom distress as measured with the MTSOSD-59R at baseline, Week 6, and Months 3, 6, and 12 post-randomization
- Safety and tolerability of a belatacept in a conversion setting− All adverse events
  - Adverse events of special interest
  - Clinically significant changes in vital signs
  - Laboratory test abnormalities
  - Clinical tolerability of the drug

[redacted]

[redacted]

5 SAMPLE SIZE AND POWER

Formal statistical testing of a research hypothesis is not being performed in this study.

The primary objective of this study is to evaluate patient and graft survival in maintenance renal transplant recipients converted from CNI to belatacept as compared to continuation of CNI based immunosuppression at 24 months post-randomization. A sample size of approximately 220 subjects per treatment group is considered to provide sufficient power to rule out an unacceptable difference in patient and graft survival.

With a confidence level (one-sided) of 0.975 and assuming the true rates of patient and graft survival by Month 24 in both treatment groups is 93%, the sample size of 220 subjects per arm will afford 90% probability to rule out a difference of 8.3% (sample size based on 1000 simulations per Newcombe methodology)[1].

This sample size will provide 93% power to detect a 10% absolute difference of mean percentage change in cGFR at Month 24 between the belatacept regimen and the CNI regimen assuming a standard deviation of 30% (alpha 0.05, 2-sided).

Given a sample size of approximately 220 subjects per treatment group, if the true AR rates by Month 24 are 7% in the belatacept regimen and 1% in the CNI regimen, the half width of the 95% confidence interval of the difference in AR rate is estimated to be 3.6% (alpha 0.05, 2-sided). With the assumed rates of AR, the confidence interval for the difference would be (2.4%, 9.6%)

Given a sample size of 220 subjects per treatment group, and assuming an event rate of PTLD of 0.74% the probability of observing at least 1 event is 80.5%.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Treatment Regimens

Subjects will be randomized in a 1:1 fashion to receive belatacept or to continue to receive their previous CNI (CsA or TAC). Subjects will be stratified by site and by screening cGFR in a 1:2 ratio (≥ 30 to < 45mL/min/1.73m^2 or ≥ 45 to 75mL/min/1.73m^2).

6.2 Populations for Analyses

- The "Intent-to-Treat" (ITT) population includes all subjects who are randomized into the study. Subjects will be grouped according to the treatment to which they are randomized.
- The "Per-Protocol" population includes all randomized subjects who do not violate terms of the protocol that might affect the efficacy outcome. The protocol specific criteria for relevant protocol deviations are described in APPENDIX 1. "Per-protocol" analyses will be performed at Month 24 on the primary endpoint and "key" secondary endpoints only if the following occurs:
  - More than 10% of the total number of subjects included into the "ITT" population at Month 24 have significant protocol violations/deviations and consequently would be excluded from the "per-protocol" population.
- The Safety population includes all randomized and treated subjects (received at least one dose of study medication). Subjects will be grouped according to the treatment received. The "as treated" treatment group is the same as the "as randomized" treatment group, except in cases where a subject received a different treatment from the one he/she was randomized to for the entire course of their participation in the study. In this case, the "as treated" treatment group is set to the treatment the subject actually received. In cases where a subject received different treatments after randomization, then the "as treated" treatment group is the first treatment received.
- The PK population includes subjects who receive at least one dose of belatacept and have at least 1 PK sample post baseline.

7 STATISTICAL ANALYSES

7.1 General Methods

All analyses of efficacy and safety endpoints will be summarized descriptively by treatment groups: belatacept and CNI.

Table 2 below provides an overview of the primary and key secondary analyses to be performed.

Table 2: Overview of Primary and Key Secondary Analyses

Measure of Interest	Analysis Method
Proportion of subjects who survive with a functioning graft at 12 and 24 months post-randomization	Point estimate of the proportion and 95% CI within each treatment group, Point estimate and 95% CI for the difference between belatacept and CNI
Proportion of subjects who experience clinically suspected, biopsy proven acute rejection by 12 and 24 months post-randomization, overall and by Banff 2007 classification of renal allograft pathology	Point estimate of the proportion and 95% CI within each treatment group, Point estimate and 95% CI for the difference between belatacept and CNI
Mean change and mean percent change from baseline to Month 12 and 24 in cGFR.	Point estimate of both the mean change and mean percent change and the corresponding 95% CI within each treatment group, Point estimate and 95% CI for the difference between belatacept and CNI treatment difference. P-value will be provided based on a linear mixed model
Absolute levels of cGFR at protocol-specified study visits.	Descriptive statistics for cGFR (mean, median, SD, minimum, maximum, and interquartile range).

7.2 Study Conduct

All subjects with protocol deviations that could affect safety/efficacy will be identified. A list of these protocol deviation criteria is provided in APPENDIX 1. These protocol deviations are referred to as "relevant" protocol deviations in this document.

All randomized subjects having at least one of these protocol deviations will be summarized by treatment group and overall. They will also be listed.

All significant protocol deviations (includes protocol deviations from APPENDIX 1) will be listed in the study report.

Refer to section 8.3 for a listing of protocol deviations to be summarized for the Month 12 analysis in the Intent to Treat population.

7.3 Study Population

7.3.1 Subject Disposition

The disposition of subjects, including the number of subjects enrolled, the number of subjects randomized, the number of randomized subjects who received at least one dose of study drug and the number of subjects who discontinued treatment during the 2-year treatment period, and the number of subjects who discontinued during the follow up period, will be tabulated by randomized treatment group. The overall disposition combining all treatment arms will also be presented.

A corresponding listing of subjects who discontinued from the treatment period and the follow up period will be provided, together with the reason for discontinuation.

The ITT analysis population (defined in Section 6.2) will be used to summarize discontinuation from study therapy by treatment group as well as the reason for the premature termination of study therapy. The proportion of subjects, who discontinue study drug, will be summarized by months 12 and 24, using point estimates within each treatment group.

The 12-month summary will include discontinuations from study therapy based on the discontinuation date (date entered on the status pages) following the algorithm for ITT analysis in section 8.3.

The 24-month summary will include the information from all status pages for all subjects, independent of the length of time since the first dose date.

Enrollment at each site and by age group will be summarized as specified in EudraCT requirements.

7.3.2 Demography and Baseline Characteristics

Demographic and baseline characteristics of recipients and donors will be summarized descriptively by means and standard deviations for continuous variables, and frequency distribution for categorical variables. Summaries will be performed based on all randomized subjects (ITT population). No statistical test will be performed to assess imbalances between belatacept arm and CNI arm with respect to any demographic or baseline characteristic of recipient or donor organ.

Baseline demographic characteristics include the following:

Donors and recipients

- Age in years
- Weight in kg (recipients only)
- Gender
- Race
- Ethnicity (recipients only)
- Geographic region (recipients only)
- Previous number of transplant (recipients only)

Baseline disease characteristics include:

- Baseline GFR (recipients)
- GFR strata (recipients) [screening values both based on information from IVRS and actual laboratory data - see section 8.1.2]
- Number of HLA –A, B, DR, and total mismatches
- Viral serology: Cytomegalovirus (CMV) and EBV

- Panel reactive antibodies (recipients)
- Primary cause of end stage renal disease (recipients)
- Specific disease history (recipients)
- Primary cause of death (donors)
- Type of transplant (donors)
- Donor condition (donors)

[redacted]

7.4 Extent of Exposure

The extent of exposure to belatacept will be summarized in two different ways: total number of infusions and length of exposure.

A frequency table summarizing the total number of infusions in the ranges of 5 infusions will be presented for belatacept treatment group.

In addition, the length of exposure to the treatment, defined as the last infusion date - first infusion date + 28 days or death date (if earlier) will be summarized. The frequency will be presented according to the duration ranges (in days): ≤ 28 (≤ 1 month), 29-84 (2-3 months), 85-168 (4-6 months), 169-252 (7-9 months), 253-364 (9-12 months), 365-448 (13-15 months), 449-532 (16-18 months), 533-616 (19-21 months), 617-728 (22-24 months), ≥ 729 (> 24 months).

For the extent of exposure to CNI treatment, only the length of exposure will be presented. This length of exposure is defined as the last dose date - first dose date + 10 days or death date (if earlier). The frequency will be presented according to the duration ranges as mentioned above. The number of subjects in each category will be displayed.

All summaries of exposure (both for total number of infusions and length of exposure) will also include a summary of the mean, the standard deviation, the median and the maximum and minimum values (i.e. range).

For the Month 12 and Month 24 summaries, doses and infusions will be included following the algorithm for Safety population analysis in section 8.3.

7.4.1 Follow up Therapies

The numbers of subjects who switch their treatments (from CNI to belatacept and from belatacept to CNI), and who continue their treatments (CNI medications or commercially available Belatacept) after completion or discontinuation will be tabulated.

For the Month 12 and Month 24 summaries, follow up therapies will be identified as those begun after the last dose or infusion in the windows specified by the algorithm for the Safety population analysis in section 8.3.

7.5 Outcomes

This section and its subsections describe the planned outcome analyses based on data included in the analysis period of interest at each of the two scheduled analysis time points (interim analysis at Month 12 and final analysis at Month 24). Randomization to the study will be stratified by site and screening cGFR. Since the number of subjects randomized at any individual site is expected to be few, site will not be included in any statistical analysis. cGFR is known to be a predictor of renal transplant outcomes. Patients with lower renal function have more complications related to their end stage renal disease, including increased mortality, and are less likely to benefit from conversion from CNI than those with higher renal function. Analyses for key endpoints will include this stratification factor. All analyses for proportions described below which require calculation of point estimates and their corresponding confidence intervals for treatment group differences will utilize minimum risk weights[2] to account for the stratification by screening cGFR, as based on the information recorded in IVRS at the time of randomization.

Any within-treatment confidence interval for the proportion analyses will be computed using normal approximation, if the number of the events in that treatment arm is at least 5. Otherwise, confidence interval using an exact method will be provided. Any between-treatment CI for the proportion difference analyses will also be computed using normal approximation, if the number of the events in each individual treatment arm is at least 5. Otherwise, non-stratification adjusted confidence interval using an exact method will be provided.

The listings of outcome measurements will also be provided.

Unless otherwise specified below, all outcome analyses will be based on all randomized subjects (ITT analysis population).

All outcome analyses will include data collected from randomization, instead of from the first dose date. The reason is that all randomized subjects (even not treated) are included in the ITT analysis population. Using the first dose date as a reference would excluded randomized but not treated subjects.

7.5.1 Primary Endpoint

7.5.1.1 Subject Survival and Graft Survival

The primary composite endpoint of patient and graft survival by 24 months will be summarized within each treatment group using point estimates of the proportion of patients surviving with a functioning graft, and the corresponding 95% CIs. The 95% CIs will also be generated for the difference between the belatacept regimen and CNI to assess the effect of belatacept. Month 24 analyses will be performed using ITT subjects as well as per-protocol subjects. All subjects who were lost of follow-up will be considered as having experienced death or graft loss. No further imputation will be performed for the primary analysis of subjects with unknown patient or graft survival status. Depending upon the particular analysis, the denominator will include all randomized subjects or all per-protocol subjects, respectively. This analysis will be adjusted for screening cGFR values and will use the methodology described in Section 7.5. No p value will be generated. The difference between treatment arms in proportions of subjects who survive with a functional graft at month 24 will be presented along with its 95.1% confidence interval (O'Brien and Fleming alpha spending function adjustment). The 95% confidence interval will also be presented for convenience.

Proportion of subjects who die, proportion of subjects who have a graft loss, and the proportion of subjects who die with a functioning allograft will all be summarized by 24 months within each treatment group.

The primary cause of death and graft loss will also be summarized by treatment arm.

In addition, Kaplan-Meier (KM) estimates of cumulative subject and graft survival rates will also be summarized and graphically displayed.

As part of the exploratory objective of this study, the patient and graft survival by 12 and 24 months will also be summarized by AR up to 12 and 24 months, respectively, within each treatment group using point estimates of the proportion of patients surviving with a functioning graft. This analysis will include only biopsy proven acute rejections during the respective analysis period. A corresponding listing will be provided.

The composite endpoint of patient and functional graft survival by 12 months post-randomization will be summarized using a similar method as for the 24 months analysis. The difference between treatment arms in terms of proportions of subjects who survive with a functional graft at month 12 will be presented along with its 99.69% confidence interval (O'Brien and Fleming alpha spending function adjustment). The 95% confidence interval will also be presented for convenience. No p-value will be produced.

For the month 12 and Month 24 summaries, all analyses of patient survival status and graft survival status, and any graft loss or death will follow the algorithm specified in section 8.3 for the ITT population. Since the protocol Month 24 visits may occur a few calendar days later than 728 days since first dose date, all data up to the upper limit for Month 24, in Table 4 in Section 8.5 will be included as Month 24 data.

A sensitivity analysis will be performed, using the imputation methods for unknown subject and graft survival status described in Section 8.4. Also, for those subjects with unknown status, the number of subjects with AR, PTLD, adverse event of polyomavirus associated nephropathy, and last cGFR < 15mL/min/1.73m^2 will be summarized.

An additional analysis will be performed using no imputation, either for subjects lost to follow-up or for subjects with unknown subject and graft survival status).

A listing of all subjects with unknown subject and graft survival status at time of analysis will be provided.

Additionally, a listing will be provided of all subjects who died or experienced graft loss at any time during the study. For the 12 month analysis, this listing will include all deaths and graft losses in the study, including any reported after Month 12.

7.5.2 Secondary Endpoints

7.5.2.1 Acute Rejection

1) Incidence and severity

   The incidence and severity of AR up to Month 12 and Month 24 post-randomization will be summarized within each treatment group using point estimates and 95% CIs. The 95% CIs will also be generated for the difference in rate of the biopsy proven acute rejection by 12 and 24 months between belatacept and CNI. If a subject has more than one episode of AR, the subject will be counted only once and the episode with the worst grade will be used for the proportion of subjects having biopsy proven AR.

   For the analyses above, only events of biopsy proven acute rejections (Banf Grade of 1A or higher, excluding any borderline or antibody mediated acute rejection) will be included. A sensitivity analysis similar to the one described above will be performed that will include all events of biopsy proven acute rejection, including borderline or antibody mediated acute rejections.

   A sensitivity analysis similar to the one described above will be performed that will include all events of clinically suspected acute rejection, regardless of biopsy confirmation.

2) Time to analysis

   In addition to the analysis of BPAR rates as described above, the time from randomization to the first BPAR episode in each treatment arm will be summarized using Kaplan-Meier curves.

   This analysis will include only biopsy proven acute rejections.

All summaries will be performed using the ITT subject population; in addition, a per-protocol analysis will be performed if in the event that more than 10% of all randomized subjects are identified with a relevant protocol deviation.

The conventions described in section 8.6.1 will apply for all of the above mentioned analyses in this section.

For the 12 month analysis, the algorithm specified in section 8.3 for the ITT population analysis will be followed. For the 24 month analysis, only acute rejections up to Day 728 will be included. Since the protocol-specified Month 24 visit may occur few calendar days later than 728 days from the first dose date, all data up to the upper limit for Month 24, in the Table 4 in Section 8.5 will be included as Month 24 data.

A listing will be provided of all subjects with clinically suspected or biopsy proven acute rejections reported at any time during the study.

7.5.2.2 Renal Function

cGFR

1) Descriptive summaries

   Descriptive summaries of cGFR (based on the 4-variable MDRD formula) will be provided for each treatment group at screening, baseline, Months 1, 3, 6, 9, 12, 15, 18, 21, and 24. (The 12 month analysis will incorporate only time points up to and including Month 12). Mean changes from baseline and Month 3 to the later time points will be summarized as well.

   Descriptive summaries, by treatment group, will be provided for mean percent change from baseline cGFR at Months 1, 3, 6, 9, 12, 15, 18, 21, and 24 months (The 12 month analysis will incorporate only time points up to and including Month 12). Month 24 summaries will be based upon all subjects in the ITT population; a separate, per protocol analysis will be performed in the event that more than 10% of the subjects are identified with a relevant protocol deviation.

   In addition 95% CI of the means will be provided.

   These analyses will be produced using: 1) all available data without any imputation; and 2) all available data **with** imputation of the cGFR to zero, where actual values are missing due to death and graft loss, as described in section 8.4.3)

2) Listing

   A listing of all cGFR values over time will be produced for all randomized subjects, independent of their status with regard to study treatment assignment. This listing will flag the values used for analysis. It will also flag the values that are imputed for some analyses using the algorithm in section 8.4.3. The corresponding change and percent change from baseline and from month 3 will also be listed.

3) Descriptive summaries of cGFR by Acute Rejection

   As part of the exploratory objectives of the study, the descriptive summaries of cGFR at 12 and 24 months post randomization and the corresponding mean change and mean percent change from baseline will also be repeated by acute rejection status up to 12 months and 24 months respectively. This analysis will include only biopsy proven acute rejections during the respective analysis period.

This analysis will be produced only the month 24 analysis.

This analysis will be produced both using 1) all available data without any imputation and 2) all available data imputing values for missing data due to death and graft loss as described in section 8.4.3)

4) Linear mixed model for repeated measures

A superiority test of the difference (CNI - belatacept) in both mean percentage change and mean change of cGFR from baseline to Month 24 between belatacept and CNI will be performed using a linear mixed model for repeated measures with terms of baseline cGFR, treatment, month, and interaction of treatment by month. The variable month will be categorical. The unstructured (UN) covariance structure will be assumed. If computation convergence becomes an issue, the compound symmetric (CS) covariance structure will be used.

For the 12 month analysis, the difference between treatment arms in the mean percent change and mean change of cGFR from baseline to Month 12 will be presented along with its 99.69% confidence interval. The 95% confidence interval will also be presented for convenience. A superiority test will also be performed using the same model and a two sided p-value will be presented and compared to the adjusted significance level 0.0031 (O'Brien and Fleming alpha spending function adjustment). For the 12 month analysis, time will include data from Months 1, 3, 6, 9, and 12.

For the 24 month analysis, the difference between treatment arms in the mean percent change and mean change of cGFR from baseline to Month 24 will be presented along with its 95.1% confidence interval. The 95% confidence interval will also be presented for convenience. A superiority test will also be performed using the same model and a two sided p-value will be presented and compared to the adjusted significance level 0.049 (O'Brien and Fleming alpha spending function adjustment). For the 24 month analysis, time will include data from Months 1, 3, 6, 9, 12, 15, 18, 21, and 24.

P-values and corresponding adjusted confidence intervals will be produced only for the 12 and 24 months in the analyses mentioned above. For all other months, the point estimates and the corresponding 95% confidence intervals will be provided.

All these analyses includes adjustment for baseline cGFR values. The randomization stratification factor of screening cGFR categories will not be included in the model.

These analyses will be produced both using 1) all available data without any imputation and 2) all available data imputing values for missing data due to death and graft loss as described in section 8.4.3).

The analysis of mean percent change from baseline using non imputed values will be considered the main analysis. All other analyses will be considered as sensitivity analyses.

5) Proportion of subjects:

The proportion of subjects with > 5% and > 10% improvement over baseline in cGFR at 12 and 24 months will be summarized for each treatment group, respectively.

For the 12 month analysis only the estimates at 12 months will be produced. For the 24 months analysis, both the estimates at 12 and 24 months will be produced.

This analysis will be produced both using 1) all available data without any imputation and 2) all available data imputing values for missing data due to death and graft loss as described in section 8.4.3)

6) Linear mixed model for trend analysis

To assess the trend in renal function, a linear mixed model will be used to analyze the changes in cGFR from baseline to months 1, 3, 6, 9, 12, 15, and 18, 21 and 24 for each regimen with terms for treatment, baseline cGFR as fixed effect, and treatment-by-month interaction as well as month (continuous covariate) as random effect. Unstructured covariance structure will be used. Population mean slopes will be estimated for each treatment group. In addition, the 95% confidence intervals will also be obtained for each mean slope.

For the 12 month analysis, all months up to and including month 12 will be used. For the 24 month analysis, all months up to and including month 24 will be used.

This analysis includes adjustment for baseline cGFR values. The randomization stratification factor of screening cGFR categories will not be included in the model.

The same analysis will be produced for the change in cGFR from Month 3. This analysis will include data from month 3 onwards up to and including month 12 and 24, respectively for the month 12 and 24 analyses.

These analyses will be produced both using 1) all available data without any imputation and 2) all available data imputing values for missing data due to death and graft loss as described in Section 8.4.3).

7) Time to analysis

As part of the exploratory study objective, to diminish the contribution that patients with slower kidney disease progression have on the analysis of change in cGFR over time and to further evaluate the treatment effect on renal function over time[3], the time to cGFR < 15 ml/min/1.73m^2 or graft loss or death from baseline and Month 3 will be summarized for both GFR strata using Kaplan-Meier curves.

This analysis will be produced only the month 24 analysis. This will be produced only using all available data without any imputation, since death and graft loss are included in the definition of the "event".

The algorithm in section 8.3 for the ITT population analysis will be followed for both the Month 12 (interim) and Month 24 (final) analyses.

Serum creatinine

1) Descriptive summaries

   A similar analysis as for cCFR will be performed including descriptive summaries of serum creatinine and change from baseline (see point 1) in the analysis of cGFR above).

2) Linear mixed model for trend analysis

   Also a similar analysis as for cCFR in 1/serum creatinine will be performed including a linear mixed model for trend analysis for 1/serum creatinine will also be performed (see point 6) in the analysis of cGFR above). This analysis will include the baseline serum creatinine value as covariate, instead of the baseline cGFR.

No imputation for missing values will be used in any of the above analyses. The algorithm in section 8.3 for the ITT population analysis will be followed for both Month 12 and Month 24 analyses.

Urine protein/ creatinine ratio

Urine protein/ creatinine ratio (UPCR) will be summarized descriptively by means and standard deviation by treatment group at baseline, 3, 6, 12, and 24 months post-randomization. The analysis at 12 months will include all months up to and including month 12. The analysis at month 24 will include all months up to and including 24 months. In addition 95% CI of the means will be provided.

No imputation for missing values will be used in any of the above analyses. The algorithm in section 8.3 for the ITT population analysis will be followed for both Month 12 and Month 24 analyses.

7.5.2.3 Hypertension

Systolic and diastolic blood pressure

Descriptive summaries of systolic and diastolic blood pressure at baseline, Months 1, 3, 6, 9, 12, 15, 18, and 24 will be provided for each treatment. Mean change in systolic and diastolic blood pressure from baseline to 12 and 24 months will be summarized descriptively.

The 12 month interim analysis will include all time points up to and including Month 12 (see section 8.3 for the ITT population analysis algorithm). The 24 month (final) analysis will include all time points up to and including month 24 (see section 8.3 for the ITT population analysis algorithm).

Intensity of anti-hypertensive treatment

The intensity of anti-hypertensive treatment regimens at 12 and 24 months will be summarized descriptively. For each analysis time point, the intensity of anti-hypertensive therapy for a

hypertensive subject will be determined by the number of unique generic medications that the subject is taking on the target day of the analysis time point (i.e., Month 12 = Day 364, Month 24 = Day 728).

The 12 month analysis will include all time points up to and including month 12 (see section 8.3 for the ITT population). The 24 month analysis will include all time points up to and including month 24 (see section 8.3 for the ITT population). Since the protocol Month 24 visits may occur few calendar days later than 728 days since first dose date, all data up to the upper limit for Month 24, in the Table 4 in Section 8.5 will be included as Month 24 data.

[redacted]

7.5.2.5 New Onset Diabetes Mellitus After Transplantation (NODAT)

Proportion of subjects who develop NODAT at 12 and 24 months post-randomization will be summarized using point estimates and 95% CIs within each treatment group. The 95% CIs will also be generated for the difference between the belatacept regimen and CNI. NODAT definition is provided in the protocol, section 5.3.11. A corresponding listing of all subjects who meet the NODAT criteria at any time during the study will be also provided. For the 12 month analysis, all cases of NODAT in the database will be included in the listing. The 12 month analysis will include all time points up to and including month 12 (see section 8.3 for the ITT population analysis algorithm). The 24 month analysis will include all time points up to and including month 24 (see section 8.3 for the ITT population analysis algorithm).

7.5.3 Subgroup Analyses

Subgroups analyses of key outcome measures (subject and graft survival by Month 12 and Month 24 and acute rejection by Month12 and Month 24 as well as mean percent changes in cGFR from baseline to Month 12 and Month 24) will be performed (refer to the sections above for the definition of the main analysis in each of these endpoints).

Summary statistics for the above outcome measures by treatment arm will be presented. Interpretation will be meaningful, for only those subgroup categories (see Table 3 below) that consist of 10% or more of the total study population.

No statistical tests will be performed for subgroups.

Table 3: Subgroup Categories for Key Endpoints

Subgroup factor	Categories
Type of Transplant	Living-Related Living-Unrelated Cadaveric
Recipient gender	Male Female
Recipient race	White Black Other
Geographic region	North America Latin America Europe
Recipient age	< 50 years old ≥ 50 years old
Donor age	< 50 years old ≥ 50 years old
End stage renal disease (Diabetes)	Yes No
Initial CNI treatment	CsA Tacrolimus
Baseline GFR (ml/min/1.73m^2)	<45 45 - <60 ≥ 60
Time from Transplantation to Randomization	6-12 months >12 months
Baseline Treatment Regimen	TAC + MMF / CsA + MMF / CsA + MPA TAC + MPA

7.6 Safety

All safety analyses will be based on Safety population. The frequencies and incidence rates starting from first dose date/time will be summarized by treatment groups. There will be no statistical testing of group differences with respect to frequencies of adverse events or laboratory marked abnormalities or changes in clinical laboratory tests from baseline.

All safety summaries will be based only on data included in the analysis period of interest at each of the scheduled analysis time points.

The stating point of all the above analysis periods is the first dose date since this analysis includes all randomized and treated subjects (safety population). The end point for the Month 12 (interim) and Month 24 (final) analysis periods is defined in section 8.3 following the algorithm for the Safety population analyses.

All safety listings will include all data reported in the database, independently of study period. All events post the analysis period window will be flagged for the respective analysis.

7.6.1 Adverse Events Analysis

7.6.1.1 All adverse events

Adverse Events are recorded by the investigators on the Serious and Non-Serious Adverse Event page(s) of the CRF. All investigators are required to report the nature, the onset and resolution date, intensity, action taken, treatment required for event, and to express their opinion regarding the relationship between the AE and the study medication.

Summary information (the number and percent of subjects by treatment) will be tabulated for:

- All AEs including clinical and laboratory adverse events
- Most common AEs (reported in at least 5% of subjects in any treatment group)
- Treatment Related AEs
- Serious adverse events (SAE)
- SAEs/AEs leading to discontinuation of study therapy
- Adverse events categorized by severity
- Serious adverse events and related serious adverse events with death as an outcome following EudraCT requirements.

Summaries will be presented by treatment groups and categorized by System Organ Classes (SOCs) and Preferred Terms (PTs) for the 12 month (for the 12 month interim analysis) and for the 24 month analysis window periods.

Listings for deaths, AEs, SAEs, and AEs/SAEs leading to discontinuation of study therapy will be provided. Detailed conventions for counting events are provided in Section 8.7.

Incidence rates for AEs/SAEs will be provided, where exposure (in days) of a subject is calculated from the first dose date to the event date, or the upper limit of the corresponding analysis period (see Section 7.6). The incidence rate = 100 * number of subjects with specified AEs/SAEs /total exposure in years which is computed as total exposure in days divided by 365.25. For a subject who had multiple occurrences of a specific event, the first occurrence date of the event will be the event date.

7.6.1.2 Adverse Events of Clinical Interest

Following adverse events of special interest obtained from the CRF pages will be listed and summarized by treatment group:

- Serious Infections
- Post-Transplant Lymphoproliferative Disorder (PTLD)
- Progressive multifocal leukoencephalopathy (PML)
- Malignancies (other than PTLD) including non-melanoma skin carcinomas
- Tuberculosis Infections (serious and non-serious)
- CNS Infections (serious and non-serious)
- Viral Infections (serious)
- Infusion related reactions

Additionally, the proportion of infections and malignancy at 12 and 24 months will be summarized by acute rejection status up to 12 and 24 months respectively. This analysis will include only biopsy proven acute rejections during the respective analysis period.

Additional summaries of PTLD, malignancies, and serious infections will be provided including all available data at the 12 months and 24 months.

Detailed conventions for counting events are provided in Section 8.7. Listing of all the above mentioned adverse events will also be based on all available data up to database lock.

Incidence rates will be calculated for SAEs and AEs of clinical interest by specified time periods (up to Year 1 for the 12 month interim analysis, up to Year 2 for the 24 months analysis, and up to database lock). The numerator is the number of subjects having the first occurrence of the event within the period specified. The denominator is the overall total exposure in years (total exposure days/365.25) within the period specified (see Section 7.6 for the definition). However, for these summaries subjects experiencing the event of interest will have their exposure censored at the time of the first occurrence of the event. The resulting incidence rate is multiplied by 100 to express the rate per 100 person-year of exposure.

7.6.1.3 Multiple Adverse Events

Descriptive summaries of adverse events that takes into account the number of occurrences that an AE was reported by individual patient will be provided. In order to prepare these summaries, the AE data will be processed according to standard BMS algorithms to categorize each line of patient data as a new occurrence or a continuation of an existing event. This determination will be based upon onset and resolution dates. All continuations of an existing event will be collapsed into a unique AE record. Each line of patient AE data will represent a unique AE record and will contain the earliest onset day, the latest resolution day (if available), highest intensity, treatment ever required, the maximum severity observed, the last known assessed relationship to study medication by the investigator as well as highest action taken in the order of (highest to lowest): drug discontinued, drug interrupted, dose reduced, dose increase, and none.

This data will be presented as the rate per 100 years of patient exposure. Exposure to study medication will be calculated according to approved standard BMS algorithms as well and following the definitions in Section 7.6.

As an example, if 10 patients report 8 unique episodes of headache and had a combined cumulative exposure of 40 years to study medication, the incidence rate is reported as 8/40*(100) or 20 cases per 100 patient years of exposure.

The summary information will be tabulated for:

- The total number and incidence rate (exposure adjusted) of occurrences for all AEs occurring in at least 5% of the subjects in Safety population (defined in Section 6.2)
- Events of clinical interest and SAEs:
  - the total number of events and incidence rate (exposure adjusted) at every 6-month time intervals
  - the number of subjects experiencing an AE once or multiple times

A listing of all unique AE records will be also provided.

EudraCT Summaries

Exposure adjusted adverse event summaries including multiple occurrences of unique adverse events for EudraCT reporting requirements will be presented by treatment. These summaries include serious adverse events, drug related serious adverse events and non-serious adverse events using a global cutoff of 5 percent.

7.6.2 Laboratory Tests Analysis

Laboratory marked abnormalities using pre-defined abnormality criteria in APPENDIX 2 will be descriptively summarized with frequency and percentage of subjects meeting them for each of the analysis periods. All laboratory values of a lab parameter (independently of study period) for subjects with at least one marked abnormality for this parameter will be listed.

All available laboratory parameters mentioned in Hematology panel, Chemistry Panel in the protocol Section 5.3.51 will also be summarized overtime for the 12 and 24 months analyses, respectively (with mean, SD, median, min, Q25, Q75, max).

7.6.3 Other Safety Considerations

[redacted]

7.6.3.2 Vital Signs

Heart rate (per minute) will be summarized by treatment (with mean, SD, median, min, Q25, Q75, max) at baseline, months 1, 3, 6, 9, 12, 18 and 24 for the 12 and 24 months analyses, respectively.

The analysis of systolic and diastolic blood pressure over time are described in Section 7.5.2.3.

Clinically significant changes in vital signs will be summarized by treatment for the 12 and 24 months analyses, respectively. Clinically significant changes are defined as

1) standardized SBP ≥ 130mmHg
2) standardized DBP ≥ 80mmHg

7.6.3.3 Pregnancy Test Results

By-subject listing of all positive pregnancy test results at any time during the study will be provided using safety analysis population.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.9.1 Modified Transplant Symptom Occurrence and Symptom Distress Scale (MTSOSD-59R)

The proportion of subjects by frequency of experiencing each symptom and the corresponding intensity of distress and the corresponding 95% CI will be reported by treatment group at

baseline, Week 6, and Months 3, 6, and 12 post - randomization. The 95% CI will also be generated for the difference between belatacept regimen and CNI in proportions experiencing each symptom at Week 6, and Months 3, 6, and 12 post - randomization. These analyses will also be performed in a sub-group of subjects who reported experiencing the symptom at baseline.

The total number of symptoms (sum of responses across all 59 items) and the total of all 59 items of the corresponding symptom distress will be summarized with mean (standard deviation) and corresponding 95% CI for each treatment group at baseline, Week 6, and Months 3, 6, and 12 post randomization.

The Month 12 (interim) and Month 24 (final) analysis periods will be defined following the algorithm in section 8.3 for analyses using the Safety population.

7.11 Interim analysis

The interim analysis at month 12 will include selected analyses as specified in the Data Presentation Plan.

8 CONVENTIONS

The conventions to be followed in the computation of summary measures of outcome and safety endpoints are described in this section.

8.1 Calculations of Key Measures

8.1.1 cGFR

MDRD: GFR = 170 x [SCr/0.95]^(-0.999) x [Age]^(-0.176) x [0.762 if patient is female] x [1.180 if patient is black] x [BUN]^(-0.170) x [Alb]^(+0.318)

{Age in years, Alb = Albumin in g/dL; SCr = Serum creatinine in mg/dL; BUN = Blood urea nitrogen in mg/dL}

8.1.2 Screening GFR

The screening cGFR is defined as the most recent value obtained prior to Day 1 (the day of randomization). The screening cGFR value will be utilized to stratify patient randomization. The screening cGFR will also be used to identify GFR categories for subgroup analyses for key outcome measures as described in the Section 7.5.3. Some patients will have 2 cGFR values collected during the screening period (D-30 to D-1) in order to confirm renal function stability. The most recent (i.e. last) value obtained prior to D1 is the screening cGFR.

8.1.3 Baseline GFR

Baseline GFR is defined as most recent measurement prior to the first dose on Day 1. Baseline cGFR will be collected on Day 1, post randomization and before the first dose of study drug is administered. The baseline cGFR will be utilized to assess subsequent changes from the baseline cGFR at various time points, a key secondary endpoint for the study. This value is collected on the day of randomization and is not expected to be missing. If it is missing, then the most recent cGFR collected prior to D1 (i.e. the screening cGFR) will be used to impute the missing value.

8.2 Definition of first dose date/time

For both treatment groups, the first dose date/time is the date/time at which the first dose of assigned study drug is administered, on or after the date/time of randomization.

For subjects assigned to the belatacept conversion arm, this corresponds to the date/time of the start of the first infusion.

For subjects assigned to the CNI continuation arm, this corresponds to the date/time of the first dose of CNI administered after the date and time of randomization.

8.3 Analysis Period of Interest

At Month 12 (Year 1) and Month 24 (Year 2), summary of outcome will be based on all available data.

For the Month 12 interim analysis, the following algorithm will be used to identify data accrued during the first 12 months of the study:

- For each subject, the visit date corresponding to the Month 12 visit will be identified, independent of whether the subject remained on study treatment or was discontinued from study treatment prior to that time point. This rule is intended to take into account the protocol allowed window around the actual Month 12 visit.

For each subject, the Month 12 visit date will be the date on which data for the Month 12 visit was collected (CRF code 170) for physical measurements and/or vital signs and/or laboratory analytes. Situations in which more than one collection date is associated with the Month 12 visit, because data collection occurred on more than one calendar day, then the date between these days that is closer to Day 364 will be considered as the Month 12 visit date.

For analyses using the **Intent-to-Treat population** (i.e. all randomized subjects), the following algorithm will be used:

- For subjects for whom a **Month 12 visit date** is available, all data up to and including this date will be considered as occurring during the first 12 Months of the study.
- For subjects for whom a **Month 12 visit date is not available** due to subject discontinuation from both study treatment and further study participation prior to their

Month 12 visit, all their data will be considered as having been collected during the first 12 Months of the study.

For analyses using the **Safety population** (i.e. all randomized and treated subjects), the following algorithm will be used:

- For subjects for whom a **Month 12 visit date** is available, all data up to and including the **earlier** of the following dates will be considered as having occurred during the first 12 months of the study: 1) the date corresponding to last dose date + 56 days; or 2) The actual Month 12 visit date.
- For subjects for whom a **Month 12 visit date is not available** due to subject discontinuation from both study treatment and study participation prior to their Month 12 visit, any data on or prior to the **earlier** of the following dates will be considered as having occurred during the first 12 months of the study: 1) the date corresponding to last dose date + 56 days; or 2) Day 364.

The above algorithm will be used in conjunction with any other algorithms (e.g. baseline definition, Table 4 in Section 8.5, etc.) for tabulations and summaries for the Month 12 analyses. All data available in the database at the time of the database lock for the Month 12 analyses will be included in the listings. Any data collected after last dose + 56 days, or after the Month 12 visit date, will be flagged in the listings.

For the Year 2 analysis, all data up to Day 728 (as defined in Table 4 in Section 8.5) will be included for summary tabulation analysis, based on the Intent-to-Treat population. For the analyses based on the Safety population, all data up to and including the last dose date +56 days will be included for tabulation analysis of Year 2. These algorithms will be used in conjunction with any other relevant algorithms (e.g. baseline definition, Table 4 in Section 8.5, etc.). Listings will include all available data; data reported after the 56-day cutoff will be flagged in the listings.

8.4 Missing Data Handling

8.4.1 Subject Survival and Graft Survival

Any subject (either randomized to belatacept or CNI) with unknown subject and graft survival status at Month 12 (Month 24) (last follow-up date is prior to Day 392 (Day 756), will be considered as having an event of graft loss or death if at least one of the following criteria are met during 12 months (24 months) post-randomization.

1) Subject has AR prior to last follow-up date;
2) Subject has PTLD prior to last follow-up date;
3) Subject's discontinuation reason for study medication is due to Lack of Efficacy;
4) Subject has polyomavirus associated nephropathy adverse event before discontinuation;
5) Subject's last cGFR < 15mL/min/1.73m^2.

For the remaining subjects with unknown status, they will be considered as having no event of graft loss or death.

This imputation method (sensitivity analysis) is applied in conjunction with any other imputation method mentioned in Section 7.5.1.1.

8.4.2 Acute Rejection

Any acute rejection-free subject who is not followed-up through the entire event-counting period due to any reason will be considered as having no acute rejection during that period.

8.4.3 Renal Function

Missing cGFR values due to death or graft loss will be imputed with value of 0 and the value of 0 will be carried forward up to month 24. Missing values of cGFR due to reason other than death/graft loss will not be imputed cGFR values calculated from serum creatinine concentrations obtained following resumption of maintenance dialysis are invalid as a biomarker of GFR and will be censored.

8.5 Day Ranges for Analysis Time Points

Subjects do not always adhere strictly to the visit schedule timing in the protocol. Therefore the designation of the visits/months during the study will be based on the day of evaluation relative to day 1 of the trial (day of randomization = study day 1) rather than the nominal visit/month recorded in the case report form (CRF).

There are different types of day ranges that will be involved in the analyses. Each is defined as below.

- Subject and graft survival and acute rejection related endpoints:

  By Month 12: Defined as Day 1 to Day 392

  By Month 24: Defined as Day 1 to Day 756

- NODAT:

  By Month 12/ Year 1: Defined as Day 29 to Day 392

  By Month 24/ Year 2: Defined as Day 29 to Day 756.

- Renal Function Parameters (cGFR, albumin, BUN, SCr), [redacted] Blood Pressure Parameters (Systolic, Diastolic), safety laboratory panel parameters, HbA1c, MTSOSD-59R, and [redacted]

Table 4: Day Ranges for Analysis Time Points

At Month	Target Day	Day Range
1	28	1-56

Table 4: Day Ranges for Analysis Time Points

At Month	Target Day	Day Range
3	84	57-112
6	168	141-196
9	252	225-280
12	364	337-392
15	448	421-476
18	532	505-560
21	616	589-644
24	728	701-756

Note that, if a subject has more than one measurement recorded within the window for that time point, the measurement closest to the target day for that time point will be used. In case of ties between observations, the later measurement will be used.

8.5.1 Baseline Measurements

Baseline measurements the most recent measurement prior to the first dose of study drug on Day 1 for cGFR analysis. For all other endpoint; labs, blood pressure, vital signs, and [redacted] baseline measurement is the one collected at randomization (Day 1).

8.6 Counting Rules for Outcome Analyses and Longitudinal Summaries

8.6.1 Conventions for Counting Outcome Events

The counting rules for computing proportions for outcome endpoints are laid out in this section.

For any endpoint under consideration, the end of the event-counting period will be first determined for each subject following the algorithm described in section 8.3. If a subject has at least one episode (evidence) of the event during this event-counting period, then he/she will be included in the analysis and the episode (evidence) with the worst grade will be counted. If there are multiple episodes with the same severity (grade), then the first incidence will be counted.

For analyses that are based on summaries of number of subjects and proportions, the following conventions will apply:

- the numerator will include all subjects with an event by the analysis Day corresponding to the analysis (e.g. Day 364 or Day 728, respectively for the month 12 and 24 analysis).
- the denominator will include:
  - all subjects in the analysis population

- or discontinued study medication but remained in the study,
- or had an event up to the analysis Day.
- Subjects who discontinued from the study for reasons other than the event prior to the analysis day will not be included in these analyses.

For analyses that are based on Kaplan-Meier estimates, all available information from all randomized subjects will be included. The time will be calculation following these conventions:

- For subjects with an event, time will be counted until the time of the event. In case a subject experience more than one events, the earlier time of the two events will be used.
- For subjects that completed the analysis period without an event, time will be counted to the end date of the period (e.g. Day 364 or Day 728).
- For subjects that discontinued the treatment period but remained in the study up to the end of the analysis period without an event, time will be counted to the end date of the period (e.g. Day 364 or Day 728).
- For subjects that discontinued both the treatment period and the study prior to the end of the analysis period without any event, time will be counted until their latest visit in the study (defined as latest study visit date or any study assessment).

Since the protocol Month 24 visit may occur few calendar days earlier or later than 728 days since first dose date, all data collected up to and including the date defined as the upper limit for Month 24, as in the Table in Section 8.5 will be included as Month 24 data.

8.7 Safety Data Conventions

Safety data will be handled according to the BMS safety data convention standards and Supplement to Safety Guidelines for BMS-224818.

8.7.1 Counting Rules for Adverse Events

All adverse events (AE) are coded and grouped into Preferred Terms (PT) by System Organ Class (SOC), using the Medical Dictionary for Regulatory Activities (MedDRA). Listings and summaries will be based on the resulting SOCs and PTs.

A clinical AE is categorized as either a concomitant event (CE; an event indicated by the investigator to be unrelated or not likely related to study medication) or an adverse drug experience (ADE; an event indicated by the investigator to be related to study medication, or a missing relationship).

Investigator-identified laboratory AEs are defined as laboratory abnormalities for which investigators record information on the AE pages of the CRF. These particular events are those that the investigator considered clinically significant.

For data analysis and reporting purposes, recurrent or continuing AEs, if any, will be counted only once based on the following factors in order of precedence:

- Relationship: ADEs will take precedence over CEs;
- Intensity: the highest intensity event will be counted;
- Onset date and time: the first occurrence will be counted.

If the investigator does not report the intensity of an AE and it is not obtainable from subsequent querying of the investigator, a classification in between severe and very severe will be assigned for the purpose of these counting rules. According to the AE dictionary, it is possible that different AEs may map to the same preferred term. If two different AEs with the same preferred term are reported by the same subject, only one will be counted.

Counting for the summaries of adverse events will begin immediately after randomization or specific day for a specified analysis time window. For the summary of adverse events and serious adverse events, during the analysis time window, the end of the event counting period will be determined as follows:

- For subjects who did not discontinue study therapy during the specified analysis time window:

  The end of analysis time window

- For subjects who discontinued study therapy during the specified analysis time window:

  The earlier date of the end of the analysis time window and 56 days after the last dose date of study medication, in conjuction with the algorithm described in section 8.3 for analyses using the Safety population.

8.8 Missing, Unknown or Partial Dates

No imputation of event dates will be performed on any outcome endpoints including acute rejection, graft loss, death, laboratory measures, blood pressures, with an exception in cases where the onset date of an episode related to acute rejection is unknown, then the date of the first biopsy for that episode will be used as the onset date of the episode.

Missing Start Dates of study therapy

No date imputation will be done for missing start dates of study therapy.

[redacted]

[redacted]

Missing or Partial Onset Dates of Adverse Events

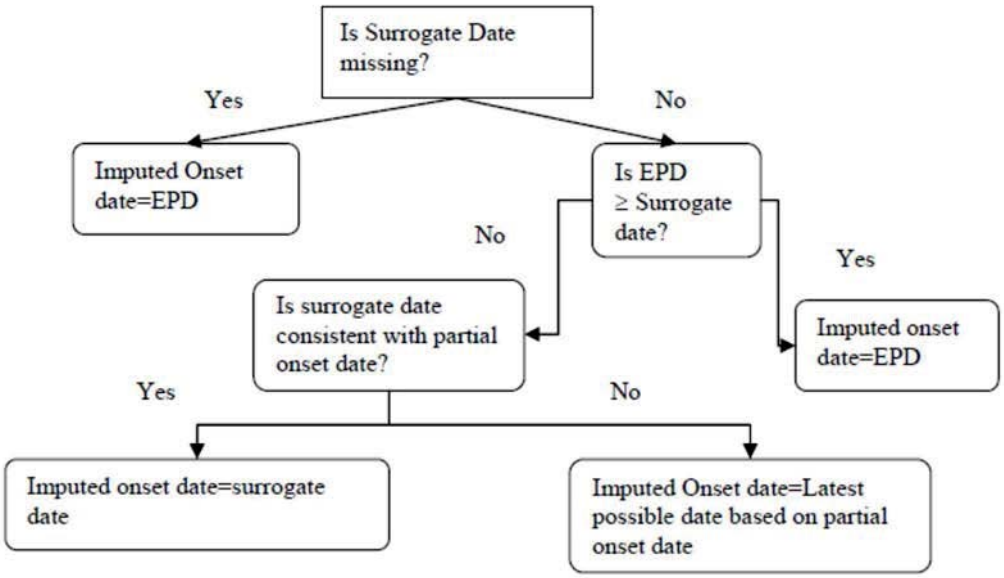
Before imputing any missing or partial onset dates, two new dates will be defined: a surrogate date for each onset date (missing or partial), and an earliest possible date (EPD) for each partial onset date. The surrogate date will be defined as the first non-missing valid date from the following list (in order of precedence):

- first active study medication date of any study medication,
- informed consent date, or
- visit date corresponding to the visit at which the event was reported if a valid non-missing date is not available for any of these dates, the surrogate date will be set to missing.

The EPD is based on the partial onset date itself. For instance, if the available partial start date is Year 2013, then the EPD will be 01 January 2013. However, if the available partial start date is May 2013, then the EPD will be 01 May 2013.

If the onset date is missing, then the imputed onset date will be the surrogate date as defined above. If the surrogate date is missing, then the imputed onset date will be the visit date.

If the onset date is only partially available, the imputation of the onset date will follow different rules depending on whether the surrogate date is missing or not. Partial date imputation is illustrated in the following diagram. (If the surrogate date is missing, then the imputed onset date will be the EPD. If the surrogate date is not missing, then the imputed onset date will depend on whether the EPD is earlier than the surrogate date or not. If the EPD is not earlier than the surrogate date, then the imputed onset date will be the EPD. Otherwise, the surrogate date will be used as the imputed onset date provided the surrogate date is consistent with the partial onset date. If the surrogate date is inconsistent with the partial onset date, then the imputed onset date will be the latest possible date based on the partial onset date.)



9 CONTENT OF REPORTS

The results of the study will be presented in a standard BMS Clinical Study Report (CSR). Key results and any unanticipated findings that are unusual for this study will be identified. A meeting for the initial dissemination of study results will be held after database lock. Attendees at this meeting will review efficacy and safety summaries and listings and will identify key results that should be highlighted in the CSR.

10 LIST OF ABBREVIATIONS

Table 5: LIST OF ABBREVIATIONS

Term	Definition
ADA	Anti-Drug Antibodies
AE	Adverse Event
ANCOVA	Analysis of covariance
AR	Acute Rejection
BPAR	Biopsy proven AR
BMS	Bristol-Myers Squibb
BMS-224818	LEA29Y (belatacept)

Table 5: LIST OF ABBREVIATIONS

Term	Definition
BP	Blood Pressure
BUN	Blood Urea Nitrogen
cGFR	Calculated Glomerular Filtration Rate
CI	Confidence Interval
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CRF	Case Report Form
CsA	Cyclosporine A (cyclosporin)
CSR	Clinical study report
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
DSA	Donor Specific Antibodies
EBV	Epstein-Barr virus
EC-MPS	Enteric-coated Mycophenolate Sodium
GFR	Glomerular Filtration Rate
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HLA	Human Leukocyte Antigen
HUS	Hemolytic Uremic Syndrome
Ig	Immunoglobulin
ITT	Intent-To-Treat
IVRS	Interactive Voice Response System
LDL	Low-density lipoprotein
MedDRA	Medical Dictionary of Drug Regulatory Activities
MMF	Mycophenolate mofetil
MPA	Mycophenolic acid
MDRD	Modification of Diet in Renal Disease (study)
MTSOSD-59R	Modified Transplant Symptom Occurrence and Symptom Distress Scale-59R
NODAT	New Onset Diabetes After Transplantation
NULOJIX	Commercial belatacept
PD	Pharmacodynamics
PK	Pharmacokinetic(s)
PML	Progressive multifocal leukoencephalopathy

Table 5: LIST OF ABBREVIATIONS

Term	Definition
PTLD	Post-Transplant Lymphoproliferative Disorder
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SCr	Serum Creatinine
TAC	Tacrolimus
TG	Triglyceride
[redacted]	[redacted]
UPCR	Urinary protein/creatinine ratio

[redacted]

APPENDIX 2 MARKED LABORATORY ABNORMALITY CRITERIA

Thresholds for defining markedly abnormal laboratory analyte values (per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0 (published 29-May-2009)

Analyte	Formated Value	Code	Lower threshold for Marked Abnormality			Upper threshold for Marked Abnormality		
			US conventional unit	Conventional units	SI Units	US conventional unit	Conventional units	SI Units
Hemoglobin	Hemoglobin	**HB**	<8.0 g/dL	<8.0 g/dL	<80 g/L	More than 4.0 g/dL > ULN*	More than 4.0 g/dL > ULN*	More than 40 g/L > ULN
White blood cell (WBC) count	Leukocytes	**WBC**	<2.0 x 10*9C/L (10*9 C/L = 10*3 C/uL)	< 2,000/mm^3	<2.0 x 10*9 C/L			
Absolute lymphocytes	Lymphocytes (absolute)	**LYMPA**	<0.5 x 10*9 C/L (10*9 C/L = 10*3 C/uL)	<500/mm^3	<0.5 x 10*9 C/L	>20 x 10*9 C/L	>20,000 /mm^3	>20 x 10*9 C/L
Absolute neutrophils	Neutrophils (absolute)	**NEUTA**	<1.0 x 10*9 C/L (10*9 C/L = 10*3 C/uL)	<1,000/mm^3	<1.0 x 10*9 C/L			
Platelets	Platelet Count	**PLAT**	<50 x 10*9 C/L (10*9 C/L = 10*3 C/uL)	<50,000/ mm^3	<50 x 10*9 C/L			
Serum creatinine	Creatinine	**CREAT**				>3.0 mg/dL	>3.0 mg/dL	>265 umol/ L
Urinary protein/creatinine ratio	Protein/Creatinine Ratio	**PRCRR**				>=3500 mg/mg creatinine	>=3.5 grams/mg creatinine	>395 mg/mmol creatinine
Serum sodium [Na]	Sodium, Serum	**NA**	<130 mEq/L	<130 mEq/L	<130 mmol /L	>155 mEq/L	>155 mEq/L	>155 mmol/ L

Analyte	Formated Value	Code	Lower threshold for Marked Abnormality			Upper threshold for Marked Abnormality		
			US conventional unit	Conventional units	SI Units	US conventional unit	Conventional units	SI Units
Serum potassium [K]	Potassium, Serum	**K**	<3.0 mEq/L	<3.0 mEq/L	<3.0 mmol/L	>6.0 mEq/L	>6.0 mEq/L	>6.0 mmol/L
Bicarbonate [HCO_3]	Bicarbonate	**HCO3**	<11 mEq/L	<11 mmol/L	<11 mmol/L			
Serum calcium [Ca]	Calcium, Total	**CA**	<7.0 mg/dL	<7.0 mg/dL	<1.75 mmol/L	>12.5 mg/dL	>12.5 mg/dL	>3.1 mmol/L
Serum magnesium [Mg]	Magnesium, Serum	**MG**	< 0.8 mEq/L	<0.9 mg/dL	<0.4 mmol/L	> 2.5 mEq/L	>3.0 mg/dL	>1.23 mmol/L
Serum phosphorus [P]	Phosphorus, Inorganic	**PHOS**	<2.0 mg/dL	<2.0 mg/dL	<0.6 mmol/L			
Serum albumin	Albumin	**ALB**	<2.0 g/dL	<2.0 g/dL	<20 g/L			
Serum uric acid	Uric Acid	**URIC**				>10.0 mg/dL	>10.0 mg/dL	>0.59 mmol/L
Fasting blood glucose	Glucose, Fasting Serum	**GLUCF**	<40 mg/dL	<40 mg/dL	<2.2 mmol/L	>250 mg/dL	>250 mg/dL	>=14.0 mmol/L
Cholesterol	Cholesterol, Total (TC)	**CHOL**				>400 mg/dL	>400 mg/dL	>10.3 mmol/L
Triglycerides	Triglycerides, Fasting	**TRIGF**				>500 mg/dL	>500 mg/dL	>5.7 mmol/L
Serum aspartate aminotransferase (AST)	Aspartate Aminotransferase (AST)	**AST**				>5.0 x ULN*	>5.0 x ULN	>5.0 x ULN
Serum alanine aminotransferase (ALT)	Alanine Aminotransferase (ALT)	**ALT**				>5.0 x ULN*	>5.0 x ULN	>5.0 x ULN
Serum alkaline phosphatase	Alkaline Phosphatase (ALP)	**ALP**				>5.0 x ULN*	>5.0 x ULN	>5.0 x ULN
Serum total bilirubin	Bilirubin, Total	**TBILI**				>3.0 x ULN*	>3.0 x ULN	>3.0 x ULN

* ULN: Upper limit of laboratory reference range. note: ULN should be in the same unit.

** Threshold not defined in NCI CTCAE v. 4.0

APPENDIX 3 DOCUMENT HISTORY

Table 7: Document history

Version Number	Author(s)	Description
1.0	[redacted]	Original Issue
2.0	[redacted]	1. Section 1: a. alignment with the protocol language b. addition of clarifications regarding the schedule of the analyses c. updates and clarification as per the correspondence with FDA 2. Section 2 a. alignment with the protocol language b. updates to the language to bring more clarity c. updates and additions of the description of the protocol amendments. 3. Sections 3, 4 and 5 a. alignment with the protocol language b. updates to the language to bring more clarity c. Sections 4: removal of the header of "Other secondary endpoints" to align with the protocol 4. Section 6 a. alignment with the protocol language b. addition of clarification for the safety population in case of treatment miss dispensation 5. Section 7 a. Language updates and addition of absolute levels of cGFR over time in the table of primary and key secondary endpoints. b. Language updates and clarifications for the analyses of protocol deviations. c. Subject disposition: addition of clarifications and the analysis for summary of disposition at 12 month interim analysis d. Demography and baseline characteristics: minor clarifications.

Table 7: Document history

Version Number	Author(s)	Description
		e. Extend of exposure: minor language updates and clarifications. f. Outcomes: addition of clarifications and re-ordering of the text in the subsections to group all analyses for the same endpoints under the same paragraph. g. Primary and secondary endpoints: addition of clarifications and alignment of the language with the correspondence with FDA (17 December 2013). h. Analysis of renal functions: clarification that all time points where cGFR is collected will be included in the mixed effect models. i. Safety: clarification of the 2 reporting periods and clarifications in the subsections. j. Addition of EudraCT summaries k. Addition of analysis of serious infections. l. Vital signs: clarifications of the clinically significant changes and removal of analysis of body temperature and respiratory rate as they are only collected at baseline. m. Addition of listing for pregnancy positive results [redacted] o. [redacted] q. Addition of section on interim analysis (reference to the DPP) 6. Section 8: a. Addition of definitions for screening cGFR, baseline cGFR, fist dose date/time (as per correspondence with FDA) b. Addition of clarifications for the conventions of the analysis periods. c. Correction of Day ranges for subject survival and graft survival imputation rule in case of subject unknown status.

Table 7: Document history

Version Number	Author(s)	Description
		d. Clarification for the imputation rule for cGFR values in cases of missing values due to death, graft loss or dialysis. e. Update of the conventions for counting Subject and graft survival and acute rejection related endpoints to align with the Day ranges for the rest of parameters. f. Clarifications for the parameters for which the Day ranges apply. g. Addition of conventions for the baseline measurements. h. Addition of the conventions for counting outcome events i. Move of the conventions for descriptive summaries to the section above. j. Correction of the reference to the CRF categories of AE relation to study medication. k. Re-arrangement of the conventions for the analysis AEs of PTLD, malignancies, serious infections in the Safety section. 7. Section 9 : deletion of the reference to long term portion as it is not relevant for this study. 8. Addition of ADA in the list of abbreviations in Section 10 9. Addition of laboratory marked abnormalities for completeness in APPENDIX 2 10. Replacement of the words "efficacy measures" with the word "outcome measures in several instances of the document. 11. Cosmetic updates to replace all instances of calculated GFR with the acronym cGFR.
3.0	[redacted]	1. Clarification regarding the cut off for Year 1 and Year 2 analyses in different sections. Updates of the corresponding definitions in sections 8.3. [redacted]. 3. Consideration of the death date in the calculation of the length of exposure. 4. Minor rewording in Appendix 1

Table 7: Document history

Version Number	Author(s)	Description
		5. Minor formatting updates.

[redacted]