Statistical Analysis Plan for

Official Title of Study

Evaluation of Acute Rejection Rates in de novo Renal Transplant Recipients Following Thymoglobulin Induction, CNI-free, Nulojix (belatacept) -based Immunosuppression

NCT02137239

26-June-2019

STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

EVALUATION OF ACUTE REJECTION RATES IN DE NOVO RENAL TRANSPLANT RECIPIENTS FOLLOWING THYMOGLOBULIN INDUCTION, CNI-FREE, NULOJIX (BELATACEPT)-BASED IMMUNOSUPPRESSION

PROTOCOL(S) IM103177

VERSION # 3.0

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Research Hypothesis:

A belatacept-based maintenance immunosuppressive regimen incorporating Thymoglobulin induction, concomitant therapy with EVL, and rapid corticosteroid withdrawal will result in acceptable rates of AR and overall safety consistent with the current standard of care in recipients of living and standard criteria deceased donor kidneys.

Schedule of Analyses:

The primary analysis of the primary endpoint of the incidence of clinically suspected, biopsy proven acute rejection (CSBPAR) will be conducted at 6 months post-transplantation, Secondary analyses of CSBPAR will be conducted at 12 and 24 months post-transplantation, after all randomized, transplanted and treated subjects have either completed the 24 months study treatment period and the follow up period or been discontinued prematurely from the study.

Periodic analyses will also be scheduled to support Data Monitoring Committee (DMC) review.

Two locks are planned for the study: one for all data except immune cell phenotyping and urine proteomics data and one for immune cell phenotyping and urine proteomics data.

This statistical analysis plan describes the analysis of all the data.

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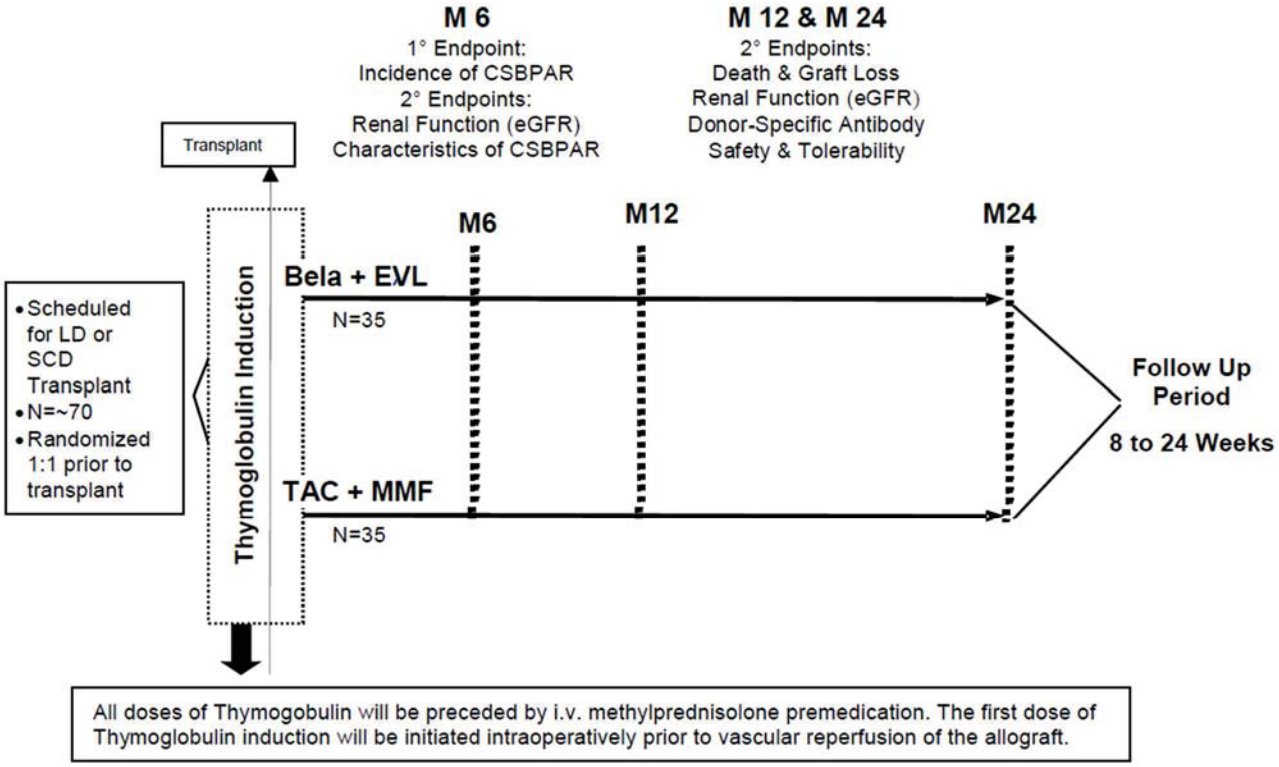
2 STUDY DESCRIPTION

2.1 Study Design

For reasons described below, only 70 of the originally targeted 240 subjects were enrolled, as shown in Figure 2.1-1:

Figure 2.1-1: Study Design Schematic



Abbreviations: M: Month; CSBPAR: Clinically Suspected and Biopsy Proven Acute Rejection; eGFR: estimated Glomerular Filtration Rate; SCD: Standard Criteria Donor; LD: Live Donor; Bela: Belatacept; MMF: Mycophenolate Mofetil; EVL: Everolimus; TAC: Tacrolimus.

This is a randomized, open-label, multicenter, parallel-group study that was to be conducted at approximately 20 sites in North and South America and the European Union. Approximately 240 subject were originally targeted for enrollment. However, enrollment was prematurely terminated as of 31-December 2016 for administrative reasons related to belatacept supply constraints associated with transition to a new manufacturing process. At that time, 70 subjects (n=35 per group), had been enrolled, each scheduled to receive a de novo kidney transplant and to be randomized (stratified by study site/center) in a 1:1 ratio, to 1 of the following 2 treatment groups:

- Thymoglobulin + Belatacept + Everolimus.
- Thymoglobulin + Tacrolimus + MMF.

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All subjects randomized on or prior to 31 December 2016 were to remain in the study on assigned therapy to complete the protocol-specified period of study participation.

This is a rapid corticosteroid withdrawal trial: corticosteroids were to be administered during the first week of study treatment only and discontinued by Day 7, except for subjects still receiving Thymoglobulin induction between Days 8-10, who could continue to receive methylprednisolone intravenous prior to beginning their Thymoglobulin infusions on those days. The duration of the study is 24 months, with a subsequent 8-week post last dose safety follow-up period for all subjects. In addition, belatacept-treated subjects who discontinue treatment or complete the study and do not continue treatment with commercially available Nulojix® thereafter, will be seen at 12 and 24 weeks post last dose for the collection of PK and/or immunogenicity samples.

2.2 Treatment Assignment

Approximately 70 subjects (n=35 per group) receiving *de novo* kidney transplants from living or standard criteria deceased donors, were to be randomized (stratified by study site/center), in a 1:1 ratio, to one of the 2 specified treatments groups. A randomization schedule was to be generated and kept by BMS.

At the time of enrollment, immediately after written informed consent was obtained, and before performing any study-specific procedures, the physician/coordinator was to contact IVRS to enroll each subject into the centralized database. Each subject was to be assigned a unique, sequential, 5-digit subject number beginning with 80001, 80002, 80003, etc. by the interactive voice response system (IVRS) for identification throughout the study. This subject number was not to be reused for any other participant in the study. SAE reporting was to begin at the time of enrollment for all subjects, immediately after written informed consent was obtained.

The subject could be randomized once all entry criteria (inclusion and exclusion) had been met. The physician/coordinator was to contact IVRS prior to transplant surgery to randomize each subject into the centralized database. The collection of non serious AE information was to begin at initiation of study drug. The IVRS was also to be contacted at each visit to obtain belatacept vial assignments and each time additional supplies of other investigational products were to be dispensed.

2.3 Blinding and Unblinding

Not applicable. This is an open-label study.

2.4 Protocol Amendments

The protocol has 7 amendments and 1 administrative letter issued. The table below summarizes the main purposes of these amendments. See the amendments for further details.

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Table 2.4-1: Protocol Amendments

Amendment #	Main purpose of the amendment
Amendment #1	Modifications were made to the WOCBP definition. Protocol was updated with Neurological Exam requirements, modification of the clinical criteria and monitoring of PTLD.
Administrative Letter 01	Clarify the Everolimus trough sampling sequence during Year 1 of treatment.
Amendment #2	This amendment is country specific for Argentina and Colombia only to incorporate post study drug access to satisfy MOH requirements in those countries.
Amendment #3	Modification of Study Design: Addition of Tacrolimus arm. Updates to the research hypothesis and study objectives. Revisions to eligibility criteria. Updates to the primary and secondary endpoints and statistical section to support the revised study design and to eliminate the allowance of crossover subjects.
Amendment #4	Syntactical edits and clarifications in support the revised study design articulated in IM103177 Revised Protocol 03, incorporating Amendment 04. The amendment removed an experimental treatment group: Thymoglobulin + belatacept + mycophenolate mofetil with rapid corticosteroid withdrawal, from the study design to eliminate a potentially higher risk of acute rejection.
Amendment #5	Clarification of antiviral prophylaxis requirement. Updates treatment and rescreening of living donor patients with a positive IGRA at screening. Revise protocol with recent administrative changes.
Amendment #6	Decrease number of sites and subjects. Statistical Sample Size Considerations updated. Clarification that all grades of acute rejection will be included in analyses of the primary and relevant secondary endpoints.
Amendment #7	Clarify timing of collection of belatacept and comparator blood levels for clinically suspected AR, PML or PTLD. Update Procedural Outline Tables 5.1-2 and 5.1-3 to allow for collection of a blood sample for determination of the belatacept or comparator blood level at the time of any clinically suspected episode of acute rejection, PML or PTLD. Provide guidance regarding the evaluation and acceptable range for oral immunosuppressive treatment compliance. The type of T-cell responses to be tested for in cases of clinically suspected PTLD or PML was clarified as being "anti-viral", rather than specifically "anti-EBV" in nature. Made modifications to secondary and exploratory endpoints to align the analyses of acute rejection with the statistical analysis

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Table 2.4-1: Protocol Amendments

Amendment #	Main purpose of the amendment
	plan, and corrected minor formatting and typographical errors throughout the protocol.

2.5 Safety Monitoring

An external Data Monitoring Committee (DMC) will review accumulating safety and efficacy data at intervals specified in a DMC Charter, and will provide recommendations to BMS regarding the emerging benefit-risk profile of the drug in this indication, and subsequent study conduct. Periodic analyses will be scheduled to support Data Monitoring Committee (DMC) review. Further details regarding the DMC will be available in the DMC charter.

3 OBJECTIVES

3.1 Primary

The primary objective is to assess the incidence of clinically suspected and biopsy proven acute rejection (CSBPAR) at 6 months post-transplant in de novo renal allograft recipients treated with thymoglobulin induction, rapid corticosteroid withdrawal, and maintenance belatacept in combination with EVL, or maintenance TAC in combination with MMF.

3.2 Secondary

The effects of each immunosuppressant regimen on the rates of acute rejection, subject and allograft survival and allograft function were to be evaluated as follows (endpoints to measure these objectives are described in further detail in protocol Section 8.3):

- The frequency and severity of CSBPAR at 12 and 24 months post-transplant.
- Rates of subject and allograft survival at 6, 12 and 24 months post-transplant.
- Changes in renal function and severity of proteinuria at 3, 6, 12 and 24 months post-transplant.
- The frequency and type of donor-specific, anti-HLA antibodies (DSA) detectable prior to, and at 12 and 24 months post-transplant.
- The safety and tolerability of each treatment regimen, as based upon the results of vital signs, and safety laboratory assessments, and cumulative rates of adverse events reported at 3, 6, 12 and 24 months post-transplant.

The frequency of cardiovascular and metabolic co-morbidities reported at 3, 6, 12 and 24 months post-transplant.

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[redacted]

4 ENDPOINTS

All primary and secondary endpoints listed below will be assessed and described for each treatment group.

4.1 Primary Endpoint

The incidence of CSBPAR at 6 months post-transplant in the individual treatment groups:

- Belatacept + EVL.
- TAC+ MMF.

4.2 Secondary Endpoint

The two treatment groups will be compared for all secondary endpoints.

Acute Rejection

- Treatment differences in the incidence of CSBPAR at 6, 12 and 24 months post transplant, in the belatacept + EVL versus TAC + MMF treatment groups.
- Time to CSBPAR.
- Treatment differences in the severity grades and therapeutic modalities used to treat all episodes of CSBPAR at 6, 12, and 24 months post-transplant:
  - Severity: To be assessed by each local pathologist using the 2007 update to the Banff 97 classification of renal allograft pathology).

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– Treatment regimen: Categorical analysis of CSBPAR episodes by treatment received, including: a) corticosteroids; b) lymphocyte depleting therapy; c) renal replacement therapy; d) plasmapheresis; e) IVIg; f) rituximab.

Subject and Graft Survival

- Proportion of all subjects who survive with a functioning graft at 6, 12 and 24 months post- transplant.
- Proportion of all subjects who experience death by 6, 12 and 24 months post-transplant.
- Proportion of all subjects who experience graft loss by 6, 12 and 24 months post-transplant.
- Time to event analysis of death or graft loss.

Renal Function

- Absolute (mean and median) cGFR values at 3, 6, 12 and 24 months post-transplant, as determined from the 4-variable Modification of Diet in Renal Disease (MDRD) formula.
- The mean changes from Month 3 cGFR at 6, 12, and 24 months post-transplant.
- Slope of the change in cGFR from Month 3 to Months 6, 12 and 24 post-transplant.
- The mean urine protein to creatinine ratio ($U_{Pr/Cr}$) at 3, 6, 12 and 24 months post-transplant.

Donor Specific Anti-HLA Antibodies (DSA)

- The percentage of subjects with, and titers of pre-existing (pre-transplant) and *de novo* (post-transplant) anti-HLA DSA on Day 1 (pre-transplant, pre-dose), and at Months 12 and 24, respectively.
- Characterization of any *de novo* DSA detected by IgM and IgG classes, and by the presence or absence of complement fixing properties.

Safety and Tolerability of each Treatment Regimen

- Incidence of all AEs and SAEs at 6, 12, and 24 months post-transplantation.
- Incidence of ESI at 6 months, 12 months, and 24 months
- Description and incidence of clinically significant changes in vital signs.
- Description and incidence of laboratory test marked abnormalities.

Cardiovascular and Metabolic Co-Morbidities

- Incidence of New Onset Diabetes After Transplantation (NODAT) at 6, 12, and 24 months post-transplant.
- Absolute (mean and median) values for Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) at 3, 6, 12 and 24 months post-transplant.
- Mean changes from baseline for SBP and DBP at months 6, 12, and 24 post-transplant.
- Absolute (mean and median) values at 3, 6, 12 and 24 months post-transplant, and mean change from baseline levels at Months 12 and 24, for the following fasting lipid levels:

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  - Serum total cholesterol.
  - Serum high density lipoprotein (HDL) cholesterol.
  - Serum low density lipoprotein (LDL) cholesterol.
  - Serum triglycerides (TG).
- Mean fasting blood glucose levels, and mean changes from baseline values at Months 6, 12 and 24 post-transplant.
- Mean whole blood HbA1C concentrations, and mean changes from baseline values at Months 6, 12 and 24 post-transplant.

[redacted]

[redacted]

5 SAMPLE SIZE AND POWER

This study is descriptive in nature and is not powered to show statistically significant treatment differences for any outcome measure. A sample of approximately 70 subjects, randomized in a 1:1 ratio to the belatacept + EVL and TAC + MMF groups, is planned.

If the true probability of CSBPAR in the belatacept + EVL treatment group is 3.8%, a sample size of 35 subjects allows the estimation of the population proportion (π) with a 95% CI[‡] of 0.2% to 16.4% around the observed proportion of CSBPAR. If the rate is 3%, in the TAC +MMF treatment group, then the 95% CI[‡] around the estimate would be 0.1% to 15.1%, for lower and upper limits, respectively.

For the secondary endpoint of assessing the difference in the incidence of CSBPAR at 6 months post-transplantation between the TAC + MMF and belatacept + EVL groups, respectively, with 35 subjects per treatment group, if the observed incidences of CSBPAR (conservatively based on study IM103034) are 3% and 3.8%, the 2-sided 95% confidence interval (CI)* of the differences between the observed incidence rates can be summarized as in Table 5-1:

Table 5-1: Confidence Intervals* for the Difference between Two Proportions

Difference of Treatments (assumed proportions)	Lower 95% Confidence Limit	Upper 95% Confidence Limit	Half Width
TAC + MMF (3%) vs. Bela + EVL (3.8%)	-13.2%	11.3%	12.25%

[‡] Confidence Interval Method: Clopper-Pearson

[*] Confidence Interval Method Score (Wilson)

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6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Treatment Regimens

Approximately 70 subjects (n=35 per arm) receiving de novo kidney transplants will be randomized (stratified by study site/center) in a 1:1 ratio to 1 of the following 2 treatment groups:

- Thymoglobulin + Belatacept + Everolimus.
- Thymoglobulin + Tacrolimus + MMF.

6.2 Populations for Analyses

- The "Intent-to-Treat" (ITT) population includes all subjects who are randomized, transplanted and treated with at least one dose of thymoglobulin and one dose of study treatment, either belatacept or TAC. Subjects will be grouped according to the treatment to which they are randomized.
- The "As Treated" (AT) population includes all subjects who are randomized, transplanted and treated with at least one dose of thymoglobulin and one dose of study drug, either belatacept or TAC. Subjects will be grouped according to the treatment which they actually 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. Safety reporting will be done in the "As Treated" population.
- The "Per-Protocol" (PP) population includes all randomized subjects who do not violate terms of the protocol that might affect key study outcomes. The protocol specific definitions for "relevant" protocol deviations are described in APPENDIX 2.
- The PK population includes subjects who receive at least one dose of belatacept and have at least 1 post baseline sample available for PK analyses.

7 STATISTICAL ANALYSES

7.1 Modifications to the Analyses Specified in the Protocol

Due to the reduction in sample size resulting from premature termination of enrollment as of 31 December 2016, it has been deemed appropriate to revise selected statistical analyses specified in the study protocol Section 8. The following modifications to and clarifications of the analyses have been made:

1) All analyses will be performed for the whole study treatment period (i.e. 24 months), including analyses at 6 or 12 months.

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2) Treatment differences will be produced only for the endpoints specified in the sections of this SAP itemized below, instead for all study endpoints.
3) Analysis of acute rejections:
   a) The treatment differences in the severity grades and therapeutic modalities will not be calculated.
   b) The sensitivity analyses using the per-protocol population will be performed if there are at least 10% of subjects with a protocol deviation in either treatment groups.
   c) The sensitivity analyses using the as-treated population will be performed if there are at least 10% of subjects in either treatment group for whom the as-randomized treatment group is different from the as-treated treatment group.
   d) The sensitivity analysis using right censoring at the time of discontinuation from assigned therapy will not be produced. Acute rejections occurring more than 56 days after the last dose date will be flagged in the listing.
   e) The descriptive summaries by treatment group for cGFR, graft and subject survival, donor specified antibodies, infection and malignancy at Month 12 for subjects with and without AR by Month 6, and at Month 24 in subjects with and without AR by Month 12, will not be produced. The information regarding these parameters will be included in listings that correspond to the specific analyses of these endpoints.
4) Analysis of subject and graft survival:
   a) A listing including all subjects who died or lost their graft will be produced. Corresponding summaries, treatment differences and time to event analysis will be produced if there are at least 5 subjects across treatment groups who died or experienced graft loss during the 24 Month treatment period.
   b) Any summaries mentioned above, if to be produced, will only be produced for the whole 24 Month treatment period. The corresponding analyses at 6 and 12 months will not be produced.
   c) Subject and allograft survival rates among those subjects who did and those who did not experience CSBPAR. This analysis will be produced only if there are at least 5 subjects across treatment groups who died or experienced graft loss during the 24 month-treatment period.
5) Analysis of the composite endpoints of CSBPAR, death, or graft loss will be produced only if there is at least one CSBPAR and at least one death or graft loss. These analyses will include the proportion of all subjects who experience CSBPAR, death, or graft loss at 12 and 24 months and a time to event analysis of the composite endpoint of CSBPAR, death, or graft loss.
6) All safety analyses will only be produced for the whole 24 Month treatment period. The corresponding safety analyses at 6 and 12 months will not be produced.
7) Analysis of immunogenicity: The protocol specifies summaries of titers of detectable anti-belatacept antibodies at Weeks 8, 12, and 24 post study termination (subjects who discontinue belatacept only). Instead of descriptive statistics, a listing will be provided for all positive subjects. Similarly, the analysis of descriptive statistics for titers of detectable anti-belatacept antibody will not be produced.

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8) Analysis of any clinical consequences of CSBPAR (and associated changes in the expression of exploratory gene sets associated with acute rejection) at 6, 12 and 24 months post-transplant will be presented as follow:
   a) The extent to which renal function recovered to the pre-rejection baseline will include the serum creatinine values related to CSBPAR in the corresponding listing.
   b) The percentage of subjects who, post-CSBPAR, are reported to have developed infection or malignancy will not be summarized. Instead, a listing will be provided.
   c) The percentage of subjects with, and titers of detectable, de novo (post-transplant) anti-belatacept antibodies will not be summarized. Instead, this information will be included in a listing of immunogenicity results with corresponding belatacept concentrations and selected laboratory parameters and events of special interest.
   d) The subject and graft survival rates among those subjects who did, and those who did not experience CSBPAR will be provided only if there are at if there are at least 5 subjects across treatment groups who died or experienced graft loss during the 24 month-treatment period.
9) The summary of median fluorescence intensity (MFI) of anti-HLA donor specific antibodies will not be produced. Instead, the number of subjects with DSA will be summarized.
10) Analysis of anti-viral T-cell responses will not be provided. The immune cell phenotypes will be summarized for all subjects and by acute rejection status (subjects experiencing at least one acute rejection vs those without any acute rejection). A corresponding listing will be provided.
11) The patterns of protein excretion, by urinary proteomics will be summarized for all subjects and by acute rejection status (subjects experiencing at least one acute rejection vs those without any acute rejection). Proteins that are below LLOQ in more than 50% of samples will not be analyzed. A corresponding listing will be provided.

Due to the fact that some data were not collected, the following analyses cannot be produced:

1) Clinically significant changes in vital signs were not collected. Thus, they will not be summarized. Instead, a summary of the number of subjects with systolic or diastolic blood pressure values above the values mentioned in section 7.6.2.5 will be provided. Also, investigators may have reported corresponding adverse events which will be summarized and listed as described in Section 7.7.
2) For the analysis of any clinical consequences of CSBPAR, and associated changes in the expression of exploratory gene sets associated with acute rejection, no summary or listing that includes gene expression will be provided.
3) The analysis on titers of DSA and of the characterization of any de novo DSA detected by IgM and IgG classes, and by the presence or absence of complement fixing properties will not be produced. Instead, the number of subjects with DSA will be summarized.
4) The IHC analyses of any remaining allograft biopsy tissue samples available at sites following clinical review will not be provided, as no such residual tissue samples were submitted for this purpose.

The following analyses will not be provided as part of this analysis plan:

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1) The analyses related to anti-viral T-cell responses and mean percent change in anti-viral T cell responses will not be produced as part of the analyses described in this analysis plan. If they are to be performed subsequently, they will be described in a separate analysis plan.
2) The analyses of peripheral blood and urinary (mRNA) gene expression profiles will not be produced as part of the analyses described in this analysis plan. If they are to be performed subsequently, they will be described in a separate analysis plan.
3) The analyses of gene expression profile, plasma and urine samples for the global and targeted quantitative determination of proteins in plasma and urine and unstained sections of allograft biopsy tissue will not be produced as part of the analyses described in this analysis plan. If they are to be performed subsequently, they will be described in a separate analysis plan.
4) The analyses related to the study endpoint to explore the exposure response relationships for selected safety, efficacy, and biomarker endpoints in each treatment group will not be described in this analysis plan. If they are to be performed subsequently, they will be described in a separate analysis plan.

The following clarifications to the study endpoints of the analyses are listed below:

1) The "description" of clinically significant changes in vital signs and of laboratory test marked abnormalities, as mentioned in the study endpoints (see Section 4.2) refers to descriptive statistics.
2) Analysis of vital signs: The protocol Section 8.4.2.5 specifies the analyses related to cardiovascular and metabolic co-morbidities as part of the efficacy analyses. These also include the summaries over time of systolic and diastolic blood pressures. In order to maintain consistency, the descriptive analysis of all vital signs over time will follow the same conventions as those for the efficacy endpoints, despite being mentioned as a safety endpoint in this analysis plan.

[redacted]

7.2 General Methods

All analyses of efficacy and safety endpoints will be summarized descriptively by the two treatment groups. No statistical tests will be performed.

Randomization to the study will be stratified by site only. Any within-treatment confidence interval (CI) for the proportion analyses will be computed using normal approximation, if the number of the events in that treatment group is at least 5. Otherwise, a CI calculated 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 group is at least 5. Otherwise, a CI using an exact method will be provided.

For time to event analyses, if a patient does not experience an event, the censoring will be done at the last follow-up date if the subject discontinues prematurely; otherwise, censoring will be

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done at the last dose date if the subject completed the 24 month-treatment period, unless specified otherwise.

The following table provides an overview of the primary and key secondary analyses to be performed.

Table 7.2-1: Overview of Primary and Key Secondary Analyses

Measure of Interest	Analysis Method
Proportion of subjects who experience a CSBPAR at 6, 12 and 24 months post-transplant	**Point estimate of the proportion and 95% CI[*] within each treatment group at 6 months.**
Difference in the incidence of CSBPAR between arms, at 6, 12 and 24 months post- transplant	**Point estimate and 95% CI[‡] for the difference between the two arms**
Time to first CSBPAR	**Kaplan-Meier (KM) estimates of survival functions. Hazard Ratio and 95% CI[§]**
Proportion of Subjects who survive with a functioning graft at 24 months post-transplant	**Point estimate of the proportion and 95% CI[*] within each treatment group at 24 months (to be produced if there are at least 5 subjects across treatment groups who died or experienced graft loss)**
Time to death or graft loss	KM estimate of subject and graft survival Hazard Ratio and 95%CI[§] (to be produced if there are at least 5 subjects across treatment groups who died or experienced graft loss)

[*] Confidence Interval Formula: Exact (Clopper-Pearson)

[‡] Confidence Interval Method: Score (Wilson)

§ Using Cox Propotional Hazard model

7.3 Study Conduct

All subjects with relevant protocol deviations that could affect efficacy will be identified. A list of these protocol deviation criteria is provided in APPENDIX 2. These protocol deviations are referred to as "relevant" protocol deviations in this document.

All randomized subjects with at least one relevant protocol deviation will be summarized by treatment group and overall. They will also be listed.

The ITT analysis population will be used for these analyses.

7.4 Extent of Exposure

7.4.1 Subject Disposition

The disposition of subjects will be presented as follows:

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- Number of subjects enrolled at screening.
- Number of subjects randomized and transplanted, presented by randomized treatment group.
- Reasons for not being randomized.
- Number of randomized and transplanted subjects who receive at least 1 dose of Thymoglobulin and 1 dose of study treatment, either belatacept or TAC.
- Number of subjects who discontinued treatment at any time during the two years, together with reasons for discontinuation, as tabulated by randomized treatment group.
- Number of subjects continuing in the follow up phase.
- Number of subjects who discontinued study during the follow up phase, together with reasons for discontinuation and tabulated by randomized treatment group.

For the items above, the overall disposition combining all treatment groups will also be presented.

A corresponding listing of subjects who discontinued from the treatment period (including subjects randomized but not treated) and the follow up period will be provided, together with the reason for discontinuation.

The ITT analysis population will be used for these analyses.

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

7.4.2 Demographic 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 testing will be performed to assess imbalances between the two treatment groups.

Baseline demographic characteristics include the following:

Donors and recipients

- Age in years.
- Weight in kg (recipients only).
- Height in cm at the Screening evaluation (recipients only).
- Body mass index (BMI, kg/m^2) (recipients only).
- Gender: Male versus Female.
- Race.
- Ethnicity (recipients only. Only for USA subjects).
- Geographic Region (recipients only).

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- Previous number of transplant (recipients only).

Baseline Disease Characteristics include:

- # of HLA –A, –B, –DR, and total mismatches.
- Percent (%) Panel Reactive Antibodies (PRA) (recipients).
- Primary etiology of end stage renal disease (ESRD; recipients only).
- Specific Disease History (recipients).
- Primary cause of death (donors).
- Recipient and Donor EBV antibody serostatus.
- Recipient and Donor CMV antibody serostatus.
- Viral serology for Hepatitis B (donors).
- Viral serology for Hepatitis C (donors).
- T Cell Cross-match for Transplant (recipients).
- B Cell Cross-match for Transplant (recipients).
- Type of transplant (donors).

[redacted]

7.5 Extent of Exposure

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

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

In addition, the length of exposure to the assigned treatment will be summarized and presented according to the following time intervals (in days): ≤ 28 (≤ 1 month), 29-84 (2-3 months), 85-168 (4-6 months), 169-252 (7-9 months), 253-364 (10-12 months), 365-448 (13-15 months), 449-532 (16-18 months), 533-616 (19-21 months), 617-728 (22-24 months), ≥ 729 (> 24 months). This summary will also be produced for the TAC treatment group. The number of subjects in each category will be displayed.

For belatacept, the length of exposure will be calculated as the last infusion date + 28 days or death date (if earlier) minus first infusion date.

For TAC, the length of exposure will be calculated as the last infusion dose + 10 days or death date (if earlier) minus first dose date.

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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).

These analyses will be produced using the as treated population.

7.5.1 Discontinuation of Study Therapy

The ITT analysis population (defined in Section 6.2) will be used to summarize discontinuation from study therapy by treatment group as indicated in Section 7.4.1 as well as the reason for the premature termination of study therapy.

7.6 Efficacy

This section and its subsections describe the planned efficacy analyses based on data included at the time of the final database lock.

All analyses for efficacy endpoints below will be assessed and described for each of the 2 treatment groups and for the overall study population, unless otherwise specified.

7.6.1 Primary Endpoints

7.6.1.1 Acute Rejection

Rates of acute rejection will be summarized by treatment group at Months 6, 12 and 24 using point estimates of the proportion of subjects experiencing at least one CSBPAR, and the corresponding 95% CIs. Two-sided 95% CIs will also be generated for the difference between the two treatment regimens. Descriptive statistics will be provided for the percentages of subjects with CSBPAR in each treatment group, including those for severity grade and treatment received (corticosteroids, lymphocyte depleting agents, renal replacement therapy, plasmapheresis, IVIg, rituximab). All grades of acute rejection, excluding those assessed by the pathologist as "borderline changes" (biopsy findings “suspicious” for acute cellular rejection per the Banff criteria), will be included in the analysis of the primary and relevant secondary endpoints for acute rejection. Sensitivity analyses will be performed, including acute rejections assessed by the pathologist as ‘borderline changes’ (biopsy findings “suspicious” for acute cellular rejection per the Banff criteria).

In addition, Kaplan-Meier (KM) cumulative event rates will also be performed by treatment groups and the corresponding hazard ratio will be calculated using cox proportional hazard model for the whole study treatment period (i.e. 24 months).

A corresponding listing including all suspected acute rejection events, regardless of when they occurred, will be provided. All events occurring more than 56 days since last dose date will be flagged.

An additional listing will be produced including subjects who post-CSBPAR, are reported to have developed infection or malignancy.

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Sensitivity analyses

Sensitivity analyses will be performed on the PP population as well as on the AT population for the primary analysis, if there are in either treatment group at least 10% of subjects with a protocol deviation or subjects for which the as-randomized treatment group is different for the as-treated treatment group, respectively. The table below is a summary of the analysis along with the populations it will be performed in.

Table 7.6.1.1-1: Overview of Sensitivity Analysis

Measure of Interest	Analysis Method	Sensitivity Analysis Population
Proportion of subjects who experience a CSBPAR at 6, 12 and 24 months post-transplant	Point estimate of the proportion and 95% CI* within each treatment group at 6 months	AT and PP
Difference in the incidence of CSBPAR between arms, at 6, 12 and 24 months post-transplant	Point estimate and 95% CI‡ for the difference between the two arms	AT and PP
Time to CSBPAR	Kaplan-Meier (KM) estimates of survival functions Hazard Ratio and 95% CI§	AT and PP

* Confidence Interval Formula: Exact (Clopper-Pearson)

‡ Confidence Interval Method: Score (Wilson)

§ Using Cox Propotional Hazard model

7.6.2 Secondary Endpoints

7.6.2.1 Subject and Graft Survival

A listing will be provided of all subjects who died or experienced graft loss at any time during the study. A listing of all subjects with unknown subject and graft survival status at the end of the
24 month-treatment period will be provided.

If there are at least 5 subjects across treatment groups who died or experienced graft loss during the 24 month-treatment period, the following analyses will be produced:

- The composite endpoints of patient and graft survival at 24 months respectively will be summarized within each treatment groups, using point estimates of the proportion of subjects surviving with a functioning graft, and the corresponding 95% CIs. The point estimate and its 95% CIs will also be generated for the difference between the two treatment regimens.
- The proportion of subjects who die, proportion of subjects who have a graft loss, and the proportion of subjects who experience the following outcomes will each be summarized using point estimates and 95% CI within each treatment group.
  - Overall graft loss rates at 24 months.
  - Rates of death with a functioning graft at 24 months.

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  - Rates of pure (death-censored) graft loss at 24 months.
- In addition, Kaplan-Meier (KM) estimates of cumulative subject and graft survival rates will also be summarized.
- The subject and allograft survival rates will be summarized among those subjects who did and those who did not experience CSBPAR. This analysis will be produced only if there are at least 5 subjects across treatment groups who died or experienced graft loss during the 24 month-treatment period.

7.6.2.2 Composite Endpoints of CSBPAR, Death, or Graft Loss

The composite endpoints of CSBPAR, death, or graft loss will be analyzed only if there is at least one CSBPAR and at least one death or graft loss. These analyses will include the proportion of all subjects who experience CSBPAR, death, or graft loss at 12 and 24 months and a time to event analysis of the composite endpoint of CSBPAR, death, or graft loss.

7.6.2.3 Renal Function

The following table provides a summary/overview of the analysis performed.

Table 7.6.2.3-1: Overview of Analysis: Renal Function

Renal Function variable	Analysis	Time points for analysis
cGFR using MDRD formula	Descriptive summary of absolute values for each Treatment group	Month 3, 6, 12, 24
	Descriptive summary of change from Month 3 values for each Treatment group	Month 6, 12, 24
	Fixed Effects repeated measure model using Time and Treatment as class variables and Month 3 cGFR as a covariate	Month 6, 12, 24
	Mixed effects using Time as random variable and Treatment as class variable. Analysis on absolute cGFR value using Month 3 cGFR as a covariate	Month 6, 12, 24
Urine protein/ creatinine ratio ($U_{PR/CR}$)	Descriptive summary of absolute values for each treatment group	Month 3, 6, 12, 24
	Descriptive summary of change from Month 3 values for each Treatment group	Month 6, 12, 24
	Fixed Effects repeated measure model using Time and Treatment as class variables and Month 3 cGFR as a covariate	Month 6, 12, 24

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cGFR

Calculated GFR at Months 3, 6, 12, and 24 and change in cGFR from Month 3 to Months 6, 12 and 24, respectively, will be descriptively summarized.

A linear mixed effects model will be used to analyze changes from Month 3 cGFR. The linear mixed model for repeated measures with terms of Month 3 cGFR values, 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 each time point, the difference between treatment arms will be calculated along with the corresponding 95% confidence intervals.

Population-mean slopes will be estimated for each treatment group. In addition, the 95% confidence intervals will also be obtained for each mean slope. Intercepts will be summarized in the same manner. This analysis will be based on a linear mixed model including terms for treatment, Month 3 cGFR, treatment-by-month interaction as well as month (continuous covariate) as fixed effects. The model will also include a random intercept and slope for month. Unstructured covariance structure will be used.

For all of the analyses above, for any subject who has one or more missing values for cGFR due to a graft loss or death, the missing values will be imputed as "zero".

Urine Protein/Creatinine Ratio

Urinary protein to creatinine ratios, to be obtained from single-voided urine specimens at 3, 6, 12 and 24 months post-transplant, will be descriptively summarized.

A linear mixed effects model will be used to analyze changes from Month 3 UPCR. The linear mixed model for repeated measures with terms of Month 3 UPCR values, 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 each time point, the difference between treatment arms will be calculated along with the corresponding 95% confidence intervals.

7.6.2.4 Donor Specific Antibodies

The percentage of subjects with detectable DSA on Day 1, and of *de novo* DSA at 12 and 24 months post-transplant will be descriptively summarized by treatment group. The data from the DSA assessments will be cross-matched with the number of donor/recipient HLA mismatches to confirm the anti-donor status of any detected anti-HLA antibodies. The results will be categorized according to the results obtained by flow cytometry, as follows:

- Median fluorescence intensity(MFI) > 2000 = Positive.
- MFI 1000-2000 = Potentially Positive.

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- MFI < 1000 = Negative.

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7.6.2.5 Cardiovascular and Metabolic Co-Morbidities

Blood pressure

Descriptive summaries of SBP and DBP will be provided by treatment group at Months 3, 6, 12, and 24. In addition, the changes from baseline (last measurement prior to transplant) to the subsequent measurements obtained at each subsequent (post-transplant) time points will be summarized.

Percentage of patients in each treatment group with blood pressures above the values given below will be presented in a table to include results pre-transplant and at each subsequent Study Visit:

- > 130/80mmHg (pre-hypertension).
- > 140/90mmHg (hypertension).

Descriptive statistics regarding the number of antihypertensive medications received in each group at 6, 12 and 24 months will be provided to evaluate severity of hypertension per the protocol definition (e.g. mean/median number of antihypertensive medications).

Lipids

Descriptive summaries of fasting lipid parameters (total cholesterol, HDL cholesterol, LDL cholesterol and TG) at Months 3, 6, 12, and 24 will be presented. Changes from baseline values (last measurement prior to transplantation) for each of the fasting lipid parameters (total cholesterol, HDL cholesterol, LDL cholesterol and TG) to Month 12 and Month 24 will be descriptively summarized.

Descriptive statistics regarding the number of lipid-lowering medications received in each group at 6, 12 and 24 months will be provided (e.g. mean/median number of lipid-lowering medications).

Control of fasting blood glucose

Mean values and changes from baseline (last measurement prior to transplantation) in fasting blood glucose and HbA1C levels to Month 6, Month 12 and Month 24 will be descriptively summarized.

New Onset Diabetes Mellitus After Transplantation (NODAT)

The incidence of NODAT at 6, 12, and 24 months post-transplantation will be summarized along with the corresponding 95% CIs within each treatment regimen group.

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7.6.2.6 Subgroup Analyses

Subgroups analyses of key efficacy measures (primary endpoint of CSBPAR by Month 6 and key secondary endpoints of CSBPAR by 12 and 24 months) will be performed. Similar analyses will be performed for subject and graft survival by Month 24 if there are at least 5 subjects across treatment groups who died or experienced graft loss during the 24 month-treatment period (see Section 7.1).

Summary statistics for the above efficacy measures by treatment group will be presented for only those subgroup categories that consist of 10% or more of the total study population. No statistical tests will be performed for subgroups.

Table 7.6.2.6-1: Subgroup categories for Key Endpoints

Type of Characteristic	Subgroup factor	Categories
Donor Characteristics	Donor Condition	Living Donor
		Deceased Donor
Recipient Characteristics	Recipient Gender	Male
		Female
Recipient Characteristics	Recipient Race	White
		Black
		Other
Recipient Characteristics	Recipient Diabetic Status	Diabetic
		Non-Diabetic

7.7 Safety

Safety analysis will be based on all randomized, transplanted, and treated subjects (as treated population). All AEs will be summarized and listed by treatment groups. SAEs and AEs that result in discontinuation of the study drug will also be tabulated in detail. Laboratory marked abnormalities that are determined as "critically" out of range per the central laboratory manual, will be summarized descriptively. 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 (last measurement prior to first dose date/time).

All safety summaries except those for reports of death, graft loss, PTLD, malignancies, and serious infections, will be based only on data available at each of the scheduled analysis time points, applying 'last dose date + 56' cut counting rules. For events of death, graft loss, PTLD, malignancies, and serious infections, two different summaries will be prepared. The first summary will be based only on data available applying 'last dose date + 56' cut counting rules. The second summary will be based on all available data without applying 'last dose date + 56' cut counting rules.

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The frequencies and exposure adjusted incidence rates using person-year method will be summarized by treatment regimen groups and overall.

7.7.1 Adverse Events Analysis

7.7.1.1 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 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.

Summaries will be presented by treatment groups and categorized by System Organ Classes (SOCs) and Preferred Terms (PTs).

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 8.8.

Incidence rates for AEs/SAEs will be provided, where exposure (in days) of a subject is calculated from the randomization to the event date, or the last dose date + 56 whichever is the earlier. 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.

7.7.1.2 Events of Special Interest

The following adverse events of special interest, as obtained from the additional CRF pages or appropriate source documentation will be listed or both listed and summarized by treatment group, as specified below:

- Serious Infections (listing and summary).
- PTLD (listing).
- PML (listing).

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- Malignancies (other than PTLD) including non-melanoma skin carcinomas (listing).
- TB Infections (serious and non-serious) (listing).
- CNS Infections (serious and non-serious) (listing).
- Viral Infections (serious) (listing and summary).
- Infusion related reactions within 24 hours since belatacept infusion (listing and summary).

The conventions for counting adverse events are provided in Section 8.8. Listings of all 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 for the Month 24 analysis. 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. 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. Subjects for whom the time of onset of the first occurrence of the AE of interest is in a given interval will not be included in the exposure and incidence rates in later intervals.

7.7.1.3 Multiple Adverse Events

Descriptive summaries of adverse events that takes into account the number of times 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.

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)
- All AEs and SAEs:

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- 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 more than once (analysis to be produced only for AEs).

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

EudraCT Summaries:

Exposure adjusted 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.

7.7.2 Laboratory Test Analysis

Laboratory marked abnormalities as identified using pre-defined criteria (see APPENDIX 4), will be descriptively summarized with frequency and percentage. All laboratory values of a laboratory analyte will be listed for subjects with at least one marked abnormality for this parameter will be listed (independent of study period).

All available laboratory parameters included in the Hematology and Chemistry Panels in protocol Section 5.3.6.1 will also be summarized over time (with mean, SD, median, minimum, Q25, Q75, and maximum).

7.7.3 Other Safety Considerations

Vital Signs

Body temperature (in degrees Celsius [°C]) and Heart rate (beats per minute) will be summarized by treatment (with mean, SD, median, minimum, Q25, Q75 and maximum) at protocol-specified intervals. The same analysis conventions will be followed as those for systolic and diastolic blood pressure (see Section 7.6.2.5).

Viral Loads and Immunoglobulins

Summaries over time will be provided by treatment group for BK, CMV and EBV viral loads and Serum levels of IgG and IgG subclasses post-transplants.

[redacted]

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[redacted]

[redacted]

8 CONVENTIONS

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

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[redacted]

8.2 Analysis Period of Interest

All analyses will be produced for the 24 month-treatment period, unless specified otherwise in the sections above. For these analyses focusing at month 6 and month 12, the analyses conventions in Section 8.4 will be followed.

8.3 Missing Data Handling

The following conventions will be followed while handling missing data. Only the relevant endpoints along with the specifics of the convention are included in this section.

Subject Survival and Graft Survival

Any subject (either randomized to belatacept or CNI) with unknown subject and graft survival status at Month 12 or Month 24, that is, whose last known follow-up date occurred prior to Day 334 or Day 698, respectively, will be considered as having experienced an event of graft loss or death, if at least one of the following criteria have been met during their documented period of follow-up post-randomization:

- Subject experienced at least one episode of BPAR at the time of, or prior to the last follow-up date.
- Subject was diagnosed as having PTLD at the time of, or prior to the last follow-up date.
- Subject's reason for discontinuation of study medication was lack of efficacy.
- A diagnosis of biopsy confirmed Polyomavirus associated nephropathy was reported as an adverse event before discontinuation.
- Subject's last calculated GFR (4-variable MDRD equation) was < 15mL/min/1.73m^2.

The remaining subjects with unknown patient and/or graft survival status at Months 12 or 24 (those who do not meet any of the above criteria) will be considered missing and not be included in the analyses or listing of the death and graft loss. For example, a patient with unknown status of the graft function and patient survival, and with no records of the above mentioned criteria, will not be considered in the numerator or denominator, while computing the percentage of death or graft loss.

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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.

Renal Function

Missing cGFR values due to death or graft loss will be imputed with value of 0 and all other missing values will remain missing.

8.4 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 (first dose date = study day 1) rather than the nominal visit/month recorded in the case report form (CRF).

The following rules apply to the derived visits depending on the specific endpoint. All endpoints analyzed over time will follow the analysis windowing specified in Table 8.4-1.

Table 8.4-1: Day Ranges for Analysis Time Points

At Month	Target Day	Day Range
1	28	1-56
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: 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 any case in which both observations are equidistant from the target day, the later measurement will be used.

If data are collected at Month 2 (Week 8) then the day ranges are the following:

At Month	Target Day	Day Range
1	28	1-42
2	56	43-70
3	84	71-112

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At Month	Target Day	Day Range
...		

In addition, the analyses for subject and graft survival, acute rejection related endpoints, NODAT and adverse events will follow the windowing below:

- Month 6: Defined as Day 1 to Day 168.
- Month 12: Defined as Day 1 to Day 364.
- Month 24: Defined as Day 1 to Day 728.

8.5 Counting Rules for Efficacy Analysis

The counting rules for computing proportions for efficacy endpoints are laid out in this section. For any endpoint under consideration, the end of the event-counting period will first be determined for each subject. If a subject has at least one episode of the event during this event-counting period, then he/she will be included in the analysis and the episode with the most severe grade will be counted. If there are multiple episodes with the same severity (grade), then the calendar date of the occurrence of the first such event will be counted. For example, if a subject had multiple episodes of a given event of varying degrees of severity, for the purpose of estimating time to event the first occurrence will be used; however, for tabulation of severity, the highest grade event will be included.

8.6 Conventions for Descriptive Summaries

For the descriptive summaries of BP parameters and laboratory analytes of interest (e.g. individual components of the fasting lipid profile and measures of renal function) at any given time point: If a subject has more than one measurement recorded during the corresponding time-window, the result closest to the target day for that time point will be used. In any case in which both observations are equidistant from the target day, the later measurement will be used. Above convention will be followed unless noted otherwise.

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.

8.8 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

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experience (ADE: an event indicated by the investigator to be certainly related, probably related, or possibly related to study medication, or one with 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 query, 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 first dose date. 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 of the following dates: The end of the analysis time window or 56 days after the date of last dose of study medication.

For the summaries of adverse events of PTLD, malignancies, and serious infections, and for the listings of AEs, SAEs, and laboratory AEs*, all AEs will be counted, including those occurring after 56 days from the last dose date.

* Laboratory AE's are clinically significant laboratory values per the assessment of the investigators as reflected in the adverse event records.

8.9 Missing, Unknown or Partial Dates

No imputation of event dates will be performed on any efficacy endpoints, including acute rejection, graft loss, death, laboratory measures and blood pressures, with the exception of cases wherein the onset date of an episode related to acute rejection is unknown; in such cases, 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

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

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Missing Start Dates of concomitant medications

If start date is missing then it will be imputed differently depending on whether the consent date is available or not. If the consent date is available then the start date will be imputed by the consent date. Otherwise, the start date will be imputed as 01 January 1900.

Partial Start Dates of concomitant medications

If a partial start date is available then it will be imputed by the earliest possible date based on the partial start date. For instance, if the available partial start date is Year 2005, then the imputed start date will be 01 January 2005. However, if the available partial start date is May 2005, then the imputed start date will be 01 May 2005.

Missing or Continuing Stop Dates of concomitant medications

If a stop date is missing or treatment is continuing then it will be imputed as 31 December 2099.

Partial Stop Dates of concomitant medications

If a partial stop date is available then it will be imputed by the latest possible date based on the partial stop date. For instance, if the available partial stop date is Year 2005, then the imputed stop date will be 31 December 2005. However, if the available partial stop date is May 2005, then the imputed stop date will be 31 May 2005.

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 2005, then the EPD will be 01 January 2005. However, if the available partial start date is May 2005, then the EPD will be 01 May 2005.

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

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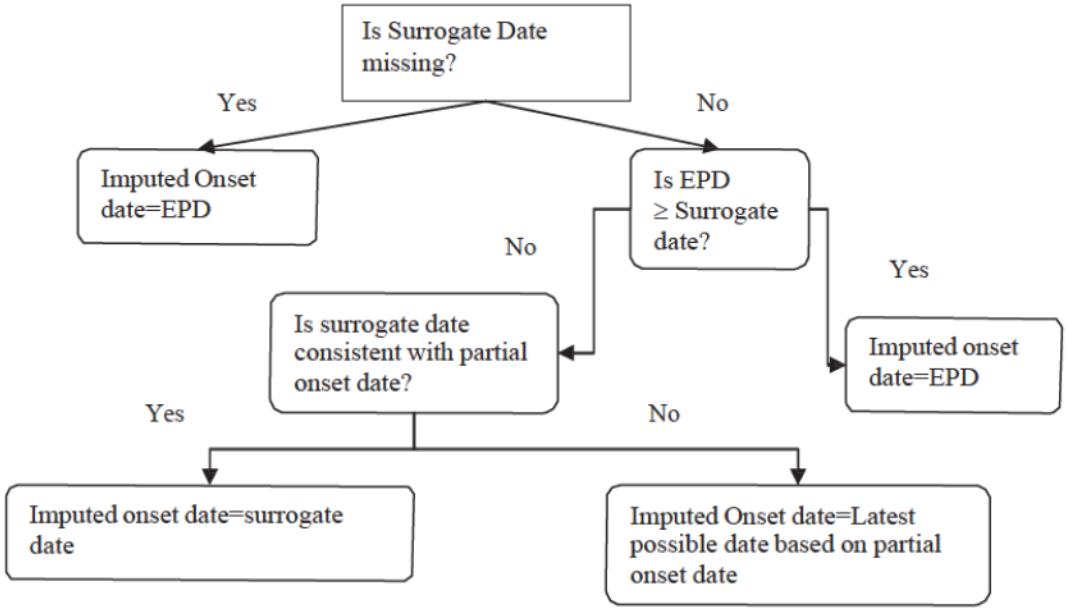
illustrated in the following diagram. (If the surrogate date is missing, then the imputed onset date will be the EPD. If the surrogate date is not missing, then the imputed onset date will depend on whether the EPD is earlier than the surrogate date or not. If the EPD is not earlier than the surrogate 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.)

Figure 8.9-1: Missing or Partial Onset Dates of Adverse Events



9 CONTENT OF REPORTS

The results of this 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 all efficacy and safety summaries and listings and will identify key results that should be highlighted in the CSR.

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APPENDIX 1 LIST OF ABBREVIATIONS

Table 9-1: List of Abbreviations

Term	Definition
AE	Adverse Event
AR	Acute Rejection
BPAR	Biopsy proven AR
BMS	Bristol-Myers Squibb
BMS-224818	LEA29Y (belatacept)
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)

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Table 9-1: List of Abbreviations

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

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APPENDIX 2 RELEVANT PROTOCOL DEVIATION CRITERIA

Table 9-2: Relevant Protocol Deviation Criteria

Per-Protocol Deviation Code	Per-Protocol Deviation	Type
1.	Recipients with EBV serostatus negative or unknown	Serious Breach
2.	Genetically-identical donor recipient pairs (i.e., identical twins)	Serious Breach
3.	• Subjects with previous graft loss due to AR • Subjects with a positive T-cell or B-cell cross match • Recipients of extended criteria deceased donor (ECD) kidney, as defined in the protocol • Subjects receiving paired (dual or en bloc) kidney transplants • CMV-negative subjects scheduled to receive a kidney from a CMV-positive donor • Subjects with a past history of or current need of desensitization therapy	Subject Violation
4.	Any of the following conditions apply: • Subjects with a recent (within 3 months prior to transplant) PRA ≥ 20% • Donor age < 10 years Recipient age < 18 or > 75 at screening	Serious Breach
5.	Subjects with underlying renal disease of: • Primary focal segmental glomerulosclerosis • Type I or II membranoproliferative glomerulonephritis Atypical hemolytic uremic syndrome (HUS) / thrombotic thrombocytopenic purpura	Serious Breach
6.	Any of the following conditions apply: • Subjects receiving maintenance immunosuppressive agents for other indications, such as	Subject Violation

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Table 9-2: Relevant Protocol Deviation Criteria

Per-Protocol Deviation Code	Per-Protocol Deviation	Type
	treatment of autoimmune disease. • Subjects received treatment other than assigned study medication	
7.	Subjects with Body mass index (BMI) > 35kg/m² for non-diabetic and >30kg/m² for diabetic subjects at screening	Serious Breach

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APPENDIX 3 LIST OF PERI-INFUSIONAL EVENTS

List of peri-infusional events (infusion related reactions) is obtained from the preferred terms that correspond to the BMS predefined list of MedDRA preferred terms (Infusion -related reactions-EU- SMQ_CODE BMS03061). The peri-infusional events are those occurring within 24 hours of Belatacept administration The latest MedDRA Version of the list of events at the time of the database lock will be used.

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APPENDIX 4 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	Formatted 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**	< 8.0g/dL	< 8.0g/dL	< 80g/L	More than 4.0g/dL > ULN*	More than 4.0g/dL > ULN*	More than 40g/L > ULN
White blood cell (WBC) count	Leukocytes	**WBC**	< 2.0 x 10 * 9C/L (10 * 9 C/L = 10 * 3C/uL)	< 2,000/mm^3	< 2.0 x 10 * 9C/L			
Absolute lymphocytes	Lymphocytes (absolute)	**LYMPA**	< 0.5 x 10 * 9C/L (10 * 9C/L = 10 * 3C/uL)	< 500/mm^3	< 0.5 x 10 * 9C/L	> 20 x 10 * 9C/L	> 20,000/mm^3	> 20 x 10 * 9C/L
Absolute neutrophils	Neutrophils (absolute)	**NEUTA**	< 1.0 x 10 * 9C/L (10 * 9C/L = 10 * 3C/uL)	< 1,000/mm^3	< 1.0 x 10 * 9C/L			
Platelets	Platelet Count	**PLAT**	< 50 x 10 * 9C/L (10 * 9C/L = 10 * 3C/uL)	< 50,000/mm^3	< 50 x 10 * 9C/L			
Serum creatinine	Creatinine	**CREAT**				> 3.0mg/dL	> 3.0mg/dL	> 265umol/L
Urinary protein/creatinine ratio	Protein/Creatinine Ratio	**PRCRR**				≥ 3500mg/mg creatinine	≥ 3.5g/mg creatinine	> 395mg/mmol creatinine
Serum sodium [Na]	Sodium, Serum	**NA**	< 130mEq/L	< 130mEq/L	< 130mmol/L	> 155mEq/L	> 155mEq/L	> 155mmol/L

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Analyte	Formatted Value	Code	Lower threshold for Marked Abnormality			Upper threshold for Marked Abnormality		
Serum potassium [K]	Potassium, Serum	**K**	< 3.0mEq/L	< 3.0mEq/L	< 3.0mmol/L	> 6.0mEq/L	> 6.0mEq/L	> 6.0mmol/L
Bicarbonate [HCO_3]	Bicarbonate	**HCO3**	< 11mEq/L	< 11mmol/L	< 11mmol/L			
Serum calcium [Ca]	Calcium, Total	**CA**	< 7.0mg/dL	< 7.0mg/dL	< 1.75mmol/L	> 12.5mg/dL	> 12.5mg/dL	> 3.1mmol/L
Serum magnesium [Mg]	Magnesium, Serum	**MG**	< 0.8mEq/L	< 0.9mg/dL	< 0.4mmol/L	> 2.5mEq/L	> 3.0mg/dL	> 1.23mmol/L
Serum phosphorus [P]	Phosphorus, Inorganic	**PHOS**	< 2.0mg/dL	< 2.0mg/dL	< 0.6mmol/L			
Serum albumin	Albumin	**ALB**	< 2.0g/dL	< 2.0g/dL	< 20g/L			
Serum uric acid	Uric Acid	**URIC**				> 10.0mg/dL	> 10.0mg/dL	> 0.59mmol/L
Fasting blood glucose	Glucose, Fasting Serum	**GLUCF**	< 40mg/dL	< 40mg/dL	< 2.2mmol/L	> 250mg/dL	> 250mg/dL	≥ 14.0mmol/L
Cholesterol	Cholesterol, Total (TC)	**CHOL**				> 400mg/dL	> 400mg/dL	> 10.3mmol/L
Triglycerides	Triglycerides, Fasting	**TRIGF**				> 500mg/dL	> 500mg/dL	> 5.7mmol/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.

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** Threshold not defined in NCI CTCAE v. 4.0

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APPENDIX 5 DOCUMENT HISTORY

Table 9-3: Document History

Version Number	Author(s)	Description
1.0	[redacted]	Original Issue
2.0	[redacted]	Syntactical edits and clarifications in support the revised study design articulated in IM103177 Revised Protocol 03, incorporating Amendment 04.
3.0	[redacted]	Syntactical edits and clarifications in order to align the revised study design articulated in IM103177 Revised Protocol 06, incorporating Amendments 05, -06 and -07 in several sections. The changes include the following: 1. Section 1: a. alignment with the protocol b. addition of clarifications regarding the schedule of the analyses 2. Section 2: a. alignment with the protocol language b. updated design according to protocol c. Included the amendments summary 3. Sections 3, 4 and 5: a. alignment with the protocol language b. Section 4: removal of the headers "Key Secondary Endpoints", "Other secondary endpoints" and subsection [redacted] to align with the protocol 4. Section 6 a. alignment with the protocol language b. addition of clarification for the as treated population c. [redacted] 5. Section 7 a. Addition of Section 7.1 summarizing the modifications to the analyses specified in the protocol b. The sensitivity analysis from Section 3) was moved to Section 7.6.1 in order to keep analysis related to AR in the same section. Also, the right censoring was included in the sensitivity analysis. c. alignment with the protocol language d. alignment between CRF and demographics and baselines characteristics in Section 7.4.2 e. added clarification for the safety conventions that will be used in Section 7.4.3 f. added "Serious adverse events and related serious adverse events with death as an outcome following EudraCT" in Section 7.7.1 g. added "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" in Section 7.7.2

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Table 9-3: Document History

Version Number	Author(s)	Description
		6. Section 8 [redacted] b. added table with different range days for time points in Section 8.4 7. APPENDIX 3 was updated to clarify that the list of peri-infusional events will be the one corresponding to the latest MedDRA version at the time of the database lock. 8. Added marked laboratory abnormalities criteria in APPENDIX 4 9. Document history was moved to APPENDIX 5

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[redacted]

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