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Revised Date: 14-Aug-2017

Clinical Protocol IM103177

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

Revised Protocol Number: 06
Incorporates amendment(s): 07

Study Director / Medical Monitor

Martin Polinsky, M.D.
[redacted]

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Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 06	14-Aug-2017	Incorporates Amendment 07
Amendment 07	14-Aug-2017	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 plan, and corrected minor formatting and typographical errors throughout the protocol.
Revised Protocol 05	11-Nov-2016	Incorporates Amendment 06
Amendment 06	11-Nov-2016	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.
Revised Protocol 04	19-Jan-2016	Incorporates Amendment 05
Amendment 05	19-Jan-2016	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.
Revised Protocol 03	25-Aug-2015	Incorporates Amendment 04
Amendment 04	25-Aug-2015	Modification of the study design to remove 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. Updates to the randomization ratio, sample size per treatment group and sample size statistical determinations. Syntactical edits and clarifications to support the revised study design.
Revised Protocol 02	23-Dec-2014	Incorporates Amendment 03 and Administrative Letter 01
Amendment 03	23-Dec-2014	Modification of the study design, including the addition of an accepted standard of care active comparator treatment group and a change in the immunosuppressive medications paradigm. Updates to the research hypothesis and study objectives. Revisions to eligibility criteria. Addition of text for pregnancy precautions and U.S. reporting requirements from the CellCept Risk Evaluation and Mitigation Strategy. Clarification of the timing of randomization in relation to transplant surgery and initial dose of study drugs, and the temporal sequence of study drug dosing. Updates to the Time & Events Table including the addition of collection of safety and biomarker specimens; and clarifications to align the tables

Document	Date of Issue	Summary of Change
		with the protocol text and other studies within belatacept clinical study program. Update the requirements for evaluation of renal biopsy specimens to include assessments for acute antibody-mediated and as T-cell mediated rejection. Updates to the primary and secondary endpoints and statistical section to support the revised study design and to eliminate the allowance of crossover subjects. Minor edits and clarifications, including section numbering
Administrative Letter 01	12-Feb-2014	Clarify the everolimus trough sampling sequence during Year 1 of treatment.
Revised Protocol 01	21-Oct-2013	Incorporates Amendment 01
Amendment 01	21-Oct-2013	Modifications were made to the WOCBP definition, including FSH requirements and HRT washout period to align with BMS standards. Exclusion criteria were updated to remove annual mammogram, WOCBP criteria that do not apply. Updates to The Time & Events Table include removal of the Annual Mammogram to allow Investigators to use standard of care practices, the addition of a Neurological Exam and clarifications to align the table with the protocol text and with BMS belatacept program clinical studies. Protocol was updated with Neurological Exam requirements, modification of the clinical criteria and monitoring of PTLD. Modifications were made to the Events of Special Interest. Inclusion of Data Monitoring Committee. Minor edits and clarifications.
Original Protocol	28-Jun-2013	Not applicable

SYNOPSIS

Clinical Protocol IM103177

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

Investigational Product(s) Dose and Mode of Administration, Duration of Treatment:

Belatacept will be administered via intravenous (i.v.) infusion according to the following regimen:

Subjects randomized to the belatacept treatment group in the study will receive a belatacept regimen consisting of 10 mg/kg i.v. on Day 1 (started at least 12 but no more than 24 hours after completion of the initial induction dose of Thymoglobulin) and on Week 1 (Day 7), and then at weeks 2, 4, 8 and 12 post-transplant. After 3 months (Week 12), subjects will receive belatacept at the maintenance dose of 5 mg/kg i.v. every 4 weeks until completion of the trial.

Thymoglobulin will be administered via i.v. infusion according to the following regimen:

All subjects will receive Thymoglobulin in a dose of up to 1.5 mg/kg i.v. on Day 1 (Day of Transplant) and daily thereafter (or less frequently, as tolerated) to reach a total cumulative dose between 3.0 and 5.5 mg/kg. Premedication with i.v. methylprednisolone is required; as well as acetaminophen and/or antihistamine, per local practice, are recommended to reduce the risk of infusion reactions.

Everolimus (EVL) will be administered orally according to the following regimen:

Subjects randomized to receive EVL will receive an initial dose of 3.0 mg/day (1.5 mg bid) starting on Day 3. In subjects who experience delayed graft function (DGF), defined as the requirement for acute dialysis during the first post-transplant week, initiation of EVL may be delayed up to Day 7. In order to guide dose modifications, EVL pre dose trough levels should be obtained from the local laboratory per the protocol required schedule and 4 to 5 days after any change in dose. The dosing will be adjusted to keep pre-dose (C0) levels at 6 to 10 ng/mL for the initial 3 months post transplantation and at 4 to 8 ng/mL after 3 months and for the remainder of the study.

Tacrolimus (TAC) will be administered orally according to the following regimen:

Subjects randomized to the tacrolimus treatment group will receive the recommended total initial dose of TAC is 0.1 mg/kg/day orally in 2 divided doses and adjusted thereafter, on the basis of therapeutic drug monitoring, to target pre-dose (approximately 12-hour trough) blood concentrations of 4-11 ng/mL. Therapy with TAC may be initiated any time within the first 24 hours post-transplant, or delayed pending improvement in renal function, e.g., after the serum creatinine (SCr) concentration has decreased to $\leq$ 4 mg/dL (in the absence of dialysis). Initiation of dosing may be delayed up to Day 7, if, in the clinical judgment of the investigator, earlier initiation of TAC therapy is not in the best interest of the subject due to postoperative impairment of allograft function.

Non-Investigational Product Dose and Mode of Administration, Duration of Treatment:

Mycophenolate Mofetil (MMF) will be given orally according to the following regimen:

Subjects randomized to receive MMF will receive a daily dose of 0.5 to 2.0 g/day divided in 2 doses. The first dose of MMF should be administered preoperatively on the Day 1 (Day of Transplant). African Americans (Blacks) are eligible to be treated with higher doses, up to 3.0 g/day in divided doses. Doses can be given 4 times a day or can be reduced if intolerance occurs, per Investigator discretion. Subjects unable to tolerate the minimum allowable dose of 0.5 g/day may be converted to mycophenolate sodium, at doses equivalent to those for MMF, at the investigator's discretion.

Corticosteroids: will be administered throughout the study according to the following regimen:

This is a rapid corticosteroid withdrawal trial; corticosteroids are to be administered during the first week of study treatment only. All subjects will receive methylprednisolone (as the sodium succinate, as premedication prior to beginning each Thymoglobulin infusion to reduce the risk of infusion reactions), to be administered i.v. over approximately 30 minutes, as follows:

1st Dose of Thymoglobulin: 500 mg methylprednisolone i.v.

2nd Dose of Thymoglobulin: 250 mg methylprednisolone i.v.

3rd Dose of Thymoglobulin: 100 to150 mg methylprednisolone i.v.

Any additional doses of Thymoglobulin:

4th Dose of Thymoglobulin: 60 mg methylprednisolone i.v.

5th Dose and beyond of Thymoglobulin: 30 mg methylprednisolone i.v. prior to each Thymoglobulin infusion

Day 4 to Day 10:

- **Subjects completing Thymoglobulin induction before Day 7** may receive prednisone, p.o. (or the equivalent) in lieu of the same dose of i.v. methylprednisolone:
  - **Day 4:** 60 mg prednisone p.o. (or equivalent)
  - **Days 5 through 7:** 30 mg prednisone p.o. daily (or the equivalent).
- **Subjects continuing to receive Thymoglobulin induction during Days 4-10** post-transplant should still be pre-treated with methylprednisolone i.v. as indicated above in lieu of p.o. prednisone.
- All corticosteroids are to be discontinued by Day 7, except for subjects still receiving thymoglobulin induction between Days 8 - 10; those subjects must discontinue corticosteroids after the final dose of thymoglobulin induction has been completed.

Study Phase: IIb

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

Objectives:

Primary Objective(s)

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.

Secondary Objectives

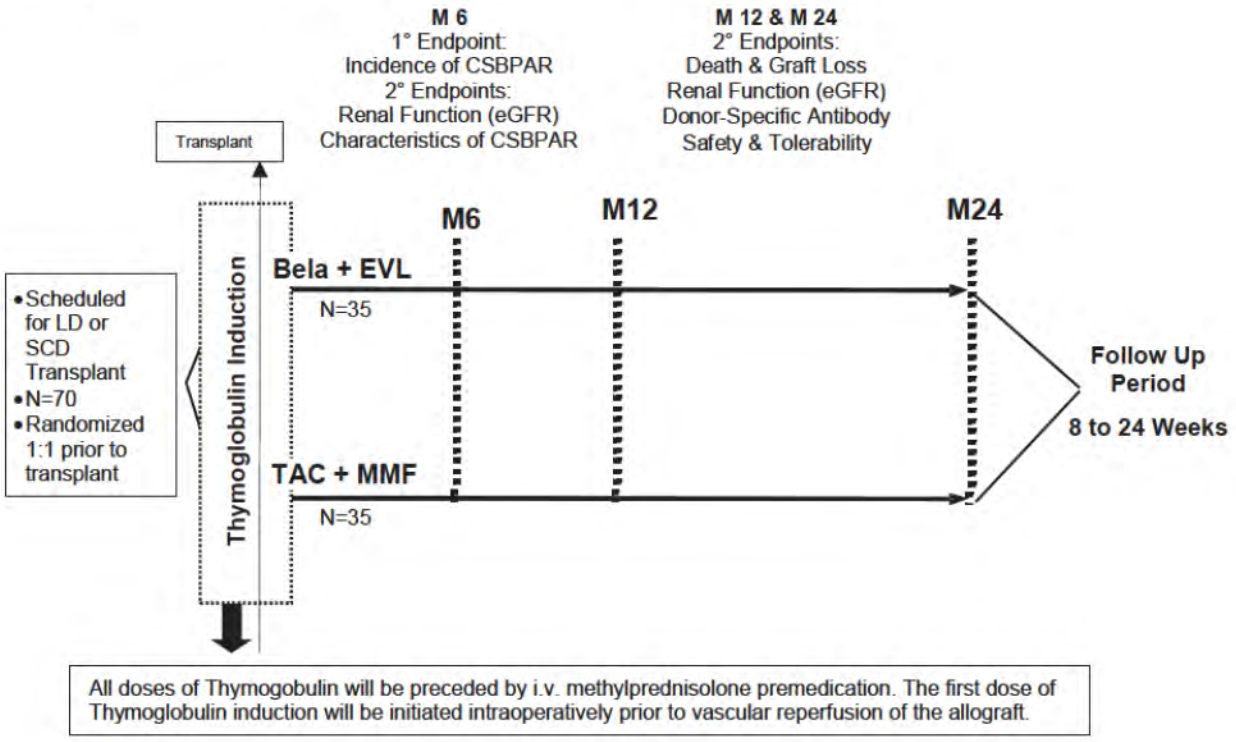
The effects of each immunosuppressant regimen on the rates of acute rejection, subject and allograft survival and allograft function will be evaluated as follows:

- The frequency and severity of acute rejection 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.

Study Design: This is a randomized, open-label, multicenter, parallel-group study to be conducted at approximately 20 sites in North and South America and the European Union. Approximately 70 subjects (n=35 per group) scheduled to receive a *de novo* kidney transplant will be randomized 1:1 ratio, to 1 of the following 2 treatment arms:

1) Thymoglobulin + Belatacept + Everolimus
2) Thymoglobulin + Tacrolimus + MMF

Figure -1: Study Design



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 rapid corticosteroid withdrawal trial; corticosteroids are 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 will continue to require methylprednisolone i.v. 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 follow-up period for safety 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, post study will be seen at 12 and 24 weeks post last dose for the collection of PK and/or immunogenicity samples.

Study Population:

Key Inclusion Criteria:

- Men and women, 18 to 75, inclusive, with end stage renal disease scheduled to undergo transplantation of a non-HLA identical, living or standard criteria deceased (SCD) donor kidney
- Subjects with serologic evidence of prior exposure to EBV. Evidence of prior exposure is to be determined locally by positive testing for IgG antibodies directed against EBV viral capsid antigen (VCA) and Epstein-Barr nuclear antigen (EBNA). Historical results are acceptable.

Key Exclusion Criteria:

- Subjects who are seronegative for prior exposure to EBV or those whose EBV serologic status is unknown at randomization
- Genetically-identical donor recipient pairs (ie, identical twins)
- Subjects with a recent (within 3 months prior to transplant) PRA ≥ 20%
- Subjects with a past history of or a current need for desensitization therapy
- Subjects with a positive T-cell lymphocytotoxic cross match or any detectable donor specific antibodies prior to transplantation
- Recipients of an extended criteria donor (ECD) kidney
- Subjects with prior or concurrent non-renal solid organ or cell (e.g., pancreas or kidney-pancreas, islet cell or stem-cell) transplants or deemed by the investigator as being likely to require a non-renal transplant in the next 3 years
- Subjects receiving paired (dual or en bloc) kidney transplants
- CMV negative subjects scheduled to receive a CMV positive donor kidney
- Subjects with the any of the following underlying conditions as the primary etiology of their end-stage renal disease (ESRD): Primary focal segmental glomerulosclerosis; Type I or II membranoproliferative glomerulonephritis; Hemolytic Uremic Syndrome (HUS) / Thrombotic Thrombocytopenic Purpura;
- Subject with current evidence or past history of active or inadequately treated latent TB infection. Subjects must have documentation of negative screening for active and latent TB infection to be eligible for randomization, specifically:
  - A chest x-ray (posterior-anterior and lateral views) that is negative for radiographic evidence of pulmonary TB within the last 6 months prior to transplant.
  - A negative screening test for latent TB infection (LTBI) [intradermal PPD, or interferon-gamma release assay (IGRA) such as QuantiFERON® TB Gold test or T-Spot-TB] that was performed *at any time* prior to the current transplant. Those subjects who do not have a documented negative result, specifically from an IGRA test performed within the last 3 months prior to randomization **must** be screened for LTBI with an IGRA test performed during the Screening Visit. Note: Results of the Screening Visit IGRA are not required for randomization when the results from a historical negative screening test (PPD or IGRA) are available.
  - If the Screening IGRA test result is positive and there is no historical negative screening test (PPD or IGRA) result for LTBI available so that the patient is a screen failure, the patient may be re-screened following completion of what is considered, per local standard of care to be an adequate course of therapy for LTBI, so long as the only cause of the screen failure was the positive IGRA test result.

- Subjects with a body mass index (BMI) at screening of > 35 kg/m^2 for nondiabetic subjects or > 30 kg/m^2 (due to higher risk of wound complications)

Study Assessments:

Study Endpoints

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

Primary Endpoint(s)

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

- Belatacept + EVL
- TAC + MMF

Secondary Endpoint(s)

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 the local pathologist, using the 2007 update to the Banff 97 classification of renal allograft pathology
  - Treatment regimen: Categorical analysis of CSBPAR episodes by treatment received, including: a) corticosteroids; b) T-cell depleting agent(s); 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 and 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 change from Month 3 cGFR at 3, 6, 12 and 24 months post-transplant;
- Slope of the change in cGFR from Month 3 to Months 6, 12 and 24 post-transplant;
- Urine protein to creatinine ratio ($U_{Pr/Cr}$) at 3, 6, 12 and 24 months post-transplant.

Donor Specific Anti-HLA Antibodies (DSA)

- Percentage of subjects with, and titers of , pre-existing (pre-transplant) and de novo (post transplant) DSA on Day 1 (pre-transplant, pre-dose), and at Months 12 and 24 post-transplant;
- Characterization of any de novo DSA detected by IgM and IgG subclasses, 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-transplant;
- Incidence of Events of Special Interest (ESI) at 6, 12 and 24 months post-transplant;
- Description and incidence of clinically significant changes in vital signs;
- Description and incidence of laboratory test abnormalities.

Cardiovascular and metabolic co-morbidities

- Incidence of NODAT at 6, 12, and 24 months post-transplant;
- Absolute (mean and median) values for SBP and DBP at 3, 6, 12 and 24 months post-transplant;

- Mean changes from baseline values for SBP and DBP at 6, 12 and 24 months 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:
  - Serum total serum 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 months post-transplant;
- Mean whole blood HbA1C concentrations and mean changes from baseline values at Months 6, 12 and 24 months post-transplant.

Statistical Considerations:

Sample Size:

This study is descriptive in nature and is not powered to show statistically significant treatment differences for any outcome measure. A sample approximately 70 subjects randomized in a 1:1 ratio to belatacept + EVL or 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 (πp) 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

Analyses:

Demographic and baseline characteristics of recipients and donors will be summarized descriptively for each treatment group, by means and standard deviation for continuous variables, and by frequency distribution for categorical variables.

Rate of acute rejection will be summarized by treatment group at Months 6, 12 and 24 using point estimates of the proportion of subjects who have experienced at least one episode of CSBPAR along with and the corresponding 95% CIs. Two-sided 95% CIs will be generated for the differences between treatment groups. Descriptive summaries will be provided for the percentages of subjects with CSBPAR in each treatment group, including those for severity grade and treatment received. 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 analyses 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.

The endpoint of subject and graft survival at 6, 12 and 24 months post-transplantation will be summarized within each treatment group using point estimates of the proportion of subjects surviving with a functioning graft, and the corresponding 95% CIs. 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 6, 12 and 24 months
- Rates of death with a functioning graft at 6, 12 and 24 months
- Rates of pure death (death censored) graft loss at 6, 12 and 24 months

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. For a subject who has one or more missing values for cGFR due to a graft loss or

death, the missing cGFR will be imputed as "zero". A linear mixed effects model will be used to analyze changes from Month 3 cGFR. Details of the analyses will be available in the Statistical Analysis Plan.

Safety analysis will be based on all randomized, transplanted, and treated subjects. 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, defined as those identified 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 randomization).

All safety summaries except those for reports of death, graft loss, PTLD, malignancies, and serious infections, will be based only on data at the scheduled analysis time point 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 at the scheduled analysis time point applying 'last dose date + 56' cut counting rules. The secondary summary will be based on all available data at the scheduled analysis time point without applying 'last dose date + 56' cut counting rules. The frequencies and incidence rates using person-year method with exposure will be summarized by treatment groups.

All other endpoints will be descriptively summarized and presented by treatment group.

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1.2 Research Hypothesis

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

1.3 Objectives(s)

1.3.1 Primary Objective

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.

1.3.2 Secondary Objectives

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

- The frequency and severity of acute rejection 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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1.4 Product Development Background

A detailed description of the preclinical and clinical studies conducted to-date is available in the current version of the Investigator Brochure.

Belatacept has been studied in a comprehensive clinical development program totaling 2366 subjects across all indications as of June/July 2010. Assessment of the efficacy and safety of belatacept is based on results from three similarly designed studies in *de novo* renal transplant recipients, collectively referred to as the core studies, these include: one Phase 2 (IM103100)[45] and two Phase 3 (IM103008 and IM103027) studies[46,47]. These trials evaluated two dosing regimens of belatacept in blinded fashion, a more intensive (MI) regimen and a less intensive (LI) regimen, each compared to a cyclosporine (CsA) active comparator treatment regimen. All treatment groups also received basiliximab induction, mycophenolate mofetil (MMF), and corticosteroids.

[redacted]

[redacted]

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2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS and/or designee immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The

investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator or BMS should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS and/or designee will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1. Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2. Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3. Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4. Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5. If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6. Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS and/or designee and regulatory authorities have direct access to subject records.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a randomized, open-label, multicenter, parallel-group study to be conducted at approximately 20 sites in North and South America and the European Union. Approximately70 subjects (n = 35 per group), scheduled to receive a *de novo* kidney transplant, will be randomized (stratified by study site/center) in a 1:1 ratio, to 1 of the following 2 treatment arms:

a) Thymoglobulin + Belatacept + Everolimus
b) Thymoglobulin + Tacrolimus + MMF

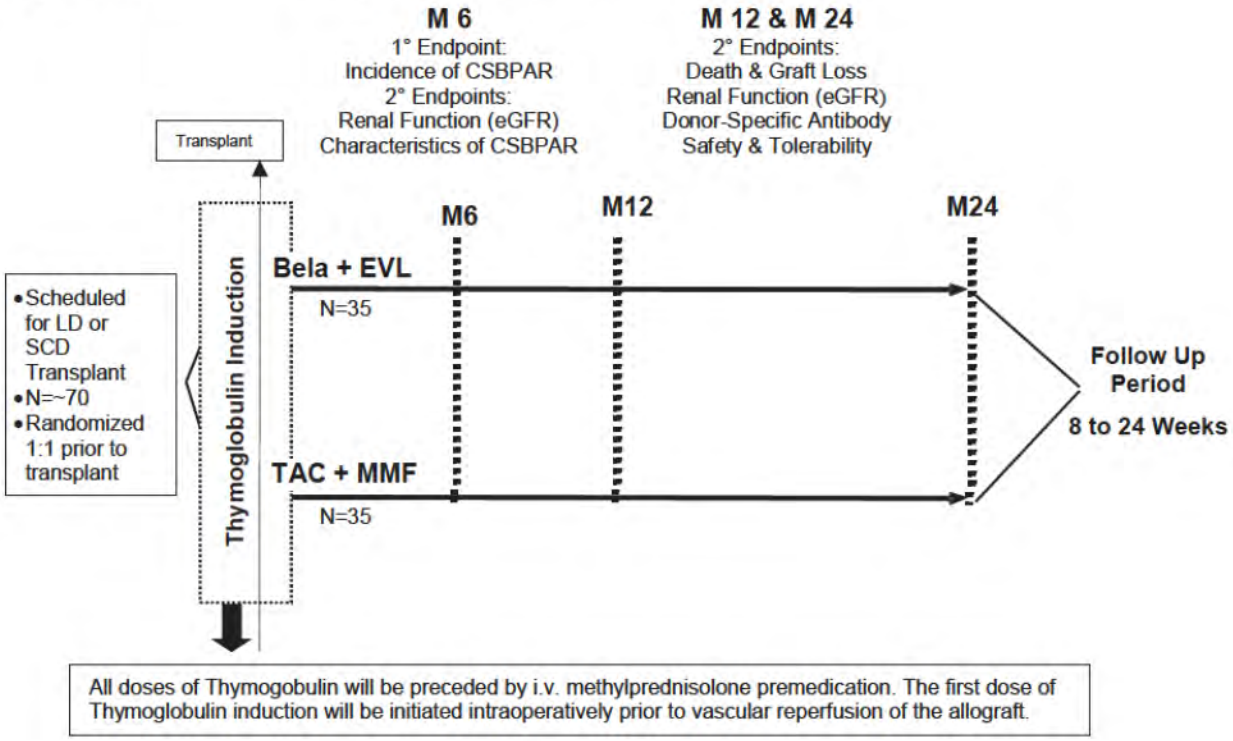
For administrative reasons related to the availability of study drug, BMS will prematurely terminate enrollment in this clinical trial according to the following schedule:

- As of 18 October 2016 at all sites without previously randomized subjects;
- As of 31 December 2016 at all remaining sites.

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

This is a rapid corticosteroid withdrawal trial; corticosteroids are 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 will continue to require methylprednisolone i.v. 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.

Figure 3.1-1: 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.

3.2 Post Study Access to Therapy

At the end of the study, BMS will not continue to supply study drug to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject continues to receive appropriate treatment.

3.3 Study Population

The study population includes recipients of a renal allograft from living donors (LD) or standard criteria donors (SCD) only.

Subjects who, in the opinion of the investigator, are at low to moderate levels of immunological risk, are eligible to participate if they meet all remaining eligibility criteria. However, the study will exclude subjects at higher immunological risk as defined, for example, by a positive lymphocytotoxic antibody cross match, current percent panel reactive antibodies [% PRA] $\geq$ 20%, and the need for desensitization therapy.

Subjects will be enrolled at approximately 20 sites globally. The number of randomized subjects for each treatment group will be controlled by the interactive voice response system (IVRS).

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.1 Inclusion Criteria

For entry into the study, the following criteria MUST be met.

1. **Signed Written Informed Consent**
   a) The subject or legal representative is willing to provide signed written informed consent
2. **Target Population**
   a) Adults with end-stage renal disease (ESRD) scheduled to undergo transplantation of a non-HLA identical, living or standard criteria deceased (SCD) donor kidney
   b) Subject Re-enrollment: This study does not permit the re-enrollment of a subject who has discontinued the study as a pre-treatment failure.
   c) Subjects with serologic evidence of prior exposure to EBV. Evidence of prior exposure is to be determined locally by positive testing for IgG antibodies directed against EBV viral capsid antigen (VCA) and Epstein-Barr nuclear antigen (EBNA). Historical results are acceptable.
3. **Age and Reproductive Status**
   a) Men and women, ages 18 to 75 years at Screening, inclusive
   b) Women of childbearing potential (WOCBP) must use method(s) of contraception based on the tables in Appendix 1. Since there is insufficient information to assess teratogenicity (preclinical studies have not been done), a highly effective method(s) of contraception (failure rate of less than 1% per year) is required. The individual methods of contraception and duration should be determined in consultation with the investigator. WOCBP must follow instructions for birth control for a period of 8 weeks after the last dose of study drug.

      NOTE: According to the US product information for mycophenolate mofetil (CellCept®), two reliable forms of contraception must be used simultaneously unless abstinence is the chosen method.
   c) WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of beta-human chorionic gonadotrophin [β-HCG]) within 24 hours prior to the start of investigational product.
   d) Women must not be breastfeeding
   e) Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. The investigator shall review contraception methods and the time period that contraception must be followed. Men that are sexually active with WOCBP must follow instructions for birth control for a period of 8 weeks after the last dose of study drug.

f) Women who are not of childbearing potential (i.e., those who are postmenopausal or surgically sterile; see Section 3.3.3 for the definition of WOCBP) and azoospermic men do not require contraception.

3.3.2 Exclusion Criteria

Subjects meeting the following criteria are prohibited from entry into the study.

1. Target Disease Exceptions

a) Subjects who are seronegative for prior exposure to EBV or those whose EBV serologic status is unknown at randomization.

b) Genetically-identical donor recipient pairs (ie, identical twins)

c) Subjects with a recent (within 3 months prior to transplant) PRA ≥ 20%

d) Subjects with a past history of, or current need for desensitization therapy

e) Subjects with previous graft loss due to acute rejection

f) Subjects with a positive T-cell lymphocytotoxic cross match or any detectable donor specific antibodies prior to transplantation

g) Recipients of kidneys from donors < 10 years old

h) Recipients of an extended criteria donor (ECD) kidney, defined as:

i) Donors ≥ 60 years old, or

ii) Donors aged 50 – 59 years with any 2 of the following:

- death from cerebrovascular accident;
- hypertension;
- serum creatinine > 1.5 mg/dL; or

iii) Not applicable per Protocol Amendment 03

iv) Recipients of kidneys donated after cardiac death

i) Subjects with prior or concurrent, non-renal solid organ or cell (e.g., pancreas, kidney-pancreas, or islet cell or stem-cell) transplants, and those deemed by the Investigator as being likely to require a non-renal transplant in the next 3 years

j) Subjects receiving paired (dual or en bloc) kidney transplants

k) CMV-negative subjects scheduled to receive a kidney from a CMV-positive donor

2. Medical History and Concurrent Diseases

a) Subjects with ESRD due to any of the following underlying chronic renal diseases:

- Primary focal segmental glomerulosclerosis (FSGS)
- Type I or II membranoproliferative glomerulonephritis (MPGN)
- Hemolytic uremic syndrome (HUS) / Thrombotic Thrombocytopenic Purpura

If a subject has ESRD of unknown etiology and/or has no histologically-confirmed underlying diagnosis, the subject may be enrolled into the study if, in the opinion of the Investigator, the patient's prior clinical, laboratory, and/or radiographic findings are unlikely to be consistent with any of the above diagnoses.

b) Hepatitis C virus (HCV): Subjects or donors known to be positive for anti-HCV antibody, or for HCV RNA detectable by polymerase chain reaction (PCR)

c) Hepatitis B virus (HBV): subjects or donors known to be positive for hepatitis B surface antigen or for HBV DNA detectable by PCR

d) Human immunodeficiency virus (HIV): subjects or donors known to be HIV positive

e) Subjects with current evidence or past history of active or inadequately* treated latent TB infection[52]. Subjects must have documentation of negative screening for active and latent TB infection to be eligible for randomization*, specifically:

i) A chest x-ray (posterior-anterior and lateral views) that is negative for radiographic evidence of pulmonary TB within the last 6 months prior to transplant.

ii) A negative screening test for latent TB infection (LTBI) [intradermal PPD, or interferon-gamma release assay (IGRA) such as QuantiFERON® TB Gold test or T-Spot-TB] that was performed *at any time* prior to the current transplant.

(1) Those subjects who do not have a documented negative result, specifically from an IGRA test performed within the last 3 months prior to randomization, **must** be screened for LTBI with an IGRA test performed during the Screening Visit.

*Notes:

- For this protocol, "adequately treated" LTBI is defined as completion of a standard course of antimicrobial therapy per a local standard of care, e.g., for the U.S., recent CDC guidelines[52].
- Results of the Screening Visit IGRA are not required for randomization when the results from a historical negative screening test (PPD or IGRA) are available [see (2) (e) (ii) above].
- If the Screening IGRA test result is positive and there is no historical negative screening test (PPD or IGRA) result for LTBI available so that the patient is a screen failure, the patient may be re-screened following completion of what is considered, per local standard of care to be an adequate course of therapy for LTBI, so long as the only cause of the screen failure was the positive IGRA test result.
- IGRA testing is to be done by the central laboratory. However, if equipment for sample preparation prior to shipment to the central laboratory is not available at the site, a local laboratory IGRA test is acceptable.
- If a historical negative screening test (PPD or IGRA) result for LTBI was available and the patient was randomized on that basis, but the Screening Visit IGRA is subsequently reported (post-transplant) to be positive, treatment for latent TB **must** be initiated upon receipt of the test result by the Investigator. Treatment may consist

of isoniazid (INH, isonicotinic acid hydrazide), 300 mg p.o. once daily for 9 months[52] or an alternative that is consistent with the local standard of care.

f) History of biopsy-confirmed malignancy (other than nonmelanoma skin cancer cured by resection) within the previous 5 years prior to the current transplant.

g) Subjects with a body mass index (BMI) at screening of > 35 kg/m^2 for nondiabetic subjects or > 30 kg/m^2 for diabetic subjects (due to higher risk of wound complications)

h) Subjects whose life expectancy is severely limited (< 6 months).

i) Subjects with a current or past history of substance abuse (drug or alcohol) within the past 5 years, or psychotic disorders that are not compatible with adequate study adherence and follow-up.

j) Subjects with active peptic ulcer disease, chronic diarrhea, or gastrointestinal malabsorption

k) Subjects with any active infection or other contraindication that would normally preclude transplantation

3. Physical and Laboratory Test Findings

a) Female subjects who had a breast cancer screening that is suspicious for malignancy, and in whom the possibility of malignancy cannot be reasonably excluded following additional clinical, laboratory or other diagnostic evaluations.

b) Subjects with laboratory values that meet any of the following criteria are to be excluded from the study:

Hematology:

- Hemoglobin < 7 g/dL
- Platelets < 80,000/mm^3
- White blood cell (WBC) count < 3000/mm^3 (3 x 109/L)

Chemistry:

- Bilirubin > 1.5 x upper limit of normal range (ULN); exception: subjects who have a clinical or genetic diagnosis of Gilbert's Syndrome and have a normal direct bilirubin are eligible.
- Aspartate aminotransferase (AST) ≥ 2 x ULN
- Alanine aminotransferase (ALT) ≥ 2 x ULN

4. Allergies and Adverse Drug Reaction

a) History of drug or other allergy which in the opinion of the principal investigator makes the subject unsuitable for participation in the study

5. Sex and Reproductive Status

a) WOCBP who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and for up to 8 weeks after the last infusion.

b) Not applicable per Protocol Amendment 03

c) Not applicable per Protocol Amendment 03

6. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

c) Subjects currently receiving immunosuppressive agent(s) (eg, methotrexate, infliximab, etanercept, etc.) for other indications, such as an autoimmune disease, or subjects with comorbidities that treatment with such agents are likely during the trial

d) Subjects who have used any investigational drug within 30 days prior to Day 1 visit

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

A woman of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or is not postmenopausal. Menopause is defined as 6 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In addition, women under the age of 55 must have a serum follicle stimulating hormone (FSH) level > 40mIU/mL to confirm menopause*.

*Women treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal:

- 1 week minimum for vaginal hormonal products, (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months.

If an FSH level is not available at enrollment and if it is deemed medically important to maintain HRT, these women will be considered as WOCBP.

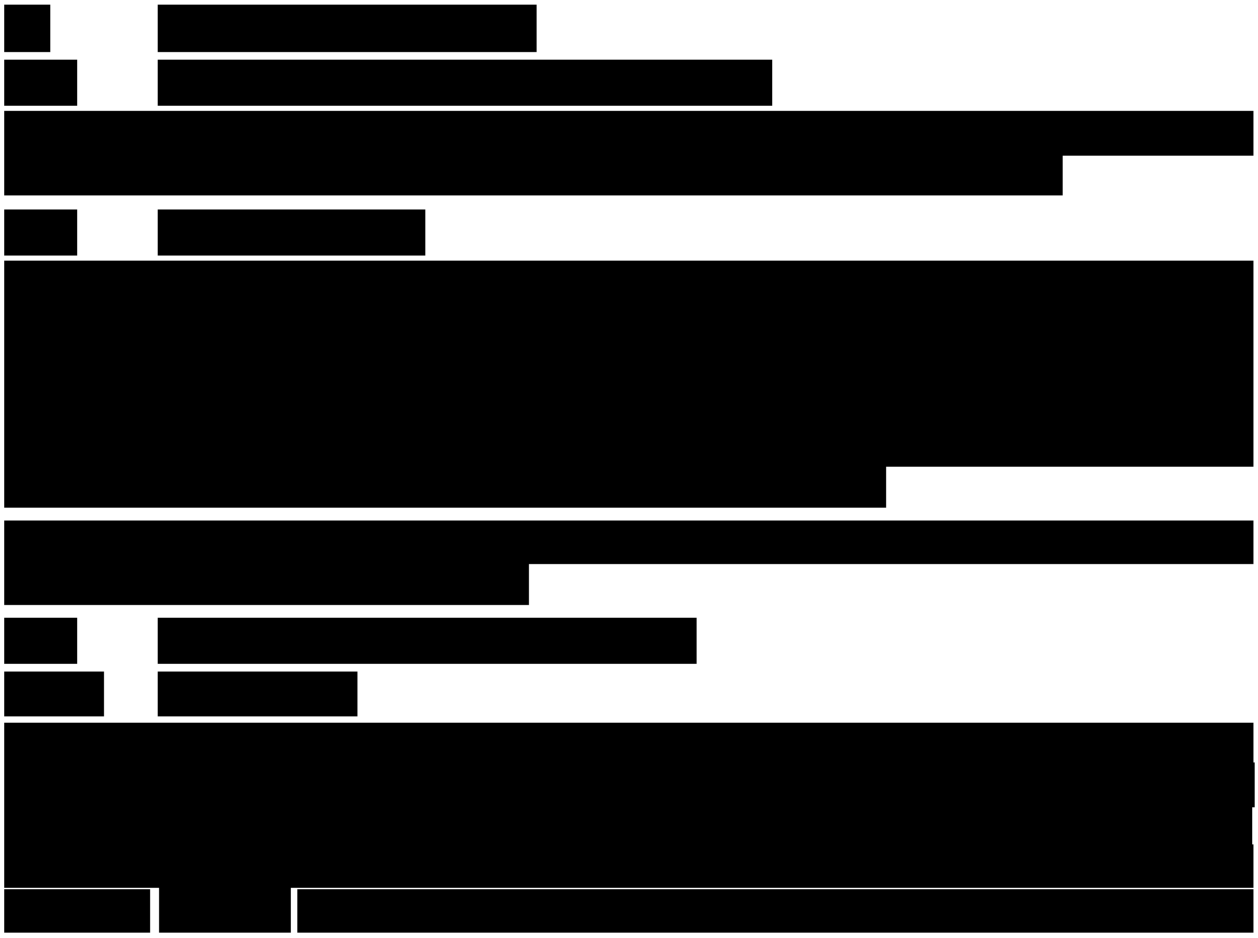
WOCBP must be made aware of the increased risk of first trimester pregnancy loss and congenital malformations with mycophenolic acid (MPA) products (both mycophenolate mofetil and mycophenolate sodium) and must be counseled regarding pregnancy prevention and planning.

As required by BMS Standard Operating Procedure, participation in this study requires the use of two forms of contraception for both WOCBP and female partners of male subjects who are WOCBP. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using 2 forms of contraception with their partner.

Acceptable birth control methods for WOCBP are listed in Appendix I to this protocol.

For WOCBP assigned to receive TAC in combination with MMF (and those who, subsequently, may be switched to mycophenolate sodium for intolerance to MMF) and who become pregnant while using either mycophenolate preparation, or within 6 weeks of discontinuing therapy:

- They should be apprised of the potential hazard to the fetus. In certain situations, the subject and her healthcare practitioner may decide that the maternal benefits outweigh the risks to the fetus.
- (U.S. sites only): The principal investigator should report the pregnancy to the Mycophenolate Pregnancy Registry (1-800-617-8191 or https://www.mycophenolatepregnancyregistry.com (as of November 13, 2014)) and should strongly encourage the patient to enroll in the pregnancy registry.)



[redacted]

3.5 Discontinuation of Subjects from Treatment

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Missing 2 consecutive belatacept infusions, unless the subject is receiving lymphocyte-depleting therapy or has approval by the medical monitor to remain in the study. Documentation will be required.
- Subjects who have met protocol defined criteria for graft loss (Section 5.3.12)

All subjects who discontinue investigational product should comply with protocol specified Early Termination (ET) and follow-up procedures as outlined in Section 5. Information on subject and allograft survival will be collected for all subjects through 24 months post-transplant. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) pages.

3.6 Post Treatment Study Follow up

Withdrawal of a subject from study medication does not imply that the subject is withdrawn from the study. Early Termination (ET) and Follow-Up Safety visit procedures must be completed per Table 5.1-3 for all subjects who discontinue study drug. Information on subject and allograft survival will be collected for all subjects through 24 months post-transplant (at 6, 12 and 24 months).

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. Since vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 TREATMENT

Study drugs include both Investigational Medicinal Products (IMP) and Non-investigational (NIMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

4.1 Study Treatments

Table 4.1-1: Product Description

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Belatacept Infusion	250 mg	Glass vial/one panel open	White cardboard container/one panel open label	White to off-white, whole or fragmented cake in a vial.	Store Refrigerated; 2-8 Degrees C 36-46 Degrees F; Protect From Light
Thymoglobulin Infusion	25 mg	Dispensed in original market product vial	Card board dispensing box (if applicable)	Lyophilized powder in a vial	Store Refrigerated at 2- 8 Degrees C
Everolimus tablet	0.25 mg and 0.75 mg tablets	Dispensed in original market product package/over label	Card board dispensing box (if applicable)	Tablet-Market product image	Store as per market product label
Tacrolimus tablet	0.5 mg and 1.0 mg tablets	Dispensed in original market product package/over label	Card board dispensing box (if applicable)	Tablet-Market product image	Store as per market product label

4.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.
The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects and only used as described in this protocol. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational product(s) is/are: belatacept, Thymoglobulin everolimus and tacrolimus.

4.1.2 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

In this protocol, non-investigational product(s) is/are: mycophenolate mofetil (MMF), mycophenolate sodium and corticosteroids, or their equivalents.

4.1.3 Handling and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

For non-investigational product, if marketed product is utilized, it should be stored in accordance with the package insert, summary of product characteristics (SmPC), or similar.

4.1.3.1 Belatacept for Injection

Description of the Dosage Form

Belatacept for Injection, 250 mg/Vial, is a sterile non pyrogenic lyophilized powder. Each vial contains 275 mg of belatacept, 550 mg of sucrose, 38.0 mg of sodium phosphate monobasic monohydrate, 6.4 mg of sodium chloride, and 1 N sodium hydroxide/1 N hydrochloric acid solution sufficient to adjust pH to 7.5. A 10% overfill is included in each vial to account for vial needle syringe (VNS) holdup.

Drug Product Preparation

Constitution and dilution of belatacept for Injection 250 mg/Vial must be performed using silicone-free disposable syringes. Suitable fluids for constitution of the lyophile include sterile water for injection (SWFI), 0.9% sodium chloride injection (NS) or 5% dextrose injection (D5W). Prior to IV administration, the constituted solution is further diluted to a sufficient infusion volume (eg, 100 mL) with NS or D5W to final belatacept concentrations between 2 mg/mL and 10 mg/mL. The infusion is to be administered through a sterile, non-pyrogenic, low protein binding in-line filter. The syringe and in line filter set will be provided by BMS. Additionally, care must be taken to ensure the sterility of the prepared solution, as the drug product does not contain antimicrobial preservatives or bacteriostatic agents.

Constitution of the Lyophile

Each 250 mg vial of belatacept for Injection should be constituted with 10.5 mL of a suitable constitution fluid (SWFI, NS or D5W) to provide a solution with a belatacept concentration of approximately 25 mg/mL. Belatacept for Injection, 250 mg/Vial, is not stoppered under vacuum. To avoid excessive foam formation in the vial, slowly inject the constitution fluid into the vial with the stream directed toward the vial wall and not into the lyophilized cake. The vial should be gently swirled and inverted until the lyophile dissolves. Although some foam may remain on the surface of the constituted solution, a sufficient excess of belatacept is included in each vial to account for withdrawal losses, thus, 10.0 mL of a 25 mg/mL belatacept solution can be withdrawn from each vial. Constituted solutions of belatacept may foam, therefore, shaking should be avoided.

Preparation of the Infusion

Prior to IV administration, the constituted belatacept solution (25 mg/mL) should be further diluted with either NS or D5W to final belatacept concentrations ranging from 2 mg/mL to 10 mg/mL. Lyophiles constituted with SWFI may be further diluted with either NS or D5W. Lyophiles constituted with NS should be further diluted with NS and lyophiles constituted with D5W should be further diluted with D5W.

The entire belatacept infusion should be administered over a period of 30 minutes and must be administered with an infusion set and a sterile, non-pyrogenic, low-protein-binding filter (with a pore size of 0.2 - 1.2 μm).

Recommended Storage Conditions

Belatacept for injection lyophilized powder is stored and refrigerated at 2°C to 8°C (36°F to 46°F). Belatacept for injection should be protected from light by storing in the original package until time of use. The reconstituted solution should be transferred from the vial to the infusion bag or bottle immediately. The belatacept for injection infusion must be completed within 24 hours of constitution of the belatacept for injection lyophilized powder. If not used immediately, the infusion solution may be stored under refrigeration conditions: 2°C to 8°C (36°C to 46°F) for up to 24 hours (a maximum of 4 hours of the total 24 hours can be at room temperature: 20°C to 25°C [68°F to 77°F] and room light).

Regardless of storage condition, the belatacept infusion must be completed within 24 hours of constitution of the lyophile.

4.1.3.2 Thymoglobulin for Injection

Thymoglobulin for injection should be stored and prepared in accordance with the package insert, SmPC, or similar document for the region.

Thymoglobulin should be administered using a 0.22-micron filter through a peripheral or central vein only. Each reconstituted Thymoglobulin vial (25 mg or 5 mg/mL) should be diluted to a recommended volume of 50 mL with NSS or D5W. Premedication with methylprednisolone (as

per Section 4.3.5) as well as with acetaminophen and/or antihistamine is recommended, as per local practice to reduce the incidence of infusion reactions.

For preparation and full prescribing information, see the package insert, SmPC, or similar.

4.1.3.3 Everolimus Tablets

Everolimus tablets should be stored in accordance with the package insert, SmPC, or similar document for the region.

For full prescribing information, see the package insert, SmPC, or similar.

4.1.3.4 Tacrolimus Tablets

Tacrolimus tablets should be stored in accordance with the package insert, SmPC, or similar document for the region.

For full prescribing information, see the package insert, SmPC, or similar.

4.2 Method of Assigning Subject Identification

Approximately 70 subjects (n = 35 per group) receiving *de novo* kidney transplants will be randomized (stratified by study site/center) in a 1:1 ratio to 1 of the 2 treatment groups. 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-specific procedures, the physician/coordinator must contact IVRS to enroll each subject into the centralized database. Each subject will be assigned a unique sequential 5 digit subject number beginning with 80001, 80002, 80003, etc. by the IVRS for identification throughout the study. This subject number must not be reused for any other participant in the study. SAE reporting will begin at the time of enrollment for all subjects, immediately after written informed consent is obtained, see Section 6, Adverse Events, for detailed (S)AE reporting requirements.

The subject may be randomized once all entry criteria (inclusion and exclusion) have been met. The physician/coordinator must contact IVRS **prior to** transplant surgery to randomize each eligible subject into the centralized database. The collection of nonserious AE information should begin at initiation of study drug. The IVRS must also be contacted at each visit to obtain belatacept vial assignments and each time additional supplies of other investigational products are dispensed.

4.3 Selection and Timing of Dose for Each Subject

4.3.1 Belatacept

Subjects randomized to a belatacept treatment group in the study will receive a belatacept regimen consisting of 10 mg/kg i.v. for the first 3 months post transplant. (Refer to Table 5.1-4) After 3 months (week 12), subjects will receive belatacept at the maintenance dose of 5 mg/kg i.v. every 4 weeks until completion of the trial. (Refer to Table 5.1-5) The entire belatacept infusion should be administered over a period of 30 minutes.

The initial infusion of belatacept should be started at least 12 but no more than 24 hours **after** completion of the initial induction dose of Thymoglobulin. If the Week 1 dose of belatacept will be infused on the same day as a dose of Thymoglobulin, the belatacept infusion must be completed: a) at least 12 hours **prior to** the initiation of the methylprednisolone premedication dose for the Thymoglobulin infusion; or b) at least 12 hours **after** completion of the Thymoglobulin infusion. To facilitate scheduling, infusion windows are permitted for belatacept infusion (Table 5.3.2-1).

Based upon Pharmacodynamic and Pharmacokinetic modeling of receptor occupancy of CD86, administration of the second belatacept dose at the end of Week 1 (Day 7, +/- 1 day) will ensure that subjects achieve receptor occupancy of > 90% through Week 4 post transplant, just as the Day 5 dose, in the phase 3 studies, was shown to achieve.

4.3.2 Thymoglobulin

All subjects will receive Thymoglobulin in a dose of up to 1.5 mg/kg by i.v. infusion on Day 1 (Day of Transplant) and daily thereafter (or less frequently, as tolerated) to reach a total cumulative dose between 3.0 and 5.5 mg/kg. Premedication with i.v. methylprednisolone (as per Section 4.3.5) is required, as well as acetaminophen and/or antihistamine, per local practice, are recommended to reduce the risk of infusion reactions.

The initial Thymoglobulin infusion (Day1) should be administered over a period of at least 6 hours, to be initiated intraoperatively, after premedication with methylprednisolone and prior to vascular reperfusion of the allograft. Subsequent doses should be administered over a period of at least 4 hours, each to begin after methylprednisolone premedication. For subjects randomized to receive belatacept, please refer to Section 4.3.1 for guidance as to the appropriate sequence and timing in which the Thymoglobulin and belatacept doses are to be infused (when both are given on the same day).

At the discretion of the Investigator, Thymoglobulin doses may be given daily (or less frequently, as tolerated), as long as the total number of days of induction does not exceed 10 days and the cumulative dose does not exceed 5.5 mg/kg.

Prior to administration of each dose, hematology lab values must be reviewed by the Investigator. If the absolute lymphocyte count is $< 100/mm^3$, Thymoglobulin will not be administered any further. If the platelet count is $< 80,000/mm^3$, the dose of Thymoglobulin will be decreased by 50%. If the platelet count is $< 50,000/mm^3$, Thymoglobulin will be withheld until laboratory values return to acceptable levels for Thymoglobulin infusion.

Thymoglobulin should be administered using a 0.22-micron filter through a peripheral or central vein only. Each reconstituted Thymoglobulin vial (25 mg or 5 mg/mL) should be diluted to a recommended volume of 50 mL with NSS or D5W.

For additional information on Thymoglobulin, see the package insert.

4.3.3 Everolimus

For subjects randomized to the EVL treatment group of the study, EVL will be given at an initial dose of 3.0 mg/day (1.5 mg bid) starting on Day 3. In subjects who experience DGF, defined as the requirement for acute dialysis during the first post transplant week, initiation of EVL may be delayed up to Day 7. In order to guide dose modifications, EVL pre-dose trough levels should be obtained from the local laboratory per the Time and Events Schedule (Table 5.1-2, Table 5.1-3) and 4 to 5 days after any change in dose. The dosing will be adjusted to keep pre-dose (C0) levels at 6 to 10 ng/mL for the initial 3 months post-transplantation and at 4 to 8 ng/mL after 3 months and for the remainder of the study.

As a guide to dose adjustment: EVL pharmacokinetics are dose-proportional. Therefore, the dose should be increased or decreased in proportion to the desired change in trough level. As a general rule:

$$\text{New EVL dose} = \text{Current dose} \times \frac{\text{New target trough concentration}}{\text{Current trough concentration}}$$

If the new dose of EVL is calculated to be more than 2-fold different from the current dose, the investigator may want to make the change in two increments/decrements rather than all at once (except when the current trough is < 3 ng/mL).

EVL may increase the incidence of hypercholesterolemia, hypertension, arthralgia, hypokalemia, thrombocytopenia, anemia, delayed wound healing, perinephric fluid collection (lymphocele), oral ulcers, acne, interstitial lung disease, and pancreatitis. In such cases, the dose may be reduced or withheld at the discretion of the investigator, as tolerated by the subject.

Subjects unable to tolerate the reduced dose of EVL should be discontinued from assigned therapy, after which they may be converted to alternative therapy per the investigator's discretion. All subjects will be followed for graft and survival status through Month 24. Although discontinued from assigned therapy, they should remain in the study to complete the protocol-specified period of follow-up. Such subjects will be counted in the EVL arm of the study in ITT analyses but may also be evaluated in other sensitivity analyses, for example, by censoring at the time of discontinuation from EVL.

For full prescribing information, see the package insert.

4.3.4 Mycophenolate Mofetil

Subjects randomized to receive MMF, will receive MMF* daily, in 2 divided doses, on a consistent schedule in relation to time of day and meals. The dose should be between 0.5 - 2.0 g per day (0.25 to 1.0 g bid), and up to 3.0 g per day in African American/Black subjects, at the investigator's discretion.

The first dose of MMF should be administered preoperatively on the Day 1 (Day of Transplant). The MMF dose should be administered orally in a capsule or solution formulation. Intravenous dosing is permitted, if needed due to intercurrent illness, postoperative ileus, or other causes at

the investigator's discretion. The recommended starting i.v. dose of MMF injection is 1 g twice daily as a slow continuous i.v. infusion over no less than 2 hours. Subsequent doses should be administered orally as soon as the subject is able to tolerate medications by mouth.

The dose schedule may be adjusted on the basis of results of laboratory tests (eg, decreased WBCs) and subject tolerability.

*Note: Mycophenolate sodium is not to be used as first line therapy for subjects randomized to the tacrolimus + MMF treatment group.

For subjects who develop nausea, diarrhea, or other MMF-related gastrointestinal adverse effects (eg, symptoms fully assessed and deemed not to have an etiology other than intolerability to MMF), the MMF dose may be decreased to a minimum allowable dose of 0.5 g daily. An attempt should be made to divide the total dose of MMF into, up to 4 daily doses. Subjects unable to tolerate the minimal protocol-defined dose of MMF may be converted to mycophenolate sodium in an equivalent dose, where possible. If further reductions or interruptions are deemed necessary by the Investigator, the medical monitor should be contacted.

Subjects unable to tolerate the reduced dose of MMF or substitution with mycophenolate sodium in an equivalent dose, should be discontinued from assigned therapy, after which they may be converted to alternative therapy per the investigator's discretion. All subjects will be followed for graft and survival status through Month 24. Although discontinued from assigned therapy, they should remain on the study to complete the protocol-specified period of follow-up. Such subjects will be counted in the TAC + MMF arm of the study in ITT analyses but may also be evaluated in other sensitivity analyses, for example, by censoring at the time of discontinuation from MMF or mycophenolate sodium.

For full prescribing information for MMF and mycophenolate sodium, see the respective package inserts.

4.3.5 Tacrolimus

The recommended total initial dose of TAC is 0.1 mg/kg/day orally in 2 divided doses and adjusted thereafter on the basis of therapeutic drug monitoring, to target pre-dose (approximately 12-hour trough) blood concentrations of 4-11 ng/mL. Subjects randomized to the TAC treatment group, therapy with TAC may be initiated any time within the first 24 hours post-transplant, or delayed pending improvement in renal function, eg, after the serum creatinine (SCr) concentration has decreased to ≤ 4 mg/dL (in absence of dialysis). Initiation of dosing may be delayed up to Day 7, if in the clinical judgment of the investigator, earlier initiation of TAC therapy is not in the best interest of the subject due to postoperative impairment of allograft function.

Tacrolimus trough (pre-dose) concentrations should be monitored per the Time and Events schedule (Refer to Table 5.1-2). More frequent monitoring is permitted per local standard of care. Doses of TAC should be taken consistently, either with or without food, because the presence and composition of food decreases its bioavailability.

Dosing should be titrated based on clinical assessment of rejection risk and tolerability, to maintain trough levels in the range of 4-11 ng/mL, wherever possible.

Acute overdosages of up to 30 times the intended dose have been reported. Almost all cases have been asymptomatic and all patients recovered with no sequelae. Based on the poor aqueous solubility and extensive erythrocyte and plasma protein binding, it is anticipated that tacrolimus is not dialyzable to any significant extent. General supportive measures and treatment of specific symptoms should be followed in all cases of overdosage.

Subjects who, in the clinical judgment of the investigator, are unable to tolerate maintenance therapy with TAC should be discontinued from assigned therapy, after which they may be converted to alternative therapy at the investigator's discretion. All subjects will be followed for graft and survival status through Month 24. Although discontinued from assigned therapy, they should remain in the study to complete the protocol-specified period of follow-up. Such subjects will be counted in the TAC arm of the study in the ITT analysis, but may also be evaluated in other sensitivity analyses, for example, by censoring at the time of discontinuation from TAC.

For full prescribing information, see the package insert.

4.3.6 Corticosteroids

This is a rapid corticosteroid withdrawal trial; corticosteroids are to be administered during the first week of study treatment only. To reduce the risk of infusion reactions, prior to beginning each Thymoglobulin infusion all subjects will receive premedication with methylprednisolone (as the sodium succinate), to be administered i.v. over approximately 30 minutes, as follows:

1st Dose of Thymoglobulin: 500 mg methylprednisolone i.v.

2nd Dose of Thymoglobulin: 250 mg methylprednisolone i.v.

3rd Dose of Thymoglobulin: 100 to150 mg methylprednisolone i.v.

Any additional doses of Thymoglobulin:

4th Dose of Thymoglobulin: 60 mg methylprednisolone i.v.

5th Dose and beyond of Thymoglobulin: 30 mg methylprednisolone i.v. prior to each Thymoglobulin infusion

Day 4 to Day 10:

- **Subjects completing Thymoglobulin induction before Day 7** may receive prednisone, p.o. (or the equivalent) in lieu of the same dose of i.v. methylprednisolone:
  - **Day 4:** 60 mg prednisone p.o. (or equivalent)
  - **Days 5 through 7:** 30 mg prednisone p.o. daily (or the equivalent).
- **Subjects continuing to receive Thymoglobulin induction during Days 4-10** post-transplant should still be pre-treated with methylprednisolone i.v. as indicated above in lieu of p.o. prednisone.

- All corticosteroids are to be discontinued by Day 7, except for subjects still receiving Thymoglobulin induction between Days 8 - 10; those subjects must discontinue corticosteroids after the final dose of Thymoglobulin induction has been completed.

For additional information on methylprednisolone, prednisone, or their equivalents, see the respective package inserts.

4.3.7 Prophylaxis After Transplantation

4.3.7.1 Antiviral

Antiviral prophylaxis for prevention of infection by CMV and other Herpesviruses is required for all subjects during the post-transplant period for at least 3 months, and should be initiated no later than Day 10. The following are guidelines only; the specific choice of antiviral drug, and the dose and duration of the regimen prescribed, should be individualized for each subject on the basis of level of infection risk, GFR, and other clinical considerations, in accordance with the local standard of care:

Table 4.3.7.1-1: Antiviral Prophylaxis for Prevention of Infection

Donor/Recipient CMV status at transplant	Antiviral drug and duration of prophylaxis
Donor seropositive / Recipient seropositive	Valganciclovir X 3 months
Donor seropositive / Recipient seronegative	Prohibited from study participation per eligibility criterion (1)(k) [See Section 3.3.2]
Donor seronegative / Recipient seropositive	Valganciclovir X 3 months
Donor seronegative / Recipient seronegative	Valganciclovir or acyclovir X 3 months

In addition, if T cell-depleting agents are initiated for the treatment of AR, valganciclovir prophylaxis should be re-administered for 3 months per local standard of care.

For subjects who are allergic to, or have a contraindication for valganciclovir, the medical monitor should be contacted.

4.3.7.2 Pneumocystis jiroveci pneumonia (PJP)

Unless contraindicated, all subjects who participate in this study **must** receive PJP prophylaxis with sulfamethoxazole/trimethoprim for 12 months following transplantation, and for 6 months following any additional courses of T cell-depleting agent used for treatment of AR. Dosing and administration of sulfamethoxazole/trimethoprim are to be determined by the Investigator according to each subject's level of renal function, and in a manner consistent with the package insert.

Subjects with intolerance to sulfa drugs or trimethoprim, or for whom either one is otherwise contraindicated, may receive prophylaxis with inhaled pentamidine, or orally administered atovaquone or dapsone, at the investigator's discretion.

For full prescribing information, see the respective package inserts.

4.3.7.3 Oral Moniliasis/Candidiasis

It is recommended that subjects receive oral moniliasis prophylaxis for at least 10 days following transplantation as well as following treatment of AR, with 4 - 6 mL of nystatin oral suspension (400,000 to 600,000 units; one-half of the dose to each side of the mouth) four times daily. The preparation should be retained in the mouth for as long as possible before swallowing.

4.3.8 Dose Modifications

The dose of belatacept to be infused is based on the baseline (Day 1) body weight, and will not be modified unless a change in body weight of ≥ 10% of the Day 1 weight has occurred. If an adjustment has been made based upon a body weight change, this weight should be considered as a new baseline weight. No further adjustment of dose based upon body weight is required thereafter, unless the subject experiences an additional body weight change ≥ 10% from the new baseline weight. If this occurs, the dose should again be modified, starting with the next belatacept infusion, and that new weight should then be considered as the new baseline weight.

Doses of Thymoglobulin, MMF, EVL and TAC may be adjusted as described in Section 4.3.

In the absence of AEs deemed at least possibly related to study drug treatment, subjects will complete their scheduled belatacept infusions as prescribed by the protocol. If the belatacept infusion can not be administered within the visit/infusion window defined in the protocol, the infusion should be skipped and the next infusion administered within the next visit/infusion window. If a belatacept infusion must be skipped, the investigator should contact the medical monitor in advance to discuss the circumstances. In the event of new, serious, and unexpected toxicity potentially related to belatacept, study drug administration should be interrupted, and the medical monitor promptly notified by the investigator. The subject will be considered eligible to receive additional study drug only after discussion with the medical monitor. Under no circumstances should the dose of belatacept be modified other than for weight changes, as described above. Subjects for whom belatacept dosing is discontinued should be placed on alternative immunosuppressive regimen, to be determined at the discretion of the investigator.

In the event that a subject receives plasmapheresis for the treatment of AR, a discussion of risks and benefits between the investigator and the medical monitor should take place to determine the subject's eligibility to remain in the study on assigned therapy.

4.4 Blinding/Unblinding

Not applicable. This study is open label.

4.5 Treatment Compliance

All medications specified in this protocol must be administered as described within the protocol. All study medications and concomitant medication usage must be reported on the appropriate case report form (CRF) pages and any deviations from specified administration should be clearly documented.

In addition, each time study medication is dispensed, compliance should be reinforced. When study drug everolimus, tacrolimus, or MMF is returned, compliance should be assessed based

upon an interview with the subject and a count of the tablets returned. Compliance should be between > = 80% and < = 120% of that prescribed. The investigator (or designee) should record the amounts of study medication dispensed and returned at each visit, as well as document reasons for non-compliance in the source document. The dates of all study medication dosing, including interruptions, missed doses or overdose, should be recorded on the eCRF. If the subject is not > = 80% compliant with recording study drug doses during the study, the period of non-compliance should be noted as a protocol deviation and the sponsor should be notified. The subject should be educated on the importance of medication compliance and to record and report any missed doses.

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on-site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.6.2 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible Study Monitor.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening and Baseline/Randomization Procedural Outline (IM103177)

Procedure	Screening Period [a]	Baseline/ Randomization/ Day of Transplant	Notes
	Day- 30	Day 1	
Informed Consent	X		Consent must be obtained prior to performance of any study-specific procedures.
Call IVRS	X	X	Upon signature of informed consent form, call IVRS to enroll subject & begin reporting of SAEs. On Day 1, prior to transplant surgery, call IVRS to randomize the subject and for study drug dispensing; Section 4.2.
Confirm Inclusion/Exclusion Criteria	X		Section 3.3
Full Medical History	X		Sections 3.3 and 5.3
Physical Exam	X		Section 5.3
Neurological Exam		X	Section 5.3
Vital Signs/Weight/Height	X	X	Blood pressure (BP) (sitting position), heart rate, temperature & respiratory rate. Weight to be used to calculate belatacept dose. Height taken at baseline only; Section 5.3
12 Lead Electrocardiogram (ECG)	X		If the subject has an ECG performed within 6 months of transplant, and the report is available, that is acceptable; Section 5.3
TB Infection Screening	X		Section 3.3
Chest X-Ray	X		Posterior-anterior and lateral views within 6 months prior to the date of transplant; Section 3.3
Adverse Event Monitoring		X	Include evaluation of Neurologic signs and symptoms for CNS events and malignancies; Section 6.
Review Concomitant Medications		X	Refer to Section 3.4 for prohibited and/or restricted treatments

Table 5.1-1: Screening and Baseline/Randomization Procedural Outline (IM103177)			
Procedure	**Screening Period [a]**	**Baseline/ Randomization/ Day of Transplant**	**Notes**
	Day- 30	**Day 1**	
Donor Information	X		Obtain information on organ donor status, including viral (EBV and CMV) serologies, T cell cross match, HLA-typing, & demographic data.
LOCAL LABS			
Recipient CMV/EBV Serology	X		Confirm locally that EBV status is positive by two tests (Anti-VCA IgG and Anti-EBNA IgG), per inclusion/exclusion criteria; Section 3.3.
Recipient HBV/HCV Serology	X		Confirm exclusion criteria; Section 3.3.
Panel Reactive Antibodies (PRA)	X		Confirm exclusion criteria; Section 3.3
Serum Creatinine	X		Section 5.3.6
Hematology w/diff	X	X	Confirm exclusion criteria; Section 3.3 Local lymphocyte, platelet, and neutrophil counts must be evaluated by Investigator prior to each thymoglobulin infusion; Section 4.3.2.
Pregnancy Test		X	A urine or serum pregnancy test (minimum sensitivity 25 IU/L of ß-HCG) must be performed at a local laboratory for all WOCBP within 24 hours prior to the first dose of study medication; Section 3.3.3 and 5.3
CENTRAL LABS			
Urine collection (central lab)	X		Urine for protein, creatinine, protein:creatinine ratio; Section 5.3.6.1
Hematology w/diff	X		Section 5.3.6.1
Hemoglobin A1c	X		Section 5.3.6.1
Chemistry Panel (Fasting)	X		Nothing to eat/drink, except water, for 8 hours prior to laboratory collection; Section 5.3.6.1

Table 5.1-1: Screening and Baseline/Randomization Procedural Outline (IM103177)			
Procedure	**Screening Period [a]**	**Baseline/ Randomization/ Day of Transplant**	**Notes**
	Day- 30	**Day 1**	
Lipid Panel (Fasting)	X		Nothing to eat/drink, except water, for 8 hours prior to laboratory collection; Section 5.3.6.1
IgG & IgG subclasses 1,2,3,4		X	
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

[a] Unless timeframe is specified in section 3.3, all screening labs and procedures must be performed within 30 days of transplant.

Table 5.1-2: Procedural Outline - Year 1 of Treatment (IM103177)

Procedure			M1		M 3			M 6			M 9				M 12	Notes
	W 1	W 2	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52	
	D 7	D 15	D 29	D 57												
Belatacept Dispensing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	For belatacept subjects only, call the IVRS for vial assignment. Section 4.2
Everolimus or Tacrolimus Dispensing	X				X			X			X				X	EVL or TAC subjects only, call the IVRS for container assignment. Section 4.2
Vital Signs/Weight	X	X	X	X	X	X	X	X	X*	X*	X	X*	X*	X*	X	All subjects will have BP (sitting position), heart rate, temperature, respiratory rate & weight; belatacept subjects will have BP and heart rate also at 30 minutes after the EoI (end of infusion). *Not required for TAC subjects completing the visit by phone. Section 5.3
Physical Exam								X							X	Section 5.3
Neurological Exam								X							X	Also required if change in neurologic status based on clinical signs and symptoms is observed; Section 5.3
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Include evaluation of Neurologic signs and symptoms for CNS events and malignancies; Section 6.

Table 5.1-2: Procedural Outline - Year 1 of Treatment (IM103177)																
Procedure			**M1**		**M 3**			**M 6**			**M 9**				**M 12**	**Notes**
	W 1	**W 2**	**W 4**	**W 8**	**W 12**	**W 16**	**W 20**	**W 24**	**W 28**	**W 32**	**W 36**	**W 40**	**W 44**	**W 48**	**W 52**	
	D 7	D 15	D 29	D 57												
Peri-Infusional AE Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Belatacept randomized subjects only. Following every belatacept infusion, subject must be contacted within 48 hours to determine if they had any adverse events within 24 hrs of their infusion; Section 6.7.1.
Review Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Refer to Section 3.4 for prohibited and/or restricted medications
LOCAL LABS																
Serum Creatinine		X	X	X	X	X	X	X			X				X	Also must be obtained at time of suspected AR, PML or PTLD; Sections 5.3.6, 5.3.7 and 5.3.8.
Hematology w/diff	Required on days when Thymo-globulin infused															Lymphocyte, platelet, and neutrophil counts must be evaluated by Investigator **prior to** each Thymoglobulin infusion; Section 4.3.2 and 5.3.6
Pregnancy Test	X	X	X	X	X	X	X	X	X*	X*	X	X*	X*	X*	X	All WOCBP: Negative pregnancy test is required prior to dosing at all study visits. *Not required for TAC

Table 5.1-2: Procedural Outline - Year 1 of Treatment (IM103177)																
Procedure			**M1**		**M 3**			**M 6**			**M 9**				**M 12**	**Notes**
	W 1	**W 2**	**W 4**	**W 8**	**W 12**	**W 16**	**W 20**	**W 24**	**W 28**	**W 32**	**W 36**	**W 40**	**W 44**	**W 48**	**W 52**	
	D 7	D 15	D 29	D 57												
																subjects completing the visit by phone; Section 3.3.3 and 5.3.
Everolimus Trough	X*	X	X	X	X	X	X	X		X		X		X	X	For everolimus subjects only: Section 4.3.3 - Hold morning dose until trough level is drawn. - Also obtained at time of suspected AR, PML, or PTLD (Sections 5.3.7 and 5.3.8) and 4-5 days after any change in dose (Sections 4.3.3 and 5.3.6) *Week 1 trough sample collection is not required if subject does not start everolimus prior to Week 1 visit.

Table 5.1-2: Procedural Outline - Year 1 of Treatment (IM103177)																
Procedure			**M1**		**M 3**			**M 6**			**M 9**				**M 12**	**Notes**
	W 1	**W 2**	**W 4**	**W 8**	**W 12**	**W 16**	**W 20**	**W 24**	**W 28**	**W 32**	**W 36**	**W 40**	**W 44**	**W 48**	**W 52**	
	D 7	D 15	D 29	D 57												
Tacrolimus Trough	X*	X	X	X	X	X	X	X			X				X	For tacrolimus subjects only: Section 4.3.5 - Hold morning dose until trough level is drawn. - Also obtained at time of suspected AR, PML, or PTLD (Sections 5.3.6, 5.3.7 and 5.3.8) and after any change in dose *Week 1 trough sample collection is not required if subject does not start tacrolimus prior to Week 1 visit.
CENTRAL LABS																
Urine collection			X		X			X							X	Section 5.3.6.1
Hematology w/diff			X		X			X							X	Section 5.3.6.1
Hemoglobin A1c					X			X							X	Section 5.3.6.1
Chemistry Panel (Fasting)			X	X	X			X							X	Nothing to eat/drink, except water, for 8 hours prior to laboratory collection; Section 5.3.6.1
Lipid Panel (Fasting)			X		X			X							X	Nothing to eat/drink, except water, for 8 hours prior to laboratory collection; Section 5.3.6.1

Table 5.1-2: Procedural Outline - Year 1 of Treatment (IM103177)

Procedure			M1		M 3			M 6			M 9				M 12	Notes
	W 1	W 2	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52	
	D 7	D 15	D 29	D 57												
IgG & subclasses 1,2,3,4			X	X	X			X							X	Also collected at the time of serious infections, CNS events, malignancies, graft loss and AR; Section 5.3.6.1
CMV/EBV/ BK Viral Load					X			X							X	Also must be obtained at the time of any suspected AR, PML or PTLD; Section 5.3.6.1
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			[redacted]				[redacted]	[redacted]							[redacted]	[redacted]

Table 5.1-2: Procedural Outline - Year 1 of Treatment (IM103177)

Procedure			M1		M 3			M 6			M 9				M 12	Notes
	W 1	W 2	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52	
	D 7	D 15	D 29	D 57												
																treatments, if employed. Section 5.5
BIOMARKER [redacted]																
[redacted]																
[redacted]																
[redacted]																
[redacted]																
[redacted]																
[redacted]																
[redacted]																
[redacted]																

Table 5.1-2: Procedural Outline - Year 1 of Treatment (IM103177)

Procedure			M1		M 3			M 6			M 9				M 12	Notes
	W 1	W 2	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52	
	D 7	D 15	D 29	D 57												
WB AR gene [redacted]			[redacted]		[redacted]			[redacted]							[redacted]	[redacted]
[redacted]	[redacted]															[redacted]

Table 5.1-3: Procedural Outline - Year 2 through End of Treatment (IM103177)

Procedure			M 15			M 18			M 21				M 24/ET[a]	FU	Notes
	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	W 100	W 104	W 8/12/24	
Belatacept Dispensing	X	X	X	X	X	X	X	X	X	X	X	X	X*		Belatacept subjects only, call the IVRS for vial assignment. Section 4.2 *No dispensing at the ET Visit.
Everolimus or Tacrolimus Dispensing			X			X			X						EVL or TAC subjects only, call the IVRS for container assignment. Section 4.2
Vital Signs/ Weight	X*	X*	X	X*	X*	X	X*	X*	X	X*	X*	X*	X	X	All subjects will have BP (sitting position), heart rate, temperature, respiratory rate & weight; belatacept subjects will have BP and heart rate also at 30 minutes after the EoI (end of infusion). *Not required for TAC subjects completing the visit by phone. Section 5.3.
Physical Exam						X							X		Section 5.3
Neurological Exam						X							X		Also required if change in neurologic status based on clinical signs and symptoms is observed; Section 5.3
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Include evaluation of Neurologic signs and symptoms for CNS events and malignancies; Section 6.
Peri-Infusion AE Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X		Belatacept subjects only. Following every belatacept infusion, subject must be contacted within 48 hours to determine if they had any adverse events within 24 hrs of their infusion; Section 6.7.1
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5.1-3: Procedural Outline - Year 2 through End of Treatment (IM103177)															
Procedure			**M 15**			**M 18**			**M 21**				**M 24/ET[a]**	**FU**	**Notes**
	W 56	**W 60**	**W 64**	**W 68**	**W 72**	**W 76**	**W 80**	**W 84**	**W 88**	**W 92**	**W 96**	**W 100**	**W 104**	**W 8/12/24**	
LOCAL LABS															
Serum Creatinine			X			X			X				X		Also must be obtained at the time of any suspected AR, PML or PTLD; Sections 5.3.7 and 5.3.8
Pregnancy Test	X*	X*	X	X*	X*	X	X*	X*	X	X*	X*	X*	X	X**	All WOCBP: Negative pregnancy test is required prior to dosing at all study visits. ; Sections 3.3.3 and 5.3. * - Not required for TAC subjects completing the visit by phone ** - Only tested at the 8-Week Post Last Dose Safety Follow Up visit.
Everolimus Trough						X							X		For everolimus subjects only; Section 4.3.3: - Hold morning dose until trough level is drawn. - Also obtained 4-5 days post dose change and at time of suspected AR, PML, or PTLD; Sections 5.3.7 and 5.3.8
Tacrolimus Trough						X							X		For tacrolimus subjects only; Section 4.3.5: - Hold morning dose until trough level is drawn. - Also obtained after change in dose and at time of suspected AR, PML, or PTLD; Sections 5.3.7 and 5.3.8
CENTRAL LABS															
Urine collection						X							X		Section 5.3.6.1
Hematology w/diff						X							X		Section 5.3.6.1
Hemoglobin A1c													X		Section 5.3.6.1

Table 5.1-3: Procedural Outline - Year 2 through End of Treatment (IM103177)

Procedure			M 15			M 18			M 21				M 24/ET[a]	FU	Notes
	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	W 100	W 104	W 8/12/24	
Chemistry Panel (Fasting)						X							X		Nothing to eat/drink, except water, for 8 hours prior to laboratory collection; Section 5.3.6.1
Lipid Panel (Fasting)						X							X		Nothing to eat/drink, except water, for 8 hours prior to laboratory collection; Section 5.3.6.1
IgG & subclasses 1,2,3,4						X							X		Also collected at the time of serious infections, CNS events, malignancies, graft loss and AR; Section 5.3.6.1
CMV/EBV/ BK Viral Load													X*		Also must be obtained at the time of any suspected AR, PML or PTLD; Section 5.3.6.1; * sample to be collected and stored for later analysis.
[redacted]						[redacted]							[redacted]	[redacted]	[redacted]

Table 5.1-3: Procedural Outline - Year 2 through End of Treatment (IM103177)

Procedure			M 15			M 18			M 21				M 24/ET[a]	FU	Notes
	W 56	W 60	W 64	W 68	W 72	W 76	W 80	W 84	W 88	W 92	W 96	W 100	W 104	W 8/12/24	
[redacted]															[redacted]
[redacted]															
[redacted]													[redacted]		[redacted]
[redacted]													[redacted]		[redacted]
[redacted]													[redacted]		[redacted]
[redacted]													[redacted]		[redacted]
[redacted]	[redacted]														[redacted]

[a] Information on subject and allograft survival will be collected for all subjects through 24 months post-transplant (at 6, 12 and 24 months).

Table 5.1-4: Dosing Schedule Day 1 (Day of transplant) - Month 6

								M 1		M 3			M 6	
	Day of Transplant 1st Dosing Day 1	**D 2**	**D 3**	**D 4**	**D 5**	**W 1**	**W 2**	**W 4**	**W 8**	**W 12**	**W 16**	**W 20**	**W 24**	**Notes**
						D 7	**D 15**	**D 29**	**D57**					
Everolimus			Daily Dosing Begin dosing on Day 3; 2 divided doses											Initiation of dosing may be delayed up to Day 7, see Section 4.3.3
MMF (mycophenolate mofetil)	Daily Dosing Begin dosing on Day 1; 2 divided doses													African Americans (Blacks) are eligible to be treated with higher doses, up to 3.0 g/day. Section 4.3.4.
Tacrolimus	Daily Dosing Begin dosing within first 24 hours post-transplant; 2 divided doses													Initiation of dosing may be delayed up to Day 7, see Section 4.3.5
Belatacept 10 mg/kg	X					X	X	X	X	X				Guidance on appropriate temporal sequence and timing of the belatacept and Thymoglobulin infusions is found in Section 4.3.1
Belatacept 5 mg/kg											X	X	X	Starting Week 16. Section 4.3.1
Methylprednisolone i.v	X	Administration on days when Thymoglobulin is infused												Premedication to be administered 30 minutes prior to each Thymoglobulin infusion. See Section 4.3.6 for dose details.
Prednisone, p.o.				60 - 0 mg, as appropriate.										See Section 4.3.6 for dose details and allowances.
Thymoglobulin i.v.	X	Administration daily (or less frequently as tolerated), up to a maximum of 10 days and the cumulative dose does not exceed 5.5 mg/kg												Premedication with methylprednisolone plus acetaminophen &/or antihistamine to reduce the incidence of infusion reactions. Section 4.3.2.

Table 5.1-4:	**Dosing Schedule Day 1 (Day of transplant) - Month 6**													
								M 1		**M 3**			**M 6**	
	Day of Transplant 1st Dosing Day 1	**D 2**	**D 3**	**D 4**	**D 5**	**W 1**	**W 2**	**W 4**	**W 8**	**W 12**	**W 16**	**W 20**	**W 24**	**Notes**
						D 7	**D 15**	**D 29**	**D57**					
CMV prophylaxis	Refer to Table 4.3.7.1-1													Restart and continue for 3 months following each use of T-cell depleting agents for treatment of acute rejection Section 4.3.7
Pneumocystis Jirovecci Prophylaxis	Sulfamethoxazole/trimethoprim, pentamidine, atovaquone, or dapsone is required for 12 months post-transplant.													And also for at least 6 months post-T-cell depleting agent use for acute rejection. Section 4.3.7

Table 5.1-5: Dosing Schedule Month 7 through Month 24

			Mo 9				Mo 12			Mo 15			Mo 18			Mo 21				Mo 24	
	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76	Wk 80	Wk 84	Wk 88	Wk 92	Wk 96	Wk 100	Wk 104	Notes
Everolimus	Daily Dosing; 2 divided doses																				Section 4.3.3
MMF (mycophenolate mofetil)	Daily Dosing; 2 divided doses																				Section 4.3.4.
Tacrolimus	Daily Dosing; 2 divided doses																				Section 4.3.5
Belatacept 5 mg/kg	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 4.3.1
CMV prophylaxis	Restart and continue for 3 months following each use of T-cell depleting agents for treatment of acute rejection																				Section 4.3.7
Pneumocystis Jirovecci Prophylaxis	Sulfamethoxazole/trimethoprim, pentamidine, atovaquone, or dapsone is required for 12 months post-transplant.																				And also for at least 6 months post-T-cell depleting agent use for acute rejection. Section 4.3.7

5.2 Study Materials

The following study materials will be provided at the study start:

- On-Site Investigator File (OSIF)
- Pharmacy Logs
- BMS-224818 Investigator Brochure
- Site manual of operation for the IVRS
- Registration worksheets for IVRS
- Case Report Form (CRF) instructions
- Laboratory kits and laboratory manual
- Pregnancy surveillance forms
- Any other materials as locally required or agreed.

The central laboratory will provide all laboratory-related materials. The investigator will need to have a centrifuge, a freezer (-20ºC or below), appropriate containers and dry ice for shipment and storage of blood and plasma samples. Enough dry ice, when indicated, should be utilized to allow samples to arrive at their designated laboratory in a frozen state.

5.3 Safety Assessments

Safety assessments will be performed throughout the study and at early termination/ discontinuation, as specified in the Time and Events Schedule (Table 5.1-1, Table 5.1-2, Table 5.1-3).

Data for the procedures and assessments specified in this protocol should be submitted on the CRF. Lab assessments that are performed and sent to central vendor do not need to be recorded on the CRF. However, any local lab assessments which are not performed by the central vendor but are part of the required study procedures should be entered into the database and recorded on the specified CRF page.

Additional procedures and assessments may be performed as part of the standard of care. However, data for those assessments should remain in the subject's medical file and should not be provided unless specifically requested by the Sponsor.

5.3.1 Imaging Assessment for the Study

Not applicable.

5.3.2 Visit Windows

For the purpose of this study, "Week" refers to the end of treatment week (eg. Week 4 = Day 29, Week 8 = Day 57, etc). Visit windows are provided for site staff and subject convenience. After Day 1, it is recommended, whenever possible, that visits be scheduled Monday through Thursday as permitted by the visit window, to allow for the timely shipment of samples to the central laboratory. See Table 5.3.2-1:

Table 5.3.2-1: Visit windows for study procedures and infusion (when applicable)	
Visit/Infusion	**Visit Window**
Day 1	Day of Transplant; see Section 4.3 for details regarding the timing of the initial dose relative to kidney transplantation and temporal sequence of study drugs.
Week 1 (Day 7)	Target date ± 1 day
Week 2 (Day 15)	Target date ± 2 days
Week 4 - Month 6	Target date ± 3 days
Month 7 - Month 24	Target date ± 5 days
Early Termination (ET)	Within 14 days after discontinuation of study drug. If the visit cannot be completed within the window (eg, due to hospitalization, etc), the visit should be completed as soon as possible thereafter.
Follow-up 8, 12, 24 weeks	Target date from date of last dose of study drug ± 5 days

Phone visits for subject randomized to receive TAC may commence after the Month 6 visit (excluding visits for months 9, 12, 15, 18, 21, and 24, which should be completed in the office). Subjects will be contacted to assess for AEs and concomitant medications. Each of these visits should occur within the prescribed visit window.

5.3.3 Vital Signs

Vital signs (body temperature, respiratory rate, blood pressure [BP], and heart rate) will be recorded as outlined in Table 5.1-1, Table 5.1-2 and Table 5.1-3. Arterial systolic and diastolic BP and radial artery pulse rate will be measured and recorded in the seated position; supine determinations are acceptable if the subject is unable to sit.

Subjects randomized to a belatacept treatment group will have vital signs measured prior to the belatacept infusion and both BP and heart rate measured 30 minutes after the end of the infusion. When the subject is unable to remain seated for at least 60 minutes, and the dose of belatacept must be administered while supine, then both pre- and post-infusion vital signs may be obtained in this position.

Results from any vital signs determination that the Investigator considers clinically significant **must** be recorded on the appropriate AE page of the CRF.

5.3.4 Physical Measurements

A 12-lead electrocardiogram (ECG) should be performed at screening. If the subject has an ECG performed within 6 months of transplant, and the report is available, those results are acceptable for use in lieu of a Screening Visit ECG.

Body weight and height will be recorded at the scheduled visits, as outlined in Table 5.1-1, Table 5.1-2, and Table 5.1-3. The following guidelines will aid in the standardization of these measurements:

- The same scale should be used to weigh a given subject throughout the study
- Scales should be calibrated and reliable; scales should be zeroed just prior to each subject's weigh-in session
- A subject should void just prior to being weighed
- Whenever possible, weight should be recorded before a subject's meal (if applicable) and at approximately the same time each day
- A subject should be minimally clothed (ie, no shoes or heavy over garments).

5.3.5 Physical Examination

Physical examinations may be performed by a Doctor of Medicine, Doctor of Osteopathy, Physician's Assistant or Nurse Practitioner. Subjects will undergo a routine physical examination during screening and at specified visits as outlined in Table 5.1-1, Table 5.1-2, and Table 5.1-3.

5.3.6 Laboratory Assessments

Blood and urine samples will be obtained as outlined in Table 5.1-1, Table 5.1-2, and Table 5.1-3 for clinical laboratory evaluations. A central laboratory vendor will be utilized for this study and a laboratory manual will be provided to each site. Subjects should be fasting for a minimum of 8 hours prior to specified fasting blood draws. However, if a subject is not fasting at a given visit, the blood draw should still be performed, and the non-fasting status should be documented. Analysis of clinical laboratory specimens will be performed by a central or local laboratory as specified below.

5.3.6.1 Central Laboratory

- Hematology: complete blood count (CBC with platelet) with differential, HbA1c
- Chemistry panel (Fasting*): sodium, potassium, chloride, bicarbonate, calcium; glucose, BUN, serum creatinine, uric acid, ALT, AST, LDH, alkaline phosphatase, total protein, albumin, total bilirubin, phosphorous and magnesium, cGFR
- Lipid panel (Fasting*): total cholesterol, LDL, HDL, triglycerides
- Single voided urine specimen for urinalysis (UA) and urine protein-to-creatinine ratio ($U_{Pr/Cr}$). The analytes tested for are to include: dipstick protein glucose and occult blood; urine protein and creatinine concentrations and, where available, calculation of the $U_{Pr/Cr}$. If results from the UA are positive for occult blood, glucose or protein, microscopic examination of the urine sediment will be performed
- Serum total IgG concentration and those of its 4 subclasses. The same samples for serum IgG determination are also to be collected at the time of serious infections, CNS events, malignancies, graft loss and clinically suspected AR. When the PI is notified of, or, for any other reason suspects that a subject has experienced any of these events, a blood sample for serum IgG determination should be collected as per the laboratory manual. Site may also be

contacted by BMS/ICON to provide a serum sample for IgG determination if any of these events are identified by BMS/ICON.

- CMV, EBV, and BK viral loads

[redacted]

[redacted]

*Fasting: nothing to eat/drink, except water, for 8 hours prior to procedures required

5.3.6.2 Local Laboratory

Collection, processing, storage, transport, and analysis of local laboratory samples should be performed based on study site practices. All study-required laboratory results performed by the local laboratory are noted below, and must be entered by site personnel onto the appropriate CRF pages.

- EVL trough levels (for everolimus-treated subjects only): begin collecting trough levels at the Week 1 Visit, unless dosing was not initiated prior to the Week 1 visit, targeting 6 - 10 ng/mL for the initial 3 months, and 4 - 8 ng/mL thereafter. Everolimus trough levels should also be collected 4-5 days after each everolimus dose change, as per the package insert, and at the time of any clinically suspected episode of acute rejection, PML or PTLD.
- TAC trough levels (for tacrolimus-treated subjects only): begin collecting trough levels at the Week 1 Visit, unless dosing was not initiated prior to the Week 1 visit, targeting 4-11 ng/mL for the initial 12 months post-transplant. Tacrolimus trough levels should also be collected after each TAC dose change, within a timeframe consistent with local standard of care, and at the time of any clinically suspected episode of acute rejection, PML or PTLD.
- Serum creatinine: The results of locally determined serum creatinine concentrations may be used for clinical patient management. Locally determined concentrations are to be used to meet the protocol criterion for a $\geq$ 25% increase from recent baseline, as it relates to suspicion of acute rejection (see Section 5.3.7 and 5.3.8 for details).

- Pregnancy Test (serum/urine): A pregnancy test (minimum sensitivity 25 IU/L of β-HCG) must be performed at a local laboratory for all WOCBP within 24 hours prior to the first dose of study medication (baseline or Day 1). Pregnancy testing must be performed in all WOCBP within 24 hours prior to dosing at all other study visits. Urine pregnancy testing kits will be provided by a central laboratory and processed at the site; serum pregnancy tests should be performed at a local laboratory, if necessary. If a female subject becomes pregnant, she will be discontinued from study medication.
- Evaluation of suspected episodes of acute rejection will require real time assessment of serum creatinine concentrations as well as that of belatacept and everolimus blood levels (belatacept/everolimus treated subjects only) or TAC trough levels (TAC treated subjects only) and the histopathologic findings from renal biopsies; these will be evaluated locally to guide patient management (see Sections 5.3.7 and 5.3.8).

Results from any laboratory test (including local laboratory tests) that the Investigator considers clinically-significant **must** be recorded on the appropriate AE page of the CRF.

5.3.6.3 Collection, Shipping and Transport

Collection, processing, transport, and storage of local laboratory clinical specimens will be performed based on study site practices. Collection, processing, transport, and storage of central laboratory clinical specimens will be detailed in a separate manual to be provided to the investigator at or before the time of study initiation.

5.3.7 Assessment of Clinical Suspicion of Acute Rejection

In this protocol, acute rejection is defined as a clinical ("clinically suspected") and pathological (biopsy proven) event. In addition to identification, on an allograft biopsy, of findings consistent with either cell- or antibody-mediated acute rejection, confirmation requires that at least one of the clinical criteria listed below be met:

- An unexplained increase in serum creatinine concentration of ≥ 25% from a recent baseline value.

  "Recent baseline" serum creatinine is defined as the average of the 3 most recent serum creatinine concentrations that were available prior to the value that prompted clinical suspicion of acute rejection and were determined by a local laboratory. These 3 serum creatinine concentrations must have been obtained from samples drawn on different days and prior to initiation of the first treatment in any course of dialysis that the subject receives.
- An unexplained decrease in urine output
- Fever and allograft tenderness that is otherwise clinically unexplained
- During the first 14 days post-transplant, an otherwise unexplained, persistent elevation in serum creatinine in the presence of clinical suspicion of acute rejection

OR

- Acute rejection that is: (a) clinically suspected for any other reason(s); and (b) is treated.

Unless a biopsy is medically contraindicated due, for example, to a risk of hemorrhage that cannot be satisfactorily mitigated by administration of fresh frozen plasma or plasma factor concentrates, no subject should be treated for AR without having a biopsy performed to confirm the diagnosis. If a subject is treated for AR without biopsy confirmation, this should be clearly indicated on the appropriate CRF pages.

Prior to obtaining any biopsy for suspected AR, the presence of other clinical conditions that could adversely affect renal function should be ruled out, including those affecting the patency of the renal artery and vein, obstruction (hydronephrosis), intravascular volume depletion, infection and drug-associated nephrotoxicity.

Notes:

- Acute rejection will not be reported as an AE or SAE in this study, see Section 6. These events will be collected on separate CRFs.
- Routine or surveillance biopsies performed according to local practice and in the absence of clinical suspicion of acute rejection are NOT permitted per protocol.

5.3.8 Renal Biopsy Procedure

All biopsy procedures and pathology assessment are to be performed locally by the site. Central pathology for assessment of AR will not be part of this study. However, non-histopathologic assessments of biopsy tissue will be performed, for example, immunohistochemistry and RNA expression, when residual tissue is available in the form of a paraffin block and/or (2-3) unstained slides that can be sent to BMS.

For all biopsy specimens, the tissue should be stained and graded according to the 2007 update to the Banff 97 classification of kidney transplant pathology[54,55]. Grading of allograft biopsies should be performed locally in order to guide acute treatment decisions.

5.3.9 Follow-up Biopsy of a Documented Acute Rejection

Subjects may have a follow-up renal allograft biopsy performed after a documented acute rejection episode.

Hospitalization intended for the biopsy procedures alone, and not complicated or prolonged due to other adverse events, will not be considered a SAEs (see Section 6)

5.3.10 Treatment of Acute Rejection

Prior to initiation of treatment for suspected AR, ensure that:

a) Local blood samples are collected for measurement of serum creatinine concentration, and trough levels of EVL or TAC (if applicable).
b) Central laboratory samples are collected for immunogenicity, CMV/EBV/BK viral load, IgG & subclasses 1-4 and biomarkers (see Section 5.6).

The severity of acute rejection will be determined using the 2007 update to the Banff 97[54,55] classification, which will also serve as a guide to treatment of any episode that is biopsy confirmed.

Guidelines for the treatment of acute rejection according to the Banff 97 classification and the 2007 update are provided below, in bullets, and in Figure 5.3.10-1 and Figure 5.3.10-2. To the extent clinically feasible, these guidelines are intended to standardize the treatment of acute rejection across clinical sites so as to improve interpretability of data. It is recognized, however, that the guidelines may not be applicable to all clinical situations, such that deviations from them may be required in individual cases. The guidelines are summarized below:

- Subjects with acute rejection of Banff severity grades up to and including IIA should be treated initially with methylprednisolone (as the sodium succinate), 250 - 500 mg i.v. per day for 3 consecutive days. Corticosteroids should then be tapered per investigator's discretion.
- Subjects with acute rejection of Banff severity grades IIB and III should be treated initially with ATGAM, Thymoglobulin, ATG-Fresenius-S, or OKT3. Use of other polyclonal antilymphocyte preparations or polyclonal antithymocyte globulins is permitted in regions where market authorization exists, and if they are indicated for the treatment of acute rejection in kidney transplantation. Use of Campath 1-H is not permitted in this protocol, as it is not indicated for use in kidney transplantation.
- Subjects with acute rejection that is either unresponsive to, or worsening despite initial corticosteroid therapy should have a repeat, percutaneous allograft biopsy performed before initiating treatment for steroid-resistant acute rejection. Subjects may be treated with Thymoglobulin, ATGAM, OKT3, ATG-Fresenius-S, or other approved agents as noted above. Following the last dose of anti-rejection medication, steroids should then be tapered per investigator's discretion.
- CMV and PJP prophylaxis **must** be administered as detailed in Section 4.3.7 whenever T-cell-depleting agents are utilized to treat AR.

The guidelines for treatment of Banff grades IA - IIA acute rejection are presented in Figure 5.3.10-1, and those for grades IIB - III, in Figure 5.3.10-2:

5.3.11 Neurological Examination

A neurologic assessment (history and examination) will be performed at designated time points (see Table 5.1-1, Table 5.1-2 and Table 5.1-3). A neurologist is not required for this assessment. Neurological examinations may be performed by a Doctor of Medicine, Doctor of Osteopathy, Physician's Assistant or Nurse Practitioner. The neurologic history will include the subject's, other family members', or other caretaker's description of neurological symptoms, such as: personality, memory, headaches, seizures, impairment of consciousness, swallowing, vision, hearing, language function, coordination, gait, weakness, alterations in sensation or sphincter function, or appearance of involuntary movements.

The neurologic exam will include assessment of mental status, gait, speech, cranial nerves, cerebellar function, deep tendon reflexes, sensory function and motor function. The onset and duration of any new symptoms, and their relationship to any intercurrent medical illnesses or recent medications, may also be relevant.

Any new or worsening findings should be reported as an adverse event and evaluated with additional diagnostic modalities and/or neurologic consultation, as considered appropriate by the investigator. In cases of unexplained neurological findings, magnetic resonance imaging (MRI),

computed tomography (CT), and/or cerebrospinal fluid (CSF) examination for John Cunningham (JC) virus should be considered. In any such case, the medical monitor (or designee) must be contacted.

Supplemental CRF forms will be provided to collect information confirming completion of the neurologic assessment.

5.3.12 Definition of Graft Loss

In this study, graft loss is defined as either functional loss or physical loss. Functional loss is defined as meeting any of the criteria:

- Regularly scheduled or chronic dialysis treatments over a period of ≥ 56 days.
- Re-transplantation (either preemptive or if first criterion above is met and subject is waiting for transplant).

Physical graft loss is defined as surgical excision (nephrectomy).

5.3.13 Suspicion of PTLD

Specific surveillance for PTLD will be incorporated for all subjects in this trial.

CNS imaging and/or neurologic consultation should be considered for any subject with a new or worsening neurologic finding.

For subjects who undergo biopsy for suspicion of PTLD, it is recommended that tissue from the biopsy specimen be evaluated for CD3, CD20, CD79-a and EBER. Additionally, locally prepared slides, as well as a portion of the tissue and/or unstained slides will be requested for standardized assessment by a central pathologist. Instructions for the preparation and shipment of biopsy specimens to the PTLD central pathologist will be provided to each investigator.

In subjects with suspected PTLD, a blood sample should be obtained for determination of anti-viral T-cell responses (U.S. sites only) as well as for belatacept and everolimus blood levels (belatacept/everolimus treated subjects only) or TAC trough levels (TAC treated subjects only) at the time the event is suspected. However, in subjects with suspected PTLD, the management of overall immunosuppression will be at the discretion of the investigator. The Medical Monitor should be advised of the planned strategy for the management of belatacept and other immunosuppressants.

The Medical Monitor must also be notified of all confirmed cases of PTLD.

5.3.14 Diagnosis and Treatment of Hypertension

Hypertension will be evaluated, defined and treated in this protocol according to the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines for subjects with renal transplants[56]. Accordingly, in adults, pre-hypertension is defined as SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg, and hypertension as SBP ≥140 mm Hg or DBP ≥ 90 mm Hg. In addition, subjects who do not meet these levels of SBP or DBP, but are receiving medication(s) for the management of hypertension, and/or those with a prior medical history of hypertension, are also to be considered as having hypertension.

Per the guidelines included in the *Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*[57] in the absence of compelling data for renal transplant recipients, no particular class of antihypertensive drugs can be considered superior to any other. Therefore, subjects should be treated per the investigator's discretion and in accordance with local standards of care to reach the target blood pressure goals.

The intensity of an anti-hypertensive treatment regimen is defined as the total number of antihypertensive medications used to control hypertension. In subjects with hypertension, whether adequately controlled or not, all antihypertensive medications will be counted in determining the presence of hypertension and the intensity of the treatment regimen, since the antihypertensive effects will be considered present regardless of the ostensible indication for which they were prescribed.

5.3.15 Diagnosis of New Onset Diabetes After Transplant

A subject who did not have diabetes prior to transplant and receives an anti-diabetic medication for a duration of at least 30 days will be considered to have new onset diabetes after transplant (NODAT). All cases of NODAT should be reported to BMS as an adverse event.

Additionally, a subject who meets the criteria below (set forth by the American Diabetes Association[57]), and did not have diabetes prior to transplant will be considered to have new onset diabetes. These criteria are summarized as:

1. Hemoglobin A1C ≥6.5%, when performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.
2. In the presence of symptoms characteristic of diabetes mellitus, a casual plasma glucose concentration ≥ 200 mg/dL (11.1 mmol/L). Casual is defined as any time of day without regard to time since last meal. Symptoms of characteristic of diabetes include polyuria, polydipsia, and unexplained weight loss.

   or
3. Fasting Plasma Glucose (FPG) ≥ 126 mg/dL (7.0 mmol/L)*. Fasting is defined as no caloric intake for at least 8 h.

   or
4. Two (2)-h post-load blood glucose concentration ≥ 200 mg/dL (11.1 mmol/L) during an Oral Glucose Tolerance Test (OGTT)*. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

*In the absence of unequivocal hyperglycemia, criteria 1 through 3 should be confirmed by repeat testing.

Any new or worsening findings must be recorded on the appropriate AE page of the CRF.

5.3.16 Treatment for Dyslipidemia

Clinical practice guidelines for the management of dyslipidemias in renal transplant subjects are available from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative[58]. Subjects should be treated in a manner consistent with these guidelines (see

Table 5.3.16-1) and local standard of care:

Table 5.3.16-1: Guidelines for the Treatment of Dyslipidemias in Renal Transplant[a]

Definition of Dyslipidemia	Goal	Initiate	Increase Regimen If Not at Goal	Alternative
TGs ≥ 500 mg/dL (≥ 5.65 mmol/L)	TGs < 500 mg/dL (< 5.65 mmol/L)	TLC	TLC + Fibrate or Niacin	Fibrate or Niacin
LDL 100 - 129 mg/dL (2.59 - 3.35 mmol/L)	LDL < 100 mg/dL (< 2.59 mmol/L)	TLC	TLC + Statin	Bile Acid Sequestrant or Niacin
LDL ≥ 130 mg/dL (≥ 3.36 mmol/L)	LDL < 100 mg/dL (< 2.59 mmol/L)	TLC + Statin	TLC + Increased Statin Dose	Bile Acid Sequestrant or Niacin
TGs ≥ 200 mg/dL (≥ 2.26 mmol/L) AND non-HDL ≥ 130 mg/dL (≥ 3.36 mmol/L)	Non-HDL < 130 mg/dL (< 3.36 mmol/L)	TLC + Statin	TLC + Increased Statin Dose	Fibrate or Niacin

[a] Notes:

1. Modified from NKF-K/DOQI guidelines[58]. 'Statin' refers to a class of compounds that inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) inhibitor. It is recommended that the maximum doses of statins be reduced in subjects receiving tacrolimus. The addition of a third agent that is also metabolized by the cytochrome P450 system increases the risk of myositis and rhabdomyolysis, and therefore, such combinations should be avoided. The effects of sirolimus on statins are unknown. Refer to the appropriate package insert for specific recommendations.
2. The NKF-K/DOQI guidelines recommend gemfibrozil as the fibrate of choice as it does not require dose modification for renal insufficiency.
3. All subjects who exceed any stated threshold value for dyslipidemia should begin recommended therapy, which should then be titrated to lower the elevated fasting lipid concentration(s) to the above target level(s).

Non-HDL = non-high-density lipoprotein, LDL = low-density lipoprotein, NKF-K/DOQI = National Kidney Foundation Kidney Disease Outcomes Quality Initiative, TGs = triglycerides, and TLC = therapeutic lifestyle changes (eg, diet and exercise).

Intensity of treatment regimen is defined as the total number of antihyperlipidemic medications used to control dyslipidemia. Each drug prescribed as an antihyperlipidemic agent will be counted individually. For example: concomitant use of a statin and an agent of another class (e.g., ezetimibe), or combination therapy (e.g., a statin and ezetimibe in one pill) will be counted as 2 medications.

All prescribed antihyperlipidemic medications will be counted as having been given for treatment of dyslipidemia in subjects with dyslipidemia regardless of the degree of control achieved, and independent of the intended indication, since the lipid-lowering effects are expected to be present in any case.

Any new or worsening findings must be recorded on the appropriate AE page of the CRF.

5.3.17 Follow-up Safety Period

NOTE: Withdrawal of a subject from study medication does not imply that the subject is withdrawn from the study. All subjects will be followed for full duration of the protocol for graft and survival status (See Section 3.6).

8-Week Post Last Dose Safety Follow-up Visit

All subjects should complete the 8-Week Post Last Dose Safety Follow-up Visit, this visit may be conducted by phone. The following procedures are required:

- Assess for AEs
- Pregnancy Test (WOCBP only)
- Concomitant medications

Belatacept-treated subjects who discontinue belatacept or complete the study and return to standard of care, the following blood sample is also required at the 8-Week Post Last Dose Safety Follow-up Visit:

- Immunogenicity

12-Week and 24-Week Post Last Dose Safety Follow-up Visits

Belatacept-treated subjects who discontinue belatacept or complete the study and return to standard of care should complete the 12-Week and 24-Week Post Last Dose Safety Follow-up visits, the following procedures are required:

- Assess for AEs
- Immunogenicity sample collection

A ± 5 day window will be allowed for each follow-up visit.

5.4 Efficacy Assessments

Only data for the procedures and assessments specified in this protocol should be submitted to BMS on a case report form. Data from additional procedures and assessments performed as part of standard of care should remain in the subject's medical record and should not be provided to BMS, unless specifically requested.

[redacted]

[redacted]

5.9 Results of Central Assessments

Blood chemistry, serology and urinalysis results will be made available to sites via an Investigator portal.

Evaluation of clinically suspected episodes of acute rejection will require real time assessment of serum creatinine and trough EVL or TAC levels; these tests should be performed locally to guide patient management.

Viral load data will be reported to sites. Immunogenicity and exploratory data (e.g., that result from immune cell phenotyping and antidonor antibody testing) will not be reported to the sites, since the exploratory nature of these assessments does not allow for single-subject interpretation. Exploratory data other than viral load will be summarized and shared with the sites at the end of the study, upon request.

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

> Related: There is a reasonable causal relationship between study drug administration and the AE.
>
> Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

Note: Acute rejection will not be reported as an AE or SAE in this study. These events will be collected on separate CRFs.

6.1 Serious Adverse Events

A S***erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential DILI are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy should be reported as SAE. For example, if death, which is a study endpoint, occurred due to anaphylaxis, "anaphylaxis" must be reported. (See Section 6.1.1 for reporting details.)

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

6.1.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs must be collected that occur during the screening period and within 56 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

All events of death, graft loss, malignancy, PTLD, and serious infections (ie, otherwise meeting SAE reporting requirements) must be reported to BMS for all randomized subjects until the end of the study, irrespective of study drug discontinuation or investigator-deemed causality.

The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) **within 24 hours** of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any abnormal laboratory test result that, in the opinion of the investigator, is clinically significant or meets the definition of an SAE
- Any abnormal laboratory test result that required the subject to have study drug discontinued or interrupted
- Any abnormal laboratory test result that required the subject to receive specific corrective therapy.

It is expected that, wherever possible, the clinical event rather than the laboratory abnormality would be used by the reporting investigator: e.g., "anemia" instead of the corresponding low hemoglobin value.

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

For women participating at US investigative sites who become pregnant while using MMF or EC-MPS/MPA in this study, the investigator should report the pregnancy to the Mycophenolate Pregnancy Reference Registry and should strongly encourage the patient to enroll in the registry.

6.5 Overdose

An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important.

However, for reporting purposes, **all** occurrences of overdose (for the investigational drugs belatacept and everolimus) **must be reported as SAEs** (see Section 6.1.1 for reporting details).

6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

a) A serum AT (ALT or AST) elevation > 3 times ULN

AND

b) A serum total bilirubin > 2 times ULN, without initial findings suggestive of cholestasis (e.g., an elevated serum alkaline phosphatase),

AND

c) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

6.7.1 Events of Special Interest (ESI)

Additional CRFs or appropriate source documentation may be required for further clarification for the following "events of special interest":

- PTLD
- PML
- Malignancies (other than PTLD) including non-melanoma skin carcinomas
- TB Infections (serious and non-serious)
- CNS Infections (serious and non-serious)
- Viral Infections (serious)
- Infusion related reactions
- Other reason deemed necessary by the Sponsor

To monitor and better understand these risks, BMS, its collaborators and/or its agents may use collected blood samples for JCV, EBV and other immune function-related tests.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

A Data Monitoring Committee (DMC) will be convened to provide oversight of benefit-risk considerations for patients in the study and if necessary make recommendations to BMS to ensure the ongoing safety of study subjects.

At periodic intervals, the DMC will review the accumulated safety and efficacy data on key outcomes, in unblinded fashion, including death, graft loss, acute rejection, infections, and malignancies; these data will be reviewed for the overall population as well as relevant subgroups. The DMC will then provide to BMS their assessment of the emerging balance between benefits and risks, and recommendations regarding the further conduct of the study.

A DMC Charter will be prepared, which will include full details of the Committee's membership and responsibilities, and how it will function; this will include the frequency of routine meetings, the types of data outputs to be provided for their review, and criteria for convening any ad hoc safety reviews. Appropriate updates will be made to the protocol, as well.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

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.

Assessment of clinical suspicion of acute rejection can be found in Section 5.3.7. As an endpoint, acute rejection events in this study will be those that are CSBPAR.

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 (πp) 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 120 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 8.1-1.

Table 8.1-1: 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)

8.2 Populations for Analyses

- The primary endpoint will be initially assessed on the ITT population in each treatment group. The ITT population will consist of all randomized and transplanted subjects treated with at least one dose of Thymoglobulin and one dose of study treatment, either belatacept or TAC, and will be included in the safety and efficacy analysis data sets. In these analyses, CSBPARs occurring after discontinuation from assigned therapy will be counted in the treatment arm to which the subject was originally randomized.
- Additionally, for CSBPAR, a sensitivity analysis will be performed with right censoring at the time of discontinuation from the assigned therapy.
- An as-treated analysis will be based on the treatment regimen received. Analysis of treatment differences in the rates of CSBPAR will only include those subjects who remain on their original therapy from the beginning, through the designated analysis time point(s) (e.g., the Months 6, 12 and 24 study visits) for these above mentioned analyses. Treatment differences in the rates of CSBPAR will also be performed using a per protocol efficacy dataset.
  - This is defined as the set of all data derived from that subset of subjects once treated, are followed up consistently with all study criteria to the extent that no relevant protocol deviations have been identified.

The primary analysis will be done on the ITT population and the sensitivity analyses on the primary endpoints will be done in the As Treated, as well as the Per Protocol population.

8.3 Endpoints

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

8.3.1 Primary Endpoint(s)

- The incidence of CSBPAR at 6 months post-transplant, in the individual treatment groups:
  - Belatacept + EVL
  - TAC + MMF

8.3.2 Secondary Endpoint(s)

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 the local pathologist, using the 2007 update to the Banff 97 classification of renal allograft pathology;
- Treatment regimen: Categorical analysis of CSBPAR episodes by treatment received, including: a) corticosteroids; b) T-cell depleting agent(s); 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 and 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 change from Month 3 cGFR at 3, 6, 12 and 24 months post-transplant;
- Slope of the change in cGFR from Month 3 to Months 6, 12 and 24 post-transplant;
- Urine protein to creatinine ratio ($U_{Pr/Cr}$) at 3, 6, 12 and 24 months post-transplant.

Donor Specific Anti-HLA Antibodies (DSA)

- Percentage of subjects with, and titers of pre-existing (pre-transplant) and *de novo* (post-transplant) DSA on Day 1 (pre-transplant, pre-dose), and at Months 12 and 24 post-transplant;
- Characterization of any *de novo* DSA detected by IgM and IgG subclasses, 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-transplant;
- Incidence of ESI at 6, 12 and 24 months post-transplant;
- Description and incidence of clinically significant changes in vital signs;
- Description and incidence of laboratory test abnormalities.

Cardiovascular and metabolic co-morbidities

- Incidence of NODAT at 6, 12 and 24 months post-transplant;
- Absolute (mean and median) values for SBP and DBP at 3, 6, 12 and 24 months post-transplant;
- Mean changes from baseline values for SBP and DBP at 6, 12 and 24 months 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:

  - 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 months post-transplant;
- Mean whole blood HbA1C concentrations, and mean changes from baseline values at Months 6, 12 and 24 months post-transplant.

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics of recipients and donors will be summarized descriptively for each treatment group, by means and standard deviation for continuous variables, and by frequency distribution for categorical variables. Summaries will be presented for the ITT population. Similar summaries will be provided for the corresponding donors.

8.4.2 Efficacy Analyses

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

8.4.2.1 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 who have experienced at least one episode of CSBPAR along with and the corresponding 95% CIs. Two-sided 95% CIs will be generated for the differences between treatment groups. Descriptive summaries will be provided for the percentages of subjects with CSBPAR in each treatment group, including those for severity grade and treatment received. 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 analyses 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).

The following analyses will provide further understanding regarding the impact of CSBPAR on renal function, graft/subject survival, donor specific antibodies, infection, and malignancy.

- Descriptive summaries of cGFR by treatment group
  - at Month 12 in subjects with and without AR by Month 6 and
  - at Month 24 in subjects with and without AR by Month 12

- Descriptive summaries of graft and subject survival, by treatment group
  - at Month 12 in subjects with and without AR by Month 6 and
  - at Month 24 in subjects with and without AR by Month 12
- Descriptive summaries of infection and malignancy, by treatment group
  - at Month 12 in subjects with and without AR by Month 6 and
  - at Month 24 (by subjects with and without AR by Month 12

In addition, Kaplan-Meier (KM) cumulative event rates will also be performed by treatment groups.

8.4.2.2 Subject and Graft Survival

The endpoint of subject and graft survival at 6, 12 and 24 months post-transplant will be summarized within each treatment group using point estimates of the proportion of subjects surviving with a functioning graft, and the corresponding 95% CIs. 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 6, 12 and 24 months
- Rates of death with a functioning graft at 6, 12 and 24 months;
- Rates of pure (death-censored) graft loss at 6, 12 and 24 months.

8.4.2.3 Renal Function

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. For a 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".

A linear mixed effects model will be used to analyze changes from Month 3 cGFR. Details of the analyses will be available in the Statistical Analysis Plan.

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.

In addition, 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.

8.4.2.4 Donor Specific Antibodies

The percentage of subjects with detectable DSA on Day 1, and of *de novo* DSA at 12 and 24 months post-transplantation 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:

- Mean Florescent Intensity (MFI) > 2000 = Positive
- MFI 1000-2000 = Potentially Positive
- MFI < 1000 = negative

8.4.2.5 Cardiovascular and Metabolic Co-morbidities

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

Changes in each of the fasting lipid variables (total cholesterol, HDL cholesterol, LDL cholesterol and TG) between the last value obtained prior to the transplant and results at Months 12 and 24 will be descriptively summarized.

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

Changes from baseline in fasting glucose and HbA1C levels will be descriptively summarized at Months 6, 12 and 24.

Additionally, descriptive summaries of antihypertensive and antihyperlipidemic therapies will also be provided. Details of the analyses will be available in the Statistical Analysis Plan.

8.4.3 Safety Analyses

Safety analysis will be based on all randomized, transplanted, and treated subjects. 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, defined as those identified 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 randomization).

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

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

[redacted]

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

Representatives of BMS (or designee) must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors (or designee) and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by BMS) is maintained at each study site where study drug and the following non-investigational product(s): methylprednisolone, prednisone or equivalent, mycophenolate mofetil, mycophenolate sodium or equivalents are inventoried and

dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS (or designee) will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool.

The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected considering the following criteria:

- National Coordinating Investigator
- Subject recruitment (eg, among the top quartile of enrollers)
- Regional representation (eg, among top quartile of enrollers from a specified region or country)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or BMS as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)
Serious Adverse Event	Serious adverse event defined as any untoward medical occurrence that at any dose: results in death; is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), requires insubject hospitalization or causes prolongation of existing hospitalization; results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect; is an important medical event (defined as a medical event(s) that may not be immediately life threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.). For reporting purposes only, BMS also considers the occurrence of pregnancy, overdose (regardless of association with an AE), and cancer as important medical events.
Casual blood glucose concentration	Blood glucose test at any time of the day without regard to time since last meal.

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
APC	antigen presenting cell
AR	acute rejection
AST	aspartate aminotransferase
AT	Aminotransaminases (ALT and AST)
β-HCG	beta-human chorionic gonadotrophin
BCAR	biopsy confirmed acute rejection
BID, bid	bis in die, twice daily
BKV	B.K.(patient's initials, in whom it was first detected) Virus
BMI	body mass index
BMS	Bristol-Myers Squibb
BMS-224818	LEA29Y (belatacept)
BP	blood pressure
BPAR	Biopsy-proven acute rejection
BUN	blood urea nitrogen
C	Celsius
C0	concentration pre-dose, trough
CAN	chronic allograft nephropathy
CBC	complete blood count
CD	cluster of differentiation
CFR	Code of Federal Regulations
cGFR	calculated glomerular filtration rate
CI	confidence interval
CKD	chronic kidney disease
Cmin, CMIN	minimum observed concentration
CMV	Cytomegalovirus
CNI	calcineurin inhibitor
CNS	Central nervous system

Term	Definition
CRF	Case Report Form, paper or electronic
CS	Corticosteroids
CsA	cyclosporine (cyclosporin)
CSBPAR	Clinically-suspected biopsy-proven acute rejection
CSF	cerebral spinal fluid
CTA	clinical trial agreement
CXR	chest x-ray
CYP	cytochrome p-450
D	Day
D_5W	dextrose 5% in water for injection
de novo	from the beginning (Latin)
DBP	diastolic blood pressure
DGF	delayed graft function
DILI	drug induced liver injury
dL	Deciliter
DMC	Data Monitoring Committee
DSA	donor specific antibody
EBV	Epstein-Barr virus
EBNA	Epstein-Barr nuclear antigen
EBER	Epstein-Barr virus-encoded small RNAs
ECD	extended criteria donor
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eg	exempli gratia (for example)
eGFR	estimated glomerular filtration rate
EoI	end of infusion
ESI	Events of Special Interest
ESRD	end-stage renal disease
ET	Early Termination
EVL	everolimus

Term	Definition
F	Fahrenheit
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
FSGS	focal segmental glomerulosclerosis (FSGS)
FSH	follicle stimulating hormone
FU	follow-up
g	Gram
GCP	Good Clinical Practice
GFR	glomerular filtration rate
h	Hour
HbA1c	hemoglobin A1c
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV	Human Immunodeficiency Virus
HLA	human leukocyte antigen
HR	heart rate
HRT	hormone replacement therapy
HUS	hemolytic uremic syndrome
ICF	informed consent form
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IGRA	interferon- gamma release assay
IHC	immunohistochemistry
IL	Interleukin
IL-2R	Interluekin-2 receptor
IL2RA	Interluekin-2 receptor alpha chain
IMP	investigational medicinal products

Term	Definition
INH	Isoniazid
IP	investigational product
IRB	Institutional Review Board
ITT	intent-to-treat
IU	International Unit
IV, i.v.	Intravenous
IVIg	Intravenous immune globulin
IVRS	interactive voice response system
JCV	John Cunningham virus
K3EDTA	potassium ethylenediaminetetraacetic acid
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
kg	Kilogram
KM	Kaplan-Meier
L	Liter
LD	living donor
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LI	less intensive
LTE	long-term extension
mAb	monoclonal antibody
MDRD	Modification of Diet in Renal Disease (study)
MFI	mean fluorescent intensity
mg	Milligram
MI	more intensive
min	minute
mL	milliliter
mm	millimeter
MMF	mycophenolate mofetil
mmHg	millimeters of mercury

Term	Definition
MPA	mycophenolic acid
MPGN	membranoproliferative glomerulonephritis
MRI	magnetic resonance imaging
mTOR	mechanistic target of rapamycin
mTORi	mTOR inhibitor
µg	microgram
N	number of subjects or observations
ng	nanogram
NIMP	non-investigational medicinal product
NKF-K/DOQI	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
NODAT	new onset diabetes after transplant
NS	0.9% normal saline solution
OGTT	Oral Glucose Tolerance Test
OPTN	Organ Procurement and Transplantation Network
OR	covariate-adjusted odds ratio
OSIF	on-site investigator file
p, πp	population sample proportion
PCR	polymerase chain reaction
PD	pharmacodynamics
PJP	Pheumocystis jiroveci pneumonia
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PO	per os (by mouth route of administration)
PPD	purified protein derivative (tuberculin skin test)
PRA	panel reactive antibodies
PTLD	Post transplant lymphoproliferative disorder
RNA	ribonucleic acid
S1P	sphingosine-1-phosphate
SAE	serious adverse event
SBP	systolic blood pressure

Term	Definition
SCD	standard criteria donors
SCr	serum creatinine
SD	standard deviation
SLAM	Signaling lymphocyte activation molecule
SmPC	Summary of product characteristics
SOP	Standard Operating Procedures
SRL	Sirolimus
SRTR	Scientific Registry of Transplant Recipients
SWFI	sterile water for injection
TAC	Tacrolimus
TB	Tuberculosis
TC	total cholesterol
T-cell	T lymphocyte cell
TG	triglyceride
TLC	therapeutic lifestyle changes
TNFα	Tumor Necrosis Factor alpha
Treg	regulatory T-lymphocyte cell
ULN	upper limit of normal
UNOS	United Network of Organ Sharing
$U_{Pr/Cr}$	urine protein/ creatinine ratio
UTI	urinary tract infection
VNS	vial-needle-syringe
W	Week
WB	whole blood
WBC	white blood cell
WHO	World Health Organization
WMD	weighted mean difference
WOCBP	women of childbearing potential

APPENDIX 1 CONTRACEPTION GUIDELINES

Investigators are expected to communicate the importance of pregnancy prevention because of the increased potential for an adverse reproductive outcome. The investigator shall describe the length of time that strict precautions against pregnancy must be observed and provide guidance on the use of appropriate methods for sexually active subjects and their partners. Women and men who are not capable of reproduction or choose to be abstinent shall be exempt from following the pregnancy prevention requirements specified below. All subjects shall be counseled on pregnancy prevention and follow pregnancy testing requirements as specified in the protocol.

DURATION OF MANDATORY CONTRACEPTION:

For female subjects who meet the criteria for WOCBP:

(Duration of treatment) plus 8 weeks after the last dose of study drug.

For male subjects who are sexually active with WOCBP:

(Duration of treatment) plus 8 weeks after the last dose of study drug.

CONTRACEPTIVE METHODS:

A. HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects who are WOCBP (unless the male is azoospermic), are expected to use one of the highly effective methods of contraception listed below:

1) Male condoms with spermicide[1]
2) Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena®
3) IUDs, such as ParaGard®
4) Tubal ligation
5) Vasectomy

1. Gabbay MB, Thomas J, Gibbs A, Hold P. A randomized crossover trial of the impact of additional spermicide on condom failure rates. Sex Transm Dis 2008; 35: 862–8.

Kestelman P. et. al., Efficacy of the Simultaneous Use of Condoms and Spermicides Family Planning Perspectives.Vol 23 (5); October 1991.

Studies that administer drugs known to be teratogenic or drugs that have not undergone requisite preclinical testing for teratogenicity **require two forms of contraception** for both WOCBP and female partners of male subjects who are WOCBP (unless the male is azoospermic)**.** One method

must be highly effective and the second method may also be highly effective or selected from the list of other contraceptive methods in Section B. WOCBP are exempt from this requirement if a commitment to abstinence is made.

B. OTHER CONTRACEPTIVE METHODS

1. Diaphragm with spermicide
2. Cervical cap with spermicide
3. Vaginal sponge
4. Male condom without spermicide
5. Progestin only pills
6. Female condom*

* A male and a female condom must not be used together

C. HORMONE BASED METHODS OF CONTRACEPTION

- The MST, which must consider a recommendation from the relevant clinical pharmacologist, must agree that the use of a hormone-based contraceptive is safe and efficacious for WOCBP. A drug-drug interaction study should have been completed, if appropriate. Or there must be compelling evidence to substantiate that the investigational product(s) or concomitant medications will not adversely affect hormone exposures such that efficacy might be compromised or present present additional risk
- Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving drug. If a woman is over 35 years of age and smokes, consideration should be given to other forms of birth control as opposed to hormonal contraception containing estrogen, due to the potential increased risk of myocardial infarction

D. ABSTINENCE

- Abstinence is defined as the complete avoidance of heterosexual intercourse.
- Abstinence is an acceptable form of contraception for all study drugs.
- It is not necessary to use a second method of contraception when abstinence is elected.
- Subjects who choose abstinence must continue to have pregnancy tests, as specified in Section 4.3.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego abstinence

E. METHODS OF CONTRACEPTION WITH INSUFFICENT DATA TO SUPPORT EFFECTIVENESS

• No method
• Withdrawal
• Rhythm
• Spermicide alone