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Date: 22-May-2012
Revised Date: 18-Apr-2018

Clinical Protocol IM103116

Evaluation of the Benefits and Risks in Maintenance Renal Transplant Recipients Following Conversion to Nulojix® (belatacept)-based Immunosuppression

Revised Protocol Number: 05
Incorporate Amendments 08, 07, 05, 03, 01
Incorporates Administrative Letter 01, 02, & 03

Study Director / Medical Monitor
Martin Polinsky, MD
[redacted]

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 05	18-Apr-2018	Incorporates Amendment 08
Amendment 08	18-Apr-2018	Update definition of serious breach per company guidelines, clarify belatacept dosing instructions for skipping of doses to include possibility of dosing out of defined visit windows, [redacted], Clarification of "end of infusion" definition, allow provision of central lab CNI trough values to sites.
Administrative Letter 03	17-Oct-2017	To clarify protocol language by aligning the wording in the Time & Events Schedule
Administrative Letter 02	30-May-2017	To correct two typographical errors on the last revised protocol version 04.
Revised Protocol 04	07-Apr-2017	Incorporates Amendment 07
Amendment 07	07-Apr-2017	Modification to decrease target enrollment from 600 to 440 randomized subjects. The clarification of wording for the following: the CSPAR endpoint for consistency throughout the protocol; the requirement for daily dosing of maintenance corticosteroids throughout study participation; to indicate that protocol-specified tacrolimus trough levels being locally determined for patient management will also be captured in the clinical database; the timing for determination of post-belatacept infusion vital signs. Limitation of study participation by patients enrolled while receiving maintenance immunosuppression with tacrolimus plus mycophenolate sodium to approximately one-third (1/3) of all subjects. Provide a proviso to allow rescreening of patients who were screen failure earlier in the study. Update the definition of menopause; Correction of typographical errors and minor edits grammatical inconsistencies throughout the protocol.
Revised Protocol 03	20-Aug-2014	Incorporates Amendment 05
Amendment 05	20-Aug-2014	Modification to the inclusion/exclusion criteria. Modification to the MDRD formula, the definition of stable renal function and stable immunosuppression regimen. Addition of re-screening subjects. Extension of screening period. Decrease the frequency of body weight measurements. Minor edits and clarifications throughout the protocol.
Administrative Letter 01	02-Jul-2014	Change in medical monitor to Martin Polinsky, MD
Revised Protocol 02	04-Sep-2013	Incorporates Amendment 03
Amendment 03	04-Sep-2013	Modification to the inclusion/exclusion criteria. [redacted] Modification to the Renal Biopsy Requirements. Clarification of Live Vaccines for subjects. Addition of re-testing for screening creatinine labs. Minor edits and clarifications throughout the protocol, including table numbering.
Revised Protocol 01	07-Jan-2013	Incorporates Amendment 01
Amendment 01	07-Jan-2013	Modification to the inclusion/exclusion criteria. [redacted]

Document	Date of Issue	Summary of Change
		[redacted]
Original Protocol	22-May-2012	Not Applicable

SYNOPSIS

Clinical Protocol IM103116

Protocol Title: Evaluation of the Benefits and Risks in Maintenance Renal Transplant Recipients Following Conversion to Nulojix® (belatacept)-based Immunosuppression

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Nulojix® (belatacept) will be supplied by BMS. 250mg/vial will be used. Mode of Administration is intravenous (IV). Duration of treatment: 24 months

Non-investigational products (Non-IMP) include calcineurin inhibitors (CNI)--tacrolimus (TAC) or cyclosporine (CsA) and maintenance background therapies mycophenolate mofetil (MMF) or enteric-coated mycophenolate sodium (EC-MPS)/mycophenolic acid (MPA) and corticosteroids. Non-IMP products are standard of care and will be supplied locally.

Study Phase: 3b

Research Hypothesis: Formal statistical testing of a research hypothesis will not be performed in this study with regard to the primary endpoint of patient and functional graft survival. Its purpose is to assess the safety and efficacy of conversion from CNI (tacrolimus [TAC] or cyclosporine [CsA)]- to belatacept-based maintenance immunosuppression in renal allograft recipients with clinically stable function at least 6 months post-transplant.

Objective(s):

Primary

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

Secondary

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

- Composite of patient and functional graft survival at 12 months post-randomization
- The incidence and severity of clinically suspected, biopsy proven acute rejection at 12 and 24 months post-randomization
- Renal function as assessed by:
  - Mean change in calculated glomerular filtration rate (cGFR, 4-variable MDRD equation) from baseline (defined as most recent measurement prior to the first dose of study drug on Day 1) to 12 and 24 months post-randomization (% and absolute)
  - Slopes of cGFR and 1/serum creatinine respectively from baseline as well as from Month 3 to 12 and 24 months post-randomization
  - Proportion of subjects with > 5% and > 10% improvement over baseline in cGFR at 12 and 24 months post-randomization
  - Urine protein/ creatinine ratio (UPCR) at baseline, 3, 6, 12, and 24 months post-randomization
- Mean change in systolic and diastolic blood pressure and intensity of the anti-hypertensive treatment regimen (defined as the total number of antihypertensive medications used to control hypertension) from baseline to 12 and 24 months post-randomization
- Proportion of subjects with donor specific antibodies (DSA) at Baseline/Day 1, Months 12 and 24 post-randomization
- Evaluation of symptom occurrence and symptom distress measured with the MTSOSD-59R at baseline, week 6, and Months 3, 6, and 12 post- randomization
- Safety and tolerability of a belatacept in a conversion setting

Study Design:

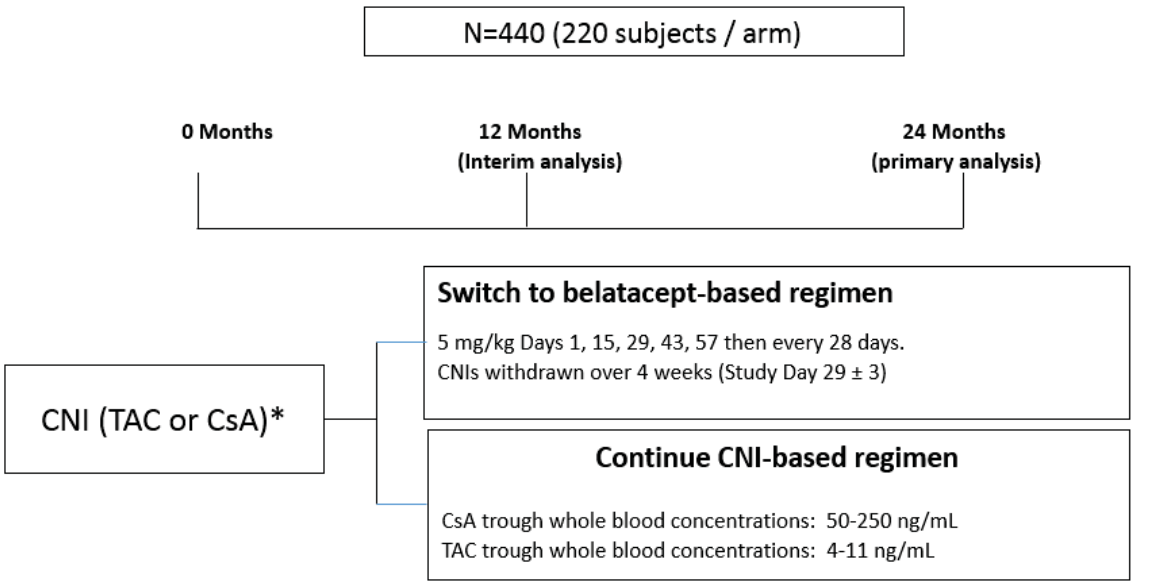
This is a randomized, open-label, active-controlled, parallel-group study. Approximately 440 subjects on CNI-based regimens will be randomized in a 1:1 ratio to treatment with either belatacept or continued treatment with their established CNI. All subjects will also receive a background maintenance immunosuppressive regimen of mycophenolate mofetil (MMF) or enteric-coated mycophenolate sodium (EC-MPS)/mycophenolic acid (MPA), with adjunctive daily corticosteroids, according to their immunosuppressive regimen at the time of enrollment. Enrollment will be monitored, and if necessary restricted, to ensure no more than 25% of patients are receiving CsA at the time of enrollment. In addition, participation by patients receiving the maintenance immunosuppressive combination of tacrolimus with mycophenolate sodium will be limited to no more than approximately 1/3 of all subjects.

Two cGFR values are required to demonstrate stable renal function prior to randomization, once at the screening evaluation and at one additional time point within 2 to 12 weeks prior to screening. Subjects will be stratified by site and screening cGFR (defined as the most recent cGFR between Day -42 and Day 1 prior to randomization). Subjects will be stratified by screening cGFR with a 1: 2 ratio (cGFR ≥ 30 to < 45 mL/min/1.73 m^2 or ≥ 45 to ≤ 75 mL/min/1.73m^2).

Subjects randomized to belatacept will receive 5 mg/kg intravenous (IV) on Days 1, 15, 29, 43, and 57, and then every 28 days thereafter. The CNI dose will be tapered to 40% - 60% of the baseline dose by Day 15, 20% - 30% of the baseline dose by Day 22, and will be discontinued by Day 29.

Subjects randomized to continue their CNI-based regimen will receive doses to achieve trough serum concentrations (C0 levels) of 50 - 250 ng/mL (CsA) or 4 - 11 ng/mL (TAC).

Figure 1: **Study Schematic**



* Background (concomitant) maintenance immunosuppressive regimen includes MMF or MPA and daily corticosteroids. Concomitant immunosuppressive medications to be kept at stable doses through Month 24 in both groups, unless otherwise indicated for clinical care of the individual subject.

Study Population:

Key Inclusion Criteria

- Men and women, ages 18 -75 inclusive
- Adult recipients of a renal allograft from a living donor or a deceased donor between 6-60 calendar months prior to enrollment
- Receiving a stable regimen of CNI (CsA or TAC), with MMF or EC-MPS/MPA and daily corticosteroids for ≥ 1 calendar month prior to randomization. CNI trough (C_0) levels must be in the range of 50-250 ng/ml for CsA and 4-11 ng/ml for TAC.
- Renal function must have remained stable during the 12 week period prior to Screening, in the opinion of the investigator and according to the following criteria:
    - Absence of ***new onset proteinuria*** during the 12-week period prior to the Screening evaluation, as documented by ≥ 1+ protein by dipstick or a random-voided urinary protein/creatinine ratio ≥ 0.3 mg protein/mg creatinine, identified during the 12-week period prior to Screening in a patient without previously diagnosed proteinuria and in the absence of intercurrent illness.
    - In patients with proteinuria documented ***prior to*** the 12-week period before Screening, urinary protein excretion at the time of the Screening evaluation must be:
        - ≤ 500 mg/24 hours OR the random urinary protein-to-creatinine ratio ($U_{Pr/Cr}$) must be ≤ 0.5:1 mg protein/mg creatinine (≤ 56.5 mg protein/mmol creatinine) at the Screening evaluation in patients with a history of diabetes mellitus; or
        - ≤ 1,000 mg/24 hours OR the random urinary protein-to-creatinine ratio must be ≤ 1.0:1 mg protein/mg creatinine (≤ 113 mg protein/mmol/creatinine) in non-diabetic patients.
- The calculated GFR (cGFR) must be ≥ 30 and ≤ 75 mL/min/1.73 m^2, as determined using the 4-variable MDRD equation, on two occasions: once at the Screening evaluation and at one additional time point between 2 and 12 weeks prior to the Screening evaluation. If a historical cGFR value is not available, then a second cGFR must be obtained at least 2 weeks later during the Screening period;
- Negative Interferon Gamma Release Assay (IGRA) such as QuantiFERON®-TB Gold test or T- Spoτ®- TB

Key Exclusion Criteria

- Recipients with EBV serostatus negative or unknown
- History of any of the following:
    - Treated for biopsy proven AR (BPAR) within 3 calendar months prior to enrollment
    - Antibody-mediated AR
    - Recurrent AR in the current allograft
    - Banff 97 Grade IIA or greater AR (or equivalent), steroid resistant AR or treatment with lymphocyte-depleting agents, plasmapheresis, or rituximab for AR since the time of transplantation of the current allograft
- Subjects with previous graft loss due to BPAR
- Subjects with a positive T-cell lymphocytotoxic cross match

Study Assessments:

Primary Endpoint(s)

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

Secondary Endpoint(s)

- Patient and Functional Graft Survival
  - Proportion of subjects who survive with a functional graft at 12 months post-randomization
- Acute Rejection
  - The incidence and severity of clinically suspected, biopsy-proven acute rejection at 12 and 24 months post-randomization
- Renal Function
  - Mean change in cGFR (per 4-variable MDRD equation) from baseline to 12 and 24 months post-randomization (% and absolute)
  - Slopes of cGFR and 1/serum creatinine respectively from baseline as well as Month 3 to 12 and 24 months post-randomization
  - Proportion of subjects with > 5% and > 10% improvement over baseline in cGFR at 12 and 24 months post-randomization
  - Urine protein/ creatinine ratio (UPCR) at baseline, 3, 6, 12, and 24 months post randomization
- Hypertension
  - Mean change in systolic and diastolic blood pressure and intensity of treatment regimen from baseline to 12 and 24 months post-randomization
- Donor Specific Antibodies
  - Proportion of subjects with donor specific antibodies at Baseline/ Day 1, Months 12 and 24 post-randomization
- The frequency of symptom occurrence and symptom distress as measured with the MTSOSD-59R at baseline, Week 6, and 3, 6, and 12 months post- randomization
- Safety and tolerability of a belatacept in a conversion setting
  - All adverse events
  - Adverse events of special interest
  - Clinically significant changes in vital signs
  - Laboratory test abnormalities
  - Clinical tolerability of the drug

Statistical Considerations:

Sample Size: Formal statistical testing of a research hypothesis is not being performed in this study. A sample size of approximately 220 subjects per treatment group is considered to provide sufficient power to rule out an unacceptable difference in patient and graft survival.

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

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

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

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

Analyses:

The primary composite endpoint of patient and graft survival by 24 months will be summarized within each treatment group using point estimates of the proportion of patients surviving with a functioning graft, and the corresponding 95% CIs. The 95% CIs will also be generated for the difference between the belatacept regimen and CNI to assess the effect of belatacept stratified by baseline cGFR.

The incidence and severity of clinically suspected, biopsy proven acute rejection up to 12 and 24 months post-randomization will be summarized within each treatment group using point estimates and 95% CIs. The 95% CIs will also be generated for the difference in rate of the acute rejection by 12 and 24 months between belatacept and CNI stratified by baseline cGFR.

Mean change in cGFR (per 4-variable MDRD equation) from baseline to 12 and 24 months post-randomization (% and absolute) will be summarized within each treatment group, point estimates and 95% CIs will also be displayed. A point estimate with two-sided 95% CI will be generated for the difference in mean percentage change of cGFR from baseline at Month 12 and Month 24, respectively, between belatacept and CNI.

To assess the trend in renal function, a linear mixed model will be used to analyze the mean changes in calculated GFR from multiple time-points (baseline and Month 3) to 12 and 24 months for each regimen. A similar analysis in 1/serum creatinine will also be performed.

The proportion of subjects with $\geq$ 5% and $\geq$10% improvement over baseline at 12 and 24 months will be summarized respectively.

The time to cGFR < 15 mL/min/1.73m^2, graft loss or death from baseline and Month 3, respectively, in each treatment group will be summarized using Kaplan-Meier curves.

All the other endpoints will be summarized descriptively by treatment group.

Interim Analysis:

At Month 12 following the last subject randomized, an interim analysis will be performed. The purpose of the interim analysis is to obtain study data to assess the evolving benefit risk profile of belatacept conversion at 12 months post-randomization. Similar methods as those used for the 24 month analyses will be performed for the 12 month interim analysis. The interim analyses will be descriptive in nature, and no statistical tests will be performed.

TABLE OF CONTENTS

[redacted]

1.3 Objectives(s)

1.3.1 Primary Objective

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

1.3.2 Secondary Objectives

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

- Composite of patient and functional graft survival at 12 months post-randomization
- The incidence and severity of clinically suspected, biopsy proven acute rejection at 12 and 24 months post- randomization.
- Renal function as assessed by:
  - Mean change in calculated glomerular filtration rate (cGFR) (4-variable MDRD equation) from baseline (defined as most recent measurement prior to the first dose of study drug on Day 1) to 12 and 24 months post-randomization (% and absolute)
  - Slopes of cGFR and 1/serum creatinine respectively from baseline as well as from Month 3 to 12 and 24 months post-randomization
  - Proportion of subjects with > 5% and > 10% improvement over baseline in cGFR at 12 and 24 months post-randomization
  - Urine protein/creatinine ratio (UPCR) at baseline, 3, 6, 12, and 24 months post-randomization
- Mean change in systolic and diastolic blood pressure and intensity of the anti-hypertensive treatment regimen (defined as the total number of anti-hypertensive medications used to control hypertension) from baseline to 12 and 24 months post-randomization
- Proportion of subjects with donor specific antibodies (DSA) at Baseline/ Day 1, Months 12 and 24 post-randomization
- Evaluation of symptom occurrence and symptom distress measured with the MTSOSD-59R at baseline, Week 6, and Months 3, 6, and 12 post- randomization
- Safety and tolerability of a belatacept in a conversion setting

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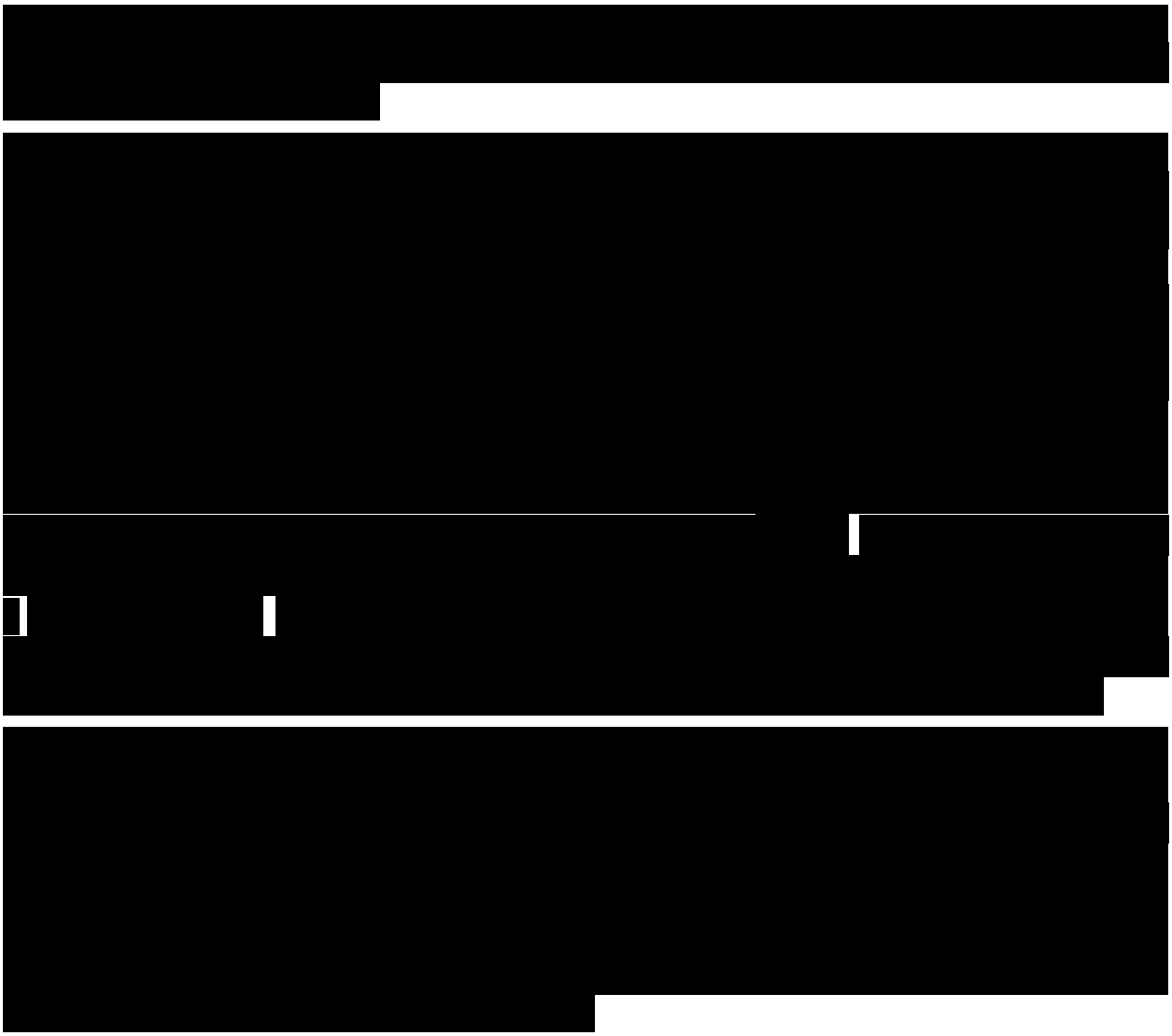


2 ETHICAL CONSIDERATIONS

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 Good Clinical Practices (GCP) (occurring in any country) in connection with the study or a protocol related to the study, which is likely to

affect, to a significant degree, the safety or physical or mental integrity of 1 or more 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 approvals / favorable opinions 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 USA, 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

3.1.1 Duration of Study

Once randomized, the duration of the study is 24 months with a subsequent 8-week follow-up period for safety post last dose. In addition, belatacept-treated subjects who discontinue treatment or complete the study and do not continue treatment with commercial belatacept post study will be seen at 12 and 24 weeks post last dose.

3.1.2 Overview

This is a randomized, open-label, active-controlled, parallel-group study. Approximately 440 subjects on CNI-based regimens will be randomized in a 1:1 ratio to treatment with either belatacept or continued treatment with their established CNI. All subjects will also receive a background maintenance immunosuppressive regimen of mycophenolate mofetil (MMF) or enteric-coated mycophenolate sodium (EC-MPS)/ mycophenolic acid (MPA), with adjunctive, daily corticosteroids, according to their immunosuppressive regimen at the time of enrollment. Enrollment will be monitored, and if necessary restricted, to ensure that no more than approximately 25% of patients are receiving CsA at the time of enrollment. In addition, participation by patients receiving the maintenance immunosuppressive combination of tacrolimus with mycophenolate sodium will be limited to no more than approximately 1/3 of all subjects.

Eligible patients must have stable renal function for 12 weeks prior to Enrollment, as defined below (Section 3.2).

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

Subjects randomized to belatacept will receive 5 mg/kg intravenous (IV) on Days 1, 15, 29, 43, and 57, and then every 28 days thereafter. The CNI dose will be tapered to 40% - 60% of the baseline dose by Day 15, 20% - 30% of the baseline dose by Day 22, and will be discontinued by Day 29.

Subjects randomized to continue their CNI-based regimen will receive doses targeted to achieve trough serum concentrations (C_0 levels) of 50 - 250 ng/mL (CsA) or 4 - 11 ng/mL (TAC). (Refer to Figure 3.1.2-1 and Table 3.1.2-1 & Table 3.1.2-2)

Table 3.1.2-1: Dosing Schedule - Year 1

			M 1			M 3			M 6			M 9				M 12
	W0	**W2**	**W4**	**W6**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**
Randomize to Treatment Arm	**D1**	**D15**	**D29**	**D43**	**D57**											
Belatacept Dosing (5mg/kg)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

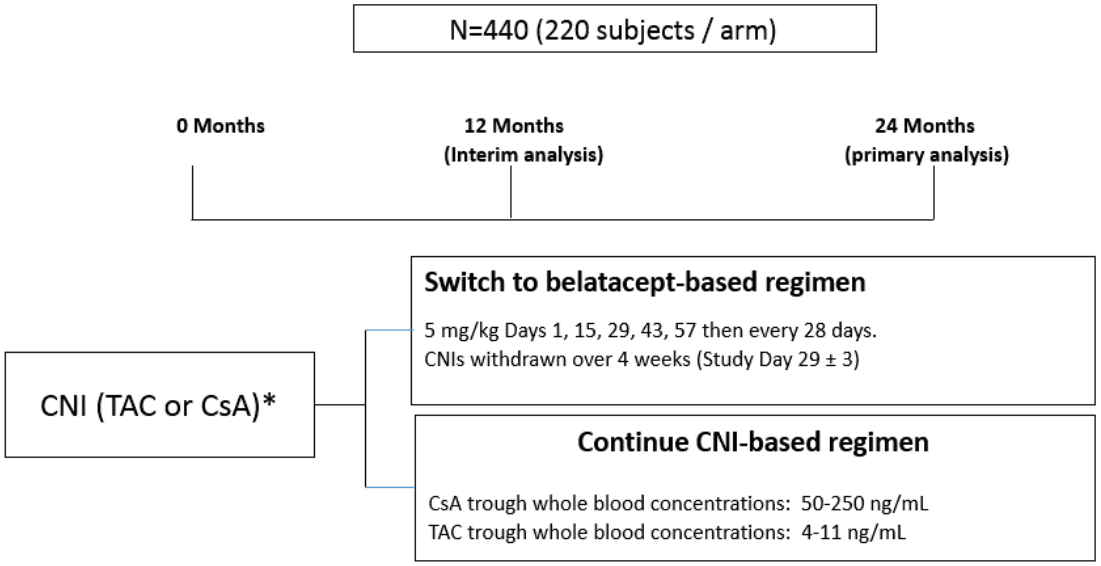
Subjects randomized to receive belatacept will reduce their CNI dose to:
40%-60% of the baseline dose by Day 15
20%-30% of the baseline dose by Day 22
0% of the baseline dose by Day 29

CNI ADMINISTRATION	
CsA Dosing	Subjects receiving CsA will be maintained at doses to achieve target trough levels (C_0 levels) of 50 - 250 ng/mL.
TAC Dosing	Subjects receiving TAC will be maintained at doses to achieve target trough concentrations of 4 - 11 ng/mL.
Adjunctive Background Immunosuppression	
Oral Corticosteroid	Daily corticosteroid use is required for study enrollment and subjects should not undergo steroid dose adjustment during the study unless medically necessary.
MMF or EC-MPS/MPA	Refer to Section 4.3
Subjects May Also Receive:	
Antiviral Prophylaxis (During and after T-Cell Depleting Therapy)	It is recommended that subjects who receive a T-cell depleting agent at any time in the trial receive prophylaxis against Pneumocystis jiroveci pneumonia (previously called PCP pneumonia), cytomegalovirus exacerbation and other herpes viruses and *Candida* infections for at least 6-12 weeks based upon the KDIGO guidelines and/or in accordance with the local standard of care practice.

Table 3.1.2-2: Dosing Schedule - Year 2

			M 15			M 18			M 21				M 24				
	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				
Belatacept Dosing (5mg/kg)	X	X	X	X	X	X	X	X	X	X	X	X	X				
CNI ADMINISTRATION																	
CsA Dosing		Subjects receiving CsA will be maintained at doses to achieve target trough levels (C_0 levels) of 50 - 250 ng/mL.															
TAC Dosing		Subjects receiving TAC will be maintained at doses to achieve target trough concentrations of 4 - 11 ng/mL.															
Adjunctive Background Immunosuppression																	
Oral Corticosteroid		Daily corticosteroid use is required for study enrollment, and subjects should not undergo steroid dose adjustment during the study unless medically necessary.															
MMF or EC-MPS/MPA		Refer to Section 4.3.															
Subjects May Also Receive:																	
Antiviral Prophylaxis (During and after T-Cell Depleting Therapy)		It is recommended that subjects who receive a T-cell depleting agent at any time in the trial receive prophylaxis against Pneumocystis jiroveci pneumonia (previously called PCP pneumonia), cytomegalovirus exacerbation and other herpes viruses and *Candida* infections for at least 6-12 weeks based upon the KDIGO guidelines and/or in accordance with the local standard of care practice.															

Figure 3.1.2-1: Study Schematic



* Background (concomitant) maintenance immunosuppressive regimen includes MMF or MPA and daily corticosteroids. Concomitant immunosuppressive medications to be kept at stable doses through Month 24 in both groups, unless otherwise indicated for clinical care of the individual subject.

3.2 Study Population

The study population includes recipients of a renal allograft from a living donor or a deceased (standard criteria and extended criteria) donor transplanted at least 6 months, but not longer than 60 months prior to enrollment (Study Day -42).

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

3.2.1 Inclusion Criteria

1) Signed Written Informed Consent

a) The subject or legal representative is willing to provide signed written informed consent

2) Target Population

a) Adult recipients of a renal allograft from a living donor or a deceased donor between 6 and 60 calendar months prior to enrollment.

b) Receiving a stable regimen of CNI (CsA or TAC), with MMF or EC-MPS/MPA and daily corticosteroids for ≥ 1 calendar month prior to randomization. CNI trough (C_0) levels must be in the range of 50-250 ng/ml for CsA and 4-11 ng/ml for TAC. [With regard to CNI therapy: "receiving a stable regimen" specifically refers to maintaining a stable level of exposure to CsA or TAC within the protocol-specified ranges, and not to maintaining a stable dose, per se. Thus, changes to the CNI dose made during the Screening period to maintain stable exposure do not exclude prospective subjects from

study participation, so long as their trough levels remain within the protocol-specified range.]

c) Renal function must have remained stable during the 12 week period prior to Screening, in the opinion of the investigator and according to the following criteria:

1) Absence of ***new onset proteinuria*** during the 12-week period prior to enrollment, as documented by ≥ 1+ protein by dipstick or a random-voided urinary protein/creatinine ratio ≥ 0.3 mg protein/mg creatinine (≥ 34 mg protein/mmol creatinine) in a patient without previously diagnosed proteinuria and in the absence of intercurrent illness.

2) In patients with ***pre-existing proteinuria*** (proteinuria known to have been present ***prior to*** the 12-week period before enrollment), urinary protein excretion at the time of the Screening evaluation must be:

- ≤ 500 mg/24 hours OR the random urinary protein-to-creatinine ratio ($U_{Pr/Cr}$) must be ≤ 0.5:1 mg protein/mg creatinine (≤ 56.5 mg protein/mmol creatinine) at the Screening evaluation in patients with a history of diabetes mellitus; or
- ≤ 1,000 mg/24 hours OR the random urinary protein-to-creatinine ratio must be ≤ 1.0:1 mg protein/mg creatinine (≤ 113 mg protein/mmol/creatinine) in non-diabetic patients.

d) The calculated GFR (cGFR) must be ≥ 30 and ≤ 75 mL/min/1.73 m^2, as calculated using the 4-variable MDRD equation [29], on two occasions: once at the Screening evaluation and at one additional time point between 2 and 12 weeks prior to the Screening evaluation. If a historical cGFR value is not available, then a second cGFR must be obtained at least 2 weeks later during the Screening period. Calculated results for cGRF should be rounded to the nearest whole number based upon conventional rounding rules.

NOTE: Both serum creatinine determinations should be from the same laboratory unless both labs use IDMS-referenced assays.

e) Negative testing for TB by an interferon gamma release assay (IGRA) such as the QuantiFERON®-TB Gold test or T- Spot®- TB test, prior to randomization.

3) Age and Reproductive Status

a) Men and women, ages 18 - 75 inclusive

Women of childbearing potential (WOCBP) must use highly effective methods of birth control to avoid pregnancy throughout the study and for up to 8 weeks after the study in such a manner that the risk of pregnancy is minimized. Please note: that according to the US product information for MMF or EC-MPS/MPA, two reliable forms of contraception must be used simultaneously unless abstinence is the chosen method (see package insert).

Acceptable methods of highly effective birth control include:

- Condom with spermicide

- Diaphragm and spermicide
- Cervical cap and spermicide
- Oral contraceptives
- Intrauterine device (IUD)

b) WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 24 hours prior to the start of study medication.

c) Women must not be breastfeeding

d) Sexually active fertile men must use highly effective birth control if their partners are WOCBP. Men who are sexually active with WOCBP must follow instructions for birth control for the entire duration of the study and a minimum of 8 weeks post study drug has been completed.

e) Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile; see Section 3.2.3 for the definition of WOCBP).

3.2.2 Exclusion Criteria

1) Target Disease Exceptions

a) Recipients with EBV serostatus negative or unknown

b) History of any of the following:
   1. Treated for biopsy proven AR (BPAR) within 3 calendar months prior to enrollment
   2. Antibody mediated AR
   3. Recurrent AR in the current allograft
   4. Banff 97 Grade IIA or greater AR (or equivalent), steroid resistant AR or treatment with lymphocyte-depleting agents, plasmapheresis, or rituximab for AR since the time of transplantation of the current allograft

c) Subjects with previous graft loss due to BPAR

d) Subjects with a positive T-cell lymphocytotoxic cross match

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

f) Donor age < 10 years

g) Subjects with underlying renal disease of:
   1. Primary focal segmental glomerulosclerosis
   2. Type I or II membranoproliferative glomerulonephritis
   3. Atypical hemolytic uremic syndrome (HUS) / thrombotic thrombocytopenic purpura (TTP)
   4. Not applicable per Protocol Amendment 05

If a subject has ESRD of unknown etiology and/or has no histologically-confirmed diagnosis, the subject may be enrolled into the study as long as, in the opinion of the investigator, the overall history and clinical findings are not consistent with a likely diagnosis of underlying primary focal segmental glomerulosclerosis, Type I or II membranoproliferative glomerulonephritis, or atypical HUS/TTP.

h) Subjects with prior non-renal solid organ transplant (subjects undergoing kidney re-transplantation are eligible pending other study criteria being met), or subjects undergoing multi-organ transplants (eg, kidney-pancreas) or subjects deemed likely to have a second solid organ or cell transplant (eg, pancreas or islet transplant) in the next 3 years by the investigator

i) Subjects receiving a concurrent solid organ (heart, liver, pancreas) or cell (islet, bone marrow, stem cell) transplant

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

2) Medical History and Concurrent Diseases

a) Subjects who are or whose allograft donor was known hepatitis C antibody-positive or polymerase chain reaction (PCR)-positive for hepatitis C

b) Subjects who are or whose allograft donor was known hepatitis B surface antigen-positive or PCR-positive for hepatitis B

c) Subjects and recipients of a graft from a donor with known human immunodeficiency virus (HIV) infection

d) Subjects with any active infection [including but not limited to cytomegalovirus (CMV), BK or Epstein-Barr virus (as determined by detection of quantifiable viral loads in plasma), BKV associated nephropathy, CMV retinitis, CMV colitis, tuberculosis, etc.]

e) Subjects with history of active or untreated latent tuberculosis (TB) or radiographic finding consistent with active TB

NOTE: Subjects must be screened for active and latent tuberculosis prior to entry into the study. Subjects must have a negative chest x-ray (posterior-anterior and lateral views) within the last 6 calendar months prior to screening and a negative IGRA test (such as QuantiFERON®-TB Gold test or T- Spot®- TB) done at screening by the central laboratory. If equipment for incubation prior to shipment to central lab is not available at the site, a local lab IGRA test is acceptable. (Refer to Table 5.1-1)

f) Subjects whose life expectancy is severely limited by disease state or other underlying medical condition

g) Subjects with a history of cancer (other than non-melanoma skin cell cancers cured by local resection) within the last 5 years

h) 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

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

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

3) Physical and Laboratory Test Findings

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

Hematology:

- Hemoglobin < 7 g/dL
- Platelets < 80,000/mm3
- White blood cell (WBC) count < 3000/mm3 (< 3 x 10^9/L)
- Serum IgG < 400 mg/dL

Chemistry:

- Bilirubin > 1.5 x upper limit of normal range (ULN); Subjects who have Gilbert's syndrome and have a normal direct bilirubin are permitted
- 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 principle investigator makes the subject unsuitable for participation in the study

5) Sex and Reproductive Status

a) Women with a positive pregnancy test on enrollment or prior to study drug administration

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 previously treated with belatacept or previously enrolled in a belatacept trial with their present allograft, except as specified below (Section 3.2.4)

d) Subjects currently receiving background immunosuppressive therapy with azathioprine, sirolimus or everolimus.

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

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

g) Subjects who are deemed clinically inappropriate for continued CNI therapy (investigator discretion).

h) Subjects who, in the opinion of the investigator, have difficult i.v. access.

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.

3.2.3 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) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, women under the age of 55 years must have a serum follicle stimulating hormone (FSH) level > 40 mIU/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.

- 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 the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal. :

3.2.4 Re-Screening

Subjects who fail screening may be considered for re-screening one time if, in the opinion of the investigator, their clinical status has changed such that they may now be eligible for study participation per all eligibility criteria. The following are requirements for re-screening:

1. Medical monitor approval
2. Rescreening is not permitted during the 42-day (initial) screening period following the date on which the initial written informed consent is obtained
3. Subjects to be re-screened must sign a new informed consent and be enrolled with a new identification number via the IVRS
4. At the discretion of the medical monitor, selected tests, such as chest radiography, will not be repeated if previous screening results remain valid per the protocol-defined window for that test.

[redacted]

3.3.4 Biopsy Restrictions

Investigators must perform a renal biopsy to assess for acute rejection in subjects who meet protocol specified clinical criteria for acute rejection. Renal biopsies performed for medical cause are allowed. Renal biopsies performed according to local practice in the absence of clinical

suspicion of AR, PTLD or for other medical cause are not permitted. A biopsy of the affected organ should be considered when there is suspicion of PTLD. (Refer to Section 5.3)

3.4 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:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), abnormal laboratory test results 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 BMS
- Loss of ability to freely provide consent through imprisonment or involuntary 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 BMS/ICON medical monitor to remain in the study. Documentation will be required.
- Subjects who experience functional graft loss (defined herein as resumption of maintenance dialysis treatments for > 56 consecutive days), and are deemed by the investigator to no longer require immunosuppression.

All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in Section 3.5. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

NOTE: Withdrawal of a subject from study medication does not imply that the subject is withdrawn from the study. All patients will be followed through study month 24 for graft and subject survival status.

3.5 Post Treatment Study Follow up

Withdrawal of a subject from study medication does not imply that the subject is withdrawn from the study. Subjects will remain in the study and will be contacted annually (either office visit or by phone) to confirm graft and vital status. All subjects will be followed for graft and survival status through the month 24 study visit.

3.5.1 Early Termination from Study Medication

An Early Termination visit and safety follow-up visits will be conducted for subjects who discontinue study medication during their participation in the study. All procedures listed in Table 5.1-2 will be performed.

The Early Termination visit should occur at the earliest possible date within a 14 day window following the discontinuation of belatacept or CNI. If the visit cannot be completed within the window (eg, due to hospitalization), the visit should be completed as soon as possible. Subsequent Follow-up visits should occur as indicated in Table 5.1-2 within a ± 5 day window.

3.5.2 Post Study Access to Therapy

At the completion of the 2-year treatment period or upon premature discontinuation of treatment, 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 receives appropriate standard of care.

3.5.3 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.

3.5.4 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 TREATMENTS

Study drugs include both Non-Investigational (NIMP) and Investigational Medicinal Products (IMP) 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 backbone therapy, rescue medications)
- Diagnostic agents: 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: Study Treatment

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Belatacept for Injection 250 mg / vial	250 mg	Vial / Open Label	Cardboard (SBS Carton)	White to off white, whole or fragmented cake in a vial	Refrigerated at 2- 8° Celsius. Protect from light

4.1.1 Investigational Product

An investigational product, also known as investigational medicinal product (IMP) in some regions, is defined 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. 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: Belatacept 250 mg vials

Subjects will receive IV belatacept on Days 1, 15, 29, 43, 57, and then every 28 days thereafter.

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: Tacrolimus (TAC), Cyclosporine A (CsA), Mycophenolate Mofetil (MMF) or Enteric-coated Mycophenolate Sodium (EC-MPS)/ Mycophenolic Acid (MPA) and corticosteroids.

4.1.2.1 Description of the Dosage Form

Belatacept for Injection, 250 mg/vial

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.

4.1.2.2 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 approximately 100 mL with NS or D5W for a final belatacept concentration 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 (see product label).

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 to approximately 100 mL 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.

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.

Recommended Storage Conditions

Belatacept for Injection 250 mg/Vial should be stored refrigerated at 2°- 8°C (36°-46°F), and protected from long-term exposure to light. The reconstituted solution should be transferred from the vial to the infusion bag or bottle immediately. After further dilution with NS or D5W to belatacept concentrations between 2 mg/mL and 10 mg/mL, the solutions may be stored in plastic, non siliconized, IV bags or glass bottles. If not used immediately, the infusion solution may be stored under refrigerated conditions at 2°- 8°C (36°-46°F) and protected from light for up to 24 hours (a maximum of 4 hours of the total 24 hours can be at room temperature: 20° - 25°C [68°-77°F] and room light). Regardless of storage condition, the belatacept infusion must be completed within 24 hours of constitution of the lyophile.

4.2 Method of Assigning Subject Identification

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

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

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

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

4.3 Selection and Timing of Dose for Each Subject

Administration of Belatacept

Subjects will receive IV belatacept 5 mg/kg on Days 1, 15, 29, 43, and 57, and every 4 weeks thereafter. The infusion dose is to be based on the Day 1 body weight (baseline weight) and will not be modified unless there is a change of body weight $\geq 10\%$ of the Day 1 weight (see Section 4.4.1 - Dose Modification). **The infusion solution should be administered over a period of approximately 30 minutes.**

Home infusion services may be available for belatacept subjects beginning at Week 16 (excluding visits for months 3, 6, 9, 12, 18 and 24) at selected sites where it is feasible and with approval from BMS. This visit should occur within the prescribed visit window for the specified visit. For details, please refer to the home infusion manual. Subjects participating in home infusion visits will also be contacted to assess for AEs and concomitant medications.

Administration of Cyclosporine (CsA)

CsA will be administered according to the package insert. The daily dose of CsA should be administered on a consistent schedule in relation to time of day and meals. On study visit days, the subject must withhold the morning CsA dose until after trough CsA blood level draws. CsA doses should be adjusted to maintain trough serum concentrations in the range of 50 - 250 ng/mL as determined by local laboratory assessment and methodology.

For additional prescribing information, see the package insert.

Administration of Tacrolimus (TAC)

TAC will be administered according to the package insert. The daily dose of TAC should be administered on a consistent schedule in relation to time of day and meals. On study visit days, the subject must withhold the morning TAC dose until after trough TAC blood level draws. TAC doses should be adjusted to maintain trough serum concentrations in the range of 4 - 11 ng/mL as determined by the local laboratory assessment and methodology.

For additional prescribing information, see the package insert.

Withdrawal of Calcineurin Inhibitors (CNIs)

Subjects randomized to receive belatacept will reduce their dose of CNI as follows: to 40% - 60% of the baseline dose by Day 15, 20% - 30% of the baseline dose by Day 22, and will discontinue CNI by Day 29.

Corticosteroids

Subjects should be maintained on a stable daily dose of corticosteroids for the duration of the study unless a change in the medical condition of the subject warrants adjustment. Withdrawal of corticosteroids during the study is not permitted.

Mycophenolate Mofetil (MMF), Enteric-coated Mycophenolate Sodium (EC-MPS)/Mycophenolic Acid (MPA)

All subjects in this study will be treated with MMF or EC-MPS/MPA in addition to belatacept / CNI. MMF or EC-MPS/MPA will be administered according to the package insert. Daily MMF or EC-MPS/MPA should be administered in 2 divided doses on a consistent schedule in relation to the time of day and meals. Intravenous dosing is permitted, if needed, due to inter-current illness or other cause, at the investigator's discretion. The dose and schedule may be adjusted determined on the basis of laboratory values and subject tolerability (see below).

Dosing in Subjects Who Develop MMF / EC-MPS/MPA-related Complications or Toxicities

For subjects who develop nausea, diarrhea, or other MMF or EC-MPS/MPA-related gastrointestinal adverse effects (eg, symptoms fully assessed and deemed not to have an etiology other than intolerability to MMF or EC-MPS/MPA), the MMF or EC-MPS/MPA dose may be decreased to a level that minimizes these effects.

For subjects who develop neutropenia (absolute neutrophil count $< 1.3 \times 10^3/\mu L$), dosing with MMF or EC-MPS/MPA should be interrupted or the dose reduced as per the package insert.

For full prescribing information, see the respective package inserts.

Anti-viral / Fungal Prophylaxis

It is recommended that subjects who receive a T-cell depleting agent at any time in the trial receive prophylaxis against Pneumocystis jiroveci pneumonia (previously called PCP pneumonia), cytomegalovirus exacerbation and other herpes viruses, and *Candida* infections for

at least 6 - 12 weeks based upon the KDIGO guidelines and/or in accordance with the local standard of care practice.[4]

4.3.1 Phone Visits CNI Subjects

Phone visits for CNI subjects may commence at the Week 16 visit (excluding visits for months 3, 6, 9, 12, 18, and 24). Subjects will be contacted to assess for AEs and concomitant medications. This visit should occur within the prescribed visit window for the specified visit.

4.4 Visit Windows

For the purpose of this study, "Week" refers to the end of treatment week (eg. Week4 = Day 29, Week 8 = Day 57, etc)

Visit	Visit Window
Day 15	Target date ± 3 days
Week 4 - Month 6	Target date ± 3 days
Month 7 – Month 24	Target date ± 5 days
Early Termination	Target Date: Within 14 day window after discontinuation of belatacept or CNI
8, 12, 24 weeks Follow-up	Target date ± 5 days

4.4.1 Dose Modification

The infusion dose is based on the baseline (Day 1) body weight, and will not be modified unless there is a change of body weight ≥ 10% of the Day 1 weight. 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, unless the subject has an additional body weight change ≥ 10% from this new baseline measure. The dose should be modified starting at the next belatacept infusion visit and the new weight should be considered as a new baseline weight.

In the absence of AEs deemed at least possibly related to study drug treatment, subjects will complete their scheduled infusions as prescribed by the protocol (refer to section 4.4 above). If the belatacept infusion cannot be administered within the visit/infusion window defined in the protocol, the infusion may need to be skipped and the next infusion administered within the next visit/infusion window. If a belatacept infusion must either be administered outside of the protocol-prescribed visit/infusion window or skipped, it is recommended that the investigator 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. The investigator must immediately notify the medical monitor. The subject will be considered eligible to receive further study drug treatment only after discussion with the medical monitor. Subjects in whom belatacept dosing is discontinued should be placed on a conventional immunosuppressive regimen.

Subjects who receive plasmapheresis for the treatment of AR may receive an additional dose(s) of belatacept. This decision must be individualized on a case-by-case basis, and the investigator must discuss any dose modification with the BMS/ICON medical monitor in advance of such modification.

4.5 Blinding/Un-blinding

Not applicable. This study is open label.

4.6 Treatment Compliance

Belatacept will be administered as an IV infusion. 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.

4.7 Destruction and Return of Study Drug

4.7.1 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 BMS and/or designee 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 and/or designee 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 BMS and/or designee 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.

4.7.2 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 BMS and/or designee 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.

4.8 Retained Samples for Bioavailability / Bioequivalence

Not Applicable

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening / Baseline and Study Evaluations - Year 1 (IM103116)

				M 1			M 3			M 6			M 9				M 12	Notes
	Screen [a]	Randomize/ Baseline [b]	W 2	W 4	W 6	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52 [c]	
Procedure	**D -42**	**D 1**	**D 15**	**D 29**	**D 43**	**D 57**												
Informed Consent	X																	
Call IVRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	At screening, call IVRS to enroll subject & record subject # assignment. At Day 1, call IVRS to randomize subject. CNI subjects do not need to call IVRS after Day 1 visit except to report discontinuation from study drug.
Inclusion / Exclusion Criteria Confirmed	X	X																Subjects who fail screening may be considered for rescreening one time if, in the opinion of the investigator, their clinical status has changed such that they may now be eligible for study participation per all eligibility criteria (**refer to Section 3.2.4**).

Table 5.1-1: Screening / Baseline and Study Evaluations - Year 1 (IM103116)																		
				M 1			**M 3**			**M 6**			**M 9**				**M 12**	**Notes**
	Screen[a]	**Randomize/ Baseline[b]**	**W 2**	**W 4**	**W 6**	**W 8**	**W 12**	**W 16**	**W 20**	**W 24**	**W 28**	**W 32**	**W 36**	**W 40**	**W 44**	**W 48**	**W 52[c]**	
Procedure	**D -42**	**D 1**	**D 15**	**D 29**	**D 43**	**D 57**												
Chest X-Ray	X*																	Chest x-ray (posterior-anterior and lateral views) * at the time of, or within 6 months prior to screening
12 Lead Electrocardiogram	X																	Must be obtained prior to randomization.
Full Medical History	X																	
Physical Exam	X																X	
Neurologic Exam		X								X							X	Also required if change in neurologic status based on clinical signs and symptoms is observed (Sect. 5.3.8)

Table 5.1-1: Screening / Baseline and Study Evaluations - Year 1 (IM103116)																		
				M 1			**M 3**			**M 6**			**M 9**				**M 12**	**Notes**
	Screen [a]	**Randomize/ Baseline[b]**	**W 2**	**W 4**	**W 6**	**W 8**	**W 12**	**W 16**	**W 20**	**W 24**	**W 28**	**W 32**	**W 36**	**W 40**	**W 44**	**W 48**	**W 52[c]**	
Procedure	**D -42**	**D 1**	**D 15**	**D 29**	**D 43**	**D 57**												
Vital Signs	X	X	X	X	X	X	X	X*	X*	X	X*	X*	X	X*	X*	X*	X	BP (sitting position) & heart rate; temperature & respiratory rate will also be taken at Screening visit. Measure blood pressure and heart rate **pre-dose and at the end of infusion** for belatacept treated subjects * Not required for CNI subjects at phone visits.
Standardized BP		X		X			X			X			X				X	Refer to Section 5.3.2.1
Height / Weight		X*	X	X	X		X			X			X				X	* Height taken at Day 1 only. Weight prior to infusions for belatacept treated subjects.
Adverse Events Monitoring		X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	* SAEs should be collected from the time subject signs informed consent.

Table 5.1-1: Screening / Baseline and Study Evaluations - Year 1 (IM103116)																		
				M 1			**M 3**			**M 6**			**M 9**				**M 12**	**Notes**
	Screen[a]	**Randomize/ Baseline[b]**	**W 2**	**W 4**	**W 6**	**W 8**	**W 12**	**W 16**	**W 20**	**W 24**	**W 28**	**W 32**	**W 36**	**W 40**	**W 44**	**W 48**	**W 52[c]**	
Procedure	**D -42**	**D 1**	**D 15**	**D 29**	**D 43**	**D 57**												
Peri-Infusion AE Monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Following every belatacept infusion, subject must be contacted within 48 hours to confirm if they have had any adverse event within 24 hrs of their infusion.
Review Con Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
MTSOSD-R59		X			X		X			X							X	
[redacted]		[redacted]					[redacted]			[redacted]							[redacted]	
Obtain Donor/Recipient Information	X																	Including type of allograft, viral (EBV & CMV) serologies, T-cell cross match, HLA, TB screening status and demographic data [if available].
CENTRAL LABS																		All labs should be drawn prior to dosing for belatacept treated subjects.
EBV Serology	X																	Collect if unknown or negative.

Table 5.1-1: Screening / Baseline and Study Evaluations - Year 1 (IM103116)																		
				M 1			**M 3**			**M 6**			**M 9**				**M 12**	**Notes**
	Screen [a]	**Randomize/ Baseline[b]**	**W 2**	**W 4**	**W 6**	**W 8**	**W 12**	**W 16**	**W 20**	**W 24**	**W 28**	**W 32**	**W 36**	**W 40**	**W 44**	**W 48**	**W 52[c]**	
Procedure	**D -42**	**D 1**	**D 15**	**D 29**	**D 43**	**D 57**												
Chemistry Panel: (Fasting) w/ cGFR	X	X					X			X			X				X	Draw prior to infusion. Nothing to eat/drink, except water, for 8 hours prior to laboratory collection.
[redacted]		[redacted]															[redacted]	[redacted]
TAC/CsA Trough Levels	X*	X		X			X			X			X				X	*All subjects - Screening. visit. Hold AM dose of CNI until trough drawn. Only subjects randomized to remain on CNI should be drawn after screening. Should also be drawn at time of SAR or PTLD/PML. Refer to section 5.3.5.2
Immunoglobulins & Isotypes, IgG1, 2, 3, 4	X*	X		X		X	X			X							X	Also collected at the time of graft loss and suspected AR. * No isotypes assessed at screening.
CBC with diff	X	X					X			X							X	
Hemoglobin A1c		X															X	

Table 5.1-1: Screening / Baseline and Study Evaluations - Year 1 (IM103116)

				M 1			M 3			M 6			M 9				M 12	Notes
	Screen [a]	Randomize/ Baseline [b]	W 2	W 4	W 6	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52 [c]	
Procedure	**D -42**	**D 1**	**D 15**	**D 29**	**D 43**	**D 57**												
Urinalysis / Spot Urine	X	X					X			X							X	Parameters include protein, glucose & blood; urine protein, creatinine, protein /creatinine ratio.
[redacted]																		

Table 5.1-1: Screening / Baseline and Study Evaluations - Year 1 (IM103116)

				M 1			M 3			M 6			M 9				M 12	Notes
	Screen [a]	Randomize/ Baseline [b]	W 2	W 4	W 6	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48	W 52 [c]	
Procedure	**D -42**	**D 1**	**D 15**	**D 29**	**D 43**	**D 57**												
[redacted]																		
[redacted]																		
Donor Specific Antibodies (DSA)		X															X	Must also obtain for any suspected AR. For belatacept subjects, draw prior to infusion.

Table 5.1-1: Screening / Baseline and Study Evaluations - Year 1 (IM103116)																		
				M 1			**M 3**			**M 6**			**M 9**				**M 12**	**Notes**
	Screen[a]	**Randomize/ Baseline[b]**	**W 2**	**W 4**	**W 6**	**W 8**	**W 12**	**W 16**	**W 20**	**W 24**	**W 28**	**W 32**	**W 36**	**W 40**	**W 44**	**W 48**	**W 52[c]**	
Procedure	**D -42**	**D 1**	**D 15**	**D 29**	**D 43**	**D 57**												
Immune Cell Phenotyping		X								X								**USA Subjects Only.** Must also obtain for any suspected AR. For belatacept subjects, draw prior to infusion.
Anti-Viral T-cell Response		X								X							X	**USA Subjects Only.** Must also obtain for any suspected PTLD/PML. For belatacept subjects, draw prior to infusion.
Belatacept Infusion Visits		X	X	X	X	X	X	X*	X*	X	X*	X*	X	X*	X*	X*	X	Dose based on D1 body weight & will not be modified unless there is a change of ≥ 10% of the D1 weight. Measure blood pressure and heart rate **pre-dose and at the end of infusion** for belatacept subjects only. *Home Infusion services can begin at Week 16 for belatacept subjects if approved.

Table 5.1-1: Screening / Baseline and Study Evaluations - Year 1 (IM103116)																		
				M 1			**M 3**			**M 6**			**M 9**				**M 12**	**Notes**
	Screen [a]	**Randomize/ Baseline[b]**	**W 2**	**W 4**	**W 6**	**W 8**	**W 12**	**W 16**	**W 20**	**W 24**	**W 28**	**W 32**	**W 36**	**W 40**	**W 44**	**W 48**	**W 52[c]**	
Procedure	**D -42**	**D 1**	**D 15**	**D 29**	**D 43**	**D 57**												
CNI Visits (TAC or CsA)	X	X	X	X	X	X	X	X*	X*	X	X*	X*	X	X*	X*	X*	X	*phone visit permitted - Assess for AEs & concomitant medications. Should occur within the prescribed visit window for the specified visit.
Biopsy																		At any time of suspected AR /PTLD.
LOCAL LABS																		
Interferon- gamma release assay (IGRA)	X																	Refer to Section 3.2.2, Exclusion Criteria, # 2e NOTE. If local lab does not provide this assay (ie, QuantiFERON- TB Gold or T-Spot-TB), analysis should be done at central lab.

Table 5.1-1: Screening / Baseline and Study Evaluations - Year 1 (IM103116)																		
				M 1			**M 3**			**M 6**			**M 9**				**M 12**	**Notes**
	Screen [a]	**Randomize/ Baseline[b]**	**W 2**	**W 4**	**W 6**	**W 8**	**W 12**	**W 16**	**W 20**	**W 24**	**W 28**	**W 32**	**W 36**	**W 40**	**W 44**	**W 48**	**W 52[c]**	
Procedure	**D -42**	**D 1**	**D 15**	**D 29**	**D 43**	**D 57**												
CsA/TAC Trough	X*																	*__All subjects__-Use local lab value for entry criteria. Hold AM dose of CNI until trough level drawn. Should also be drawn at time of SAR/PTLD/PML. Refer to section 5.3.5.2
Serum Creatinine (to estimate cGFR)	X*		X	X		X												* Two cGFR values are required to demonstrate stable renal function prior to randomization, once at the screening evaluation and at one additional time point within 2 to 12 weeks prior to screening. Should also be drawn if there is clinical suspicion of AR/PTLD/PML. Refer to section 5.3.5.2

Table 5.1-1: Screening / Baseline and Study Evaluations - Year 1 (IM103116)																		
				M 1			**M 3**			**M 6**			**M 9**				**M 12**	**Notes**
	Screen [a]	**Randomize/ Baseline[b]**	**W 2**	**W 4**	**W 6**	**W 8**	**W 12**	**W 16**	**W 20**	**W 24**	**W 28**	**W 32**	**W 36**	**W 40**	**W 44**	**W 48**	**W 52[c]**	
Procedure	**D -42**	**D 1**	**D 15**	**D 29**	**D 43**	**D 57**												
Pregnancy Test	X	X	X	X	X	X*	X	X*	X*	X	X*	X*	X	X*	X*	X*	X	All woman of child-bearing potential (WOCBP) must have urine or serum pregnancy test performed within 24 hours prior to the first dose of belatacept, & may be performed at either screening or baseline visit. Negative pregnancy tests are required prior to each belatacept infusion. A **positive** urine result should be confirmed using a quantitative serum test performed at a local lab. * Not required for CNI subjects at specified visits.

[a] Screening = enrollment **(Must occur within 42 days prior to randomization)**

[b] For statistical purposes, Day 1 /Randomization will be considered baseline for all analyses unless noted.

[c] Information on subject and allograft survival will be collected for all subjects through 12 months post-randomization.

Table 5.1-2: Study Evaluations - Year 2 (IM103116)															
			M 15			**M 18**			**M 21**				**M 24/ ET[a]**	**8, 12, 24 Week Follow-up**	**Notes**
Procedure	**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**		
Call IVRS	X	X	X	X	X	X	X	X	X	X	X	X	X*		* CNI subjects do not need to call IVRS except to report discontinuation from study drug.
Physical Examination													X		
Neurologic Exam						X							X		Also required if change in neurologic status based on clinical signs and symptoms is observed (Sect 5.3.8)..
Vital Signs	X*	X*	X*	X*	X*	X	X*	X*	X*	X*	X*	X*	X	X*	BP (sitting position), heart rate, temperature & respiratory rate will be taken. Measure blood pressure and heart rate **pre-dose and at the end of the infusion** for belatacept treated subjects * Not required for CNI subjects at phone visits.
Standardized BP						X							X		Refer to Section 5.3.2.1
Weight						X							X		Weight prior to infusions for belatacept treated subjects.
Adverse Events Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 5.1-2: Study Evaluations - Year 2 (IM103116)															
			M 15			**M 18**			**M 21**				**M 24/ ET[a]**	**8, 12, 24 Week Follow-up**	**Notes**
Procedure	**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**		
Peri-Infusion AE Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X		Following every belatacept infusion, subject must be contacted within 48 hours to confirm if they have had any adverse event within 24 hrs of their infusion.
[redacted]	[redacted]														
CENTRAL LABS															All labs should be drawn prior to dosing for belatacept treated subjects.
Chemistry Panel: w/ c GFR						X							X		Nothing to eat/drink, except water, for 8 hours prior to laboratory collection.
[redacted]													[redacted]		[redacted]
TAC/CsA Trough Levels						X							X		Hold AM dose of CNI until trough drawn. Should also be drawn if there is clinical suspicion of AR/PTLD/PML. Refer to section 5.3.5.2
Immunoglobulins & Isotypes, IgG1, 2, 3, 4						X							X		Also collected at the time of graft loss and suspected AR.
CBC with diff													X		

Table 5.1-2: Study Evaluations - Year 2 (IM103116)															
			M 15			**M 18**			**M 21**				**M 24/ ET[a]**	**8, 12, 24 Week Follow-up**	**Notes**
Procedure	**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**		
Hemoglobin A1c													X		
Urinalysis / Spot Urine						X							X		Parameters include protein, glucose & blood; urine protein, creatinine, protein/creatinine ratio.
[redacted]						[redacted]							[redacted]	[redacted]	[redacted]

Table 5.1-2: Study Evaluations - Year 2 (IM103116)															
			M 15			**M 18**			**M 21**				**M 24/ ET[a]**	**8, 12, 24 Week Follow-up**	**Notes**
Procedure	**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**		
[redacted]						[redacted]							[redacted]	[redacted]	[redacted]
Gene Expression / Transcriptional Profiling (mRNA)													X		Must also obtain for any suspected AR. For belatacept subjects, draw prior to infusion.
Donor Specific Antibodies (DSA)													X		Must also obtain for any suspected AR. For belatacept subjects, draw prior to infusion.

Table 5.1-2: Study Evaluations - Year 2 (IM103116)															
			M 15			**M 18**			**M 21**				**M 24/ ET[a]**	**8, 12, 24 Week Follow-up**	**Notes**
Procedure	**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**		
Anti-Viral T-cell Response													X		**<u>USA subjects only.</u>** Must also obtain for any suspected PTLD/PML. For belatacept subjects, draw prior to infusion.
Belatacept Infusion Visit	X*	X*	X*	X*	X*	X	X*	X*	X*	X*	X*	X*	X		Dose based on D1 body wt & will not be modified unless there is a change of ≥ 10% of the D1 weight. Measure blood pressure and heart rate **pre dose and at the end of infusion.**for belatacept subjects only. *Home Infusion services can begin at Week 16 for belatacept subjects. (Excluding vists for months 3,6, 9, 12, 18, 24).
CNI Visits	X*	X*	X*	X*	X*	X	X*	X*	X*	X*	X*	X*	X		*allowable phone visit - Assess for AEs & concomitant medications. Should occur within the prescribed visit window for the specified visit.

Table 5.1-2: Study Evaluations - Year 2 (IM103116)															
			M 15			**M 18**			**M 21**				**M 24/ ET[a]**	**8, 12, 24 Week Follow-up**	**Notes**
Procedure	**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**		
Biopsy															At any time of suspected acute rejection or suspected PTLD.
LOCAL LABS															
Serum Creatinine															Should also be drawn if there is clinical suspicion of AR/ PTLD/PML. Refer to section 5.3.5.2
Pregnancy Test	X*	X*	X*	X*	X*	X	X*	X*	X*	X*	X*	X*	X	X*	Negative pregnancy tests (urine or serum) are required prior to each belatacept infusion. A **positive** urine result should be confirmed using a quantitative serum test performed at a local lab. 8 week post last dose (WOCBP). * Not required for CNI subjects at specified visits.

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

5.2 Study Materials

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

- On-Site Investigator File (OSIF)
- Pharmacy Logs
- Sample source documents, where applicable
- BMS-224818 Investigator Brochure
- Site manual of operation for the interactive voice response system (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. If required, 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 as outlined in Table 5.1-1 and Table 5.1-2. Vital signs will be performed throughout the study. Standard clinical laboratory tests will be performed throughout the study and at early termination/ discontinuation, if applicable.

Physical examinations may be performed by a Doctor of Medicine, Doctor of Osteopathy, Physician's Assistant or Nurse Practitioner.

A chest x-ray (CXR) is required for all subjects at the screening visit unless a previous CXR, performed within 6 calendar months of enrollment, is negative for any evidence of TB. (See also TB exclusion criterion in Section 3.2.2).

Urine or serum pregnancy tests will be performed prior to dosing for all WOCBP. If any female subject becomes pregnant, she will be immediately discontinued from study medication.

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 a supplemental 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 patient's medical file and should not be provided unless specifically requested from the Sponsor.

5.3.1 Follow-up Safety Period

8-Week Post Last Dose Safety Follow-up Visit

For belatacept-treated subjects who complete the study and transition to commercially available Nulojix®, as well as CNI-treated subjects, the following procedures are required. This visit may be conducted by phone.

- Assess for AEs
- Concomitant medications

For belatacept-treated subjects who discontinue belatacept **(either prematurely or after week 104)**, and return to non-belatacept-based immunosuppression, the following procedures are required:

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

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

For belatacept subjects who discontinue belatacept **(either prematurely or after week 104)**, completed the study and return to non-belatacept-based immunosuppression for their standard of care, the following procedures are required:

- Assess for AEs
- Immunogenicity

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

5.3.2 Vital Signs

Vital signs will be recorded as outlined in Table 5.1-1 and Table 5.1-2. Sitting arterial systolic and diastolic blood pressure and radial artery pulse rate will be measured.

5.3.2.1 Standardized Blood Pressure Monitoring

BP measurements should be done soon after the subject's arrival at the clinic, before venipuncture, study medication administration, and any other study procedures scheduled for the visit are performed.

Instructions for Subjects

CNI subjects should withhold the AM dose of CNI until after BP measurements are completed for the visit.

No smoking is permitted within 2 hours prior to a BP measurement. No alcoholic beverage consumption is permitted within 6 hours prior to a BP measurement. Usual caffeine intake is permissible. (Appendix 1)

Standardization of Procedures

BP and heart rate are to be measured with a calibrated automatic BP monitor. If a calibrated automatic BP monitor is not available, standardized BP measurements are to be performed with a calibrated aneroid device or mercury sphygmomanometer.

At entry, if there is a difference in BP readings between arms, the arm with the higher reading should be used. The same arm should be used at all visits for BP measurements throughout the study.

The following instructions are standard, irrespective of the device being utilized:

Situate the subject in a quiet environment so that the subject may **rest for at least 10 minutes in the seated position.**

Select an appropriately sized cuff. Bladder width should be at least 40% of the arm circumference, and bladder length should be at least 80% of the arm circumference.

With feet flat on the floor, the back against the chair, and with the arm resting on a table or other support so that the midpoint of the cuff is at the level of the heart, obtain 3 replicated measurements at least 1 minute apart (to permit the release of blood trapped in the arm veins). If 3 consecutive seated DBP readings are not within 8 mm Hg of each other, an additional 2 BP readings must be obtained (total = 5). The mean SBP and DBP from these measurements will be used as the subject's BP for this assessment.

Record the measurements with the date and time on source documents and appropriate CRF pages.

Refer to Appendix 1.

5.3.3 Physical Measurements

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

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

5.3.4 Physical Examination

Patients will undergo a routine physical examination during the Screening Phase and at specified visits as outlined in Table 5.1-1 and Table 5.1-2.

5.3.5 Laboratory Assessments

Blood and urine samples will be obtained as outlined in Table 5.1-1 and Table 5.1-2 for clinical laboratory evaluations. A central laboratory vendor will be utilized for this study and a laboratory manual will be provided to each site. Patients should be fasting for a minimum of 8 hours prior to specified blood draws as outlined in Table 5.1-1 and Table 5.1-2 and Section 5.3.5.1. However, if a patient 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.

5.3.5.1 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, C-reactive protein, Calculated GFR (cGFR)

[redacted]

*Note: For clarification, fasting is - nothing to eat/drink, except water, for 8 hours prior to procedures required.

Urinalysis (UA)/ Spot Urine (random void): Parameters include dipstick UA for protein, glucose and occult blood; urine protein and creatinine concentrations for calculation of a random urinary protein/creatinine ratio. If occult blood, protein or glucose dipstick results are positive, a microscopic examination will be done.

Immunoglobulins: IgG, IgM, and IgA. Total IgG (4 sub-types of IgG: IgG1, IgG2, IgG3, and IgG4).

EBV Serology: as outlined in Table 5.1-1 and Lab Manual

[redacted]

Anti-viral T-cell Response: as outlined in Table 5.1-1 and Table 5.1-2.

Transcription Profiling (mRNA): as outlined in Table 5.1-1 and Table 5.1-2.

Donor Specific Antibody (DSA): as outlined in Table 5.1-1 and Table 5.1-2.

CsA/TAC Trough: as outlined in Table 5.1-1 and Table 5.1-2.

IGRA- Interferon gamma release assay: QuantiFERON-TB Gold or T-Spot. Either assay may be done at local lab if assay is supported by local lab. If neither assay is available at local lab, assay must be done at central lab. A 37ºC incubator is required for processing samples if using the central lab. (Refer to lab manual for detailed instructions).

5.3.5.2 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.

IGRA (Interferon gamma release assay): such as QuantiFERON-TB Gold or T-Spot TB.

Serum Creatinine: as outlined in Table 5.1-1 and Table 5.1-2. Two cGFR values are required to demonstrate stable renal function prior to randomization, once at the screening evaluation and at one additional time point within 2 to 12 weeks prior to screening. If a historical value within 12 weeks of screening is not available, a second cGFR must be obtained prior to randomization. (This value must be at least 2 weeks after the screening value). A serum creatinine concentration must also be obtained at the time of any episode of suspected acute rejection or PTLD.

Trough CsA/TAC Blood Levels (for CNI-treated Subjects Only): as outlined in Table 5.1-1 and Table 5.1-2. Must also be obtained at the time of suspected acute rejection or PTLD

NOTE: Additional specimens needed for the periodic monitoring of CNI trough levels as part of routine clinical patient management, should be obtained and determined locally, per local standard of care. The results of the locally determined whole blood tacrolimus trough levels will also be collected and entered into the database.

Pregnancy Test: (serum/urine), as outlined in Table 5.1-1 and Table 5.1-2. A serum or urine 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 (baseline or Day 1). Urine or serum pregnancy testing must be performed in all WOCBP within 24 hours prior to dosing at all other study visits (including 'infusion-only' visits for belatacept subjects). Urine pregnancy testing kits will be provided by a central laboratory; 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.

Any laboratory test result that the investigator considers clinically significant must be recorded on the appropriate AE page of the CRF.

5.3.5.3 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.

5.3.6 Kidney Allograft Biopsy

Investigators must perform allograft biopsies to assess for suspected acute rejection in subjects who meet protocol-specified clinical criteria for acute rejection.(Refer to Table 5.3.6-1) Routine biopsies performed according to local practice, in the absence of clinical suspicion of acute rejection, PTLD or other medical cause are not permitted.

Table 5.3.6-1: Criteria for Clinically Suspected AR
1. An unexplained rise of serum creatinine ≥ 25% from baseline creatinine
2. An unexplained decreased urine output
3. Fever and graft tenderness
4. A reason other than those listed above and the subject was treated for this episode

Baseline SCr is defined as the average of the 3 preceding SCr values determined by local laboratories. Serum creatinine values must be obtained from samples drawn on different days. Only local laboratory (as opposed to central laboratory) SCr values will be used for establishment of the baseline SCr and for determining rises in SCr that should trigger performance of an allograft biopsy.

For all biopsy specimens, the tissue should be stained and graded according to the Banff 97 & 2007 update to the Banff 97 classification of kidney transplant pathology.[31] [32] Initial grading of allograft biopsies should be performed locally in order to guide acute treatment decisions. All allograft biopsies will be reviewed by a central pathologist. These biopsy samples will be provided to the central pathologist in a blinded fashion. In cases of disparity in the interpretation of the renal graft biopsy, for study analysis purposes, the grading by the central pathologist will supersede the local interpretation. If the central pathologist is unable to provide an interpretation, the local pathology reading will be used for analysis purposes.

The preparation and shipment of biopsy specimens to the central pathologist will be detailed in a separate manual to be provided to the investigator at or before the time of study initiation.

Follow-up Biopsy of a Documented Acute Rejection

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

5.3.7 Diagnosis and Treatment of Acute Rejection

Signs and symptoms consistent with AR include worsening renal function (≥ 25% increases from baseline SCr) and/or other clinical signs (for example unexplained decreased urine output or fever and graft tenderness) (See Table 5.3.6-1 above.).

Additionally, other factors affecting renal function (eg, dehydration, urosepsis, drug toxicity, polyoma viral infection, etc) should be evaluated.

Unless a biopsy is medically contraindicated (eg, hemorrhagic risk and the subject is not able to receive plasma/concentrated factors/etc), no subject, including a CNI-treated subject, should be

treated for AR without a biopsy 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 any treatment for suspected AR, the following procedures/test shall be completed:

a) Kidney allograft biopsy: the tissue should be stained and graded as specified in Section 5.3.6.

b) Initial grading of allograft biopsies should be performed locally in order to guide acute treatment decisions. The preparation and shipment of biopsy specimens to the central pathologist will be detailed in a separate manual to be provided to the investigator at or before the time of study initiation.

c) Central laboratory blood samples for determination of the following:

   a. All patients: serum creatinine concentration, DSA and transcriptional profiling;

   b. Subjects at U.S. sites only: immune cell phenotyping and T-cell response testing;

   c. All subjects randomized to continue CsA/TAC treatment: CsA/TAC levels; and

   d. All subjects randomized to belatacept treatment: Immunogenicity testing and PK (trough) samples.

Treatment of suspected AR should be based on the local biopsy reading and should be consistent with standard practice.

Definition of Graft Loss

Graft loss is defined as either functional loss or physical loss. Functional loss is defined as either:

- A sustained level of GFR < 15 ml/min/1.73m^2 for ≥ 4 weeks as determined by the local laboratory
- Resumption of regularly scheduled dialysis treatments for a period of ≥ 56 days; or
- Re-transplantation.

5.3.8 Neurological Examination

Neurologic assessment (examination and history) will be performed at designated time points (see Table 5.1-1 and Table 5.1-2). A neurologist is **not** required for this assessment. The neurologic history will include the subject's description of any new neurological symptoms, such as: personality, memory, headaches, pain, seizures, impairment of consciousness, swallowing, vision, hearing, language function, coordination, gait, weakness, sensory alterations, sphincter disturbance, involuntary movements, time course of any new symptoms (onset and duration), corroboration of any complaints with other individuals, medical illnesses, and medications.

The neurologic exam will include assessment of mental status, gait, speech, cranial nerves, cerebellar function, deep tendon reflexes, sensory function and motor function. Any new or

worsening findings should be reported as an adverse event and evaluated with additional modalities and/or neurologic consultation as appropriate. In cases of unexplained neurological findings, a magnetic resonance imaging (MRI) study, a computed tomography (CT) scan and a cerebrospinal fluid (CSF) examination for John Cunningham (JC) virus should be considered. The BMS/ICON medical monitor (or designee) must be contacted.

Any new or worsening findings should be reported as an adverse event and evaluated with a follow-up neurologic exam, additional diagnostic modalities and/or neurologic consultation as appropriate. Supplemental CRF forms will be provided to collect information confirming completion of the neurologic assessment.

[redacted]

5.3.10 Diagnosis and Treatment of Hypertension

Hypertension will be as defined in this study according to the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure for subjects with chronic kidney disease.[33,34] Hypertension is defined as SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg or SBP < 130 mm Hg and DBP < 80 mm Hg while receiving antihypertensive medication or with a medical history of hypertension.

Intensity of treatment regimen is defined as the total number of antihypertensive medications used to control hypertension. All antihypertensive medications will be counted for the indication of hypertension in subjects with hypertension or controlled hypertension, since the antihypertensive effects are present irrespective of indication.

5.3.11 Diagnosis of New Onset Diabetes After Transplant (NODAT)

A subject who did not have diabetes prior to randomization and receives an anti-diabetic medication for a duration of at least 30 days will be considered to have new onset diabetes.

Additionally, a subject who meets the criteria below (set forth by a recent international consensus guideline)[34] and did not have diabetes prior to randomization will be considered to have new onset diabetes.

These criteria are summarized as:

- Symptoms of diabetes plus casual plasma glucose (PG) concentration ≥ 200 mg/dL (11.1 mmol/L)

OR

- Fasting plasma glucose (FPG) ≥ 126 mg/dL (7.0 mmol/L)

OR

- 2-hour PG ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (GTT) (75 g test)

AND

- A confirmatory laboratory test based on measurements of venous PG done on another day in the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation.

[redacted]

5.4 Efficacy Assessments

Calculated GFR and Serum Creatinine

Baseline measurements of SCr, albumin, and BUN for the calculated GFR assessment will be based on the last measurement prior to first dose on Day 1.

Calculated Glomerular Filtration Rate

Numerous formulae have been developed that incrementally improve the correlation between SCr and GFR by accounting for the effect of demographic and biometric factors. For this study, the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation will be used to estimate GFR. Accordingly, renal function will be estimated using one or the other of the following formulae, depending upon whether or not the local laboratory uses an "IDMS (isotope dilution mass spectrophotometry)-traceable" automated assay for serum creatinine; that is, an assay traceable to the standard reference material (SRM) maintained at the National Institute of Standards and Technology (NIST) [29]:

- For laboratories that **do use** a serum creatinine (SCr) assay that **is** IDMS-traceable:
  - GFR (mL/min/1.73 m^2) = 175 x $(SCr)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American)
- For laboratories that **do not use** a serum creatinine assay that is IDMS-traceable[29]:
  - GFR (mL/min/1.73 m^2) = 186 x $(SCr)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American)

Data for the procedures and assessments specified in this protocol should be submitted to BMS on the CRF. Additional procedures and assessments may be performed as part of standard of care; however, data for these assessments should remain in the patient's medical record and should not be provided to BMS, unless specifically requested from the Sponsor.

[redacted]

[redacted]

5.8.2 Events of Special Interest

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
- Tuberculosis 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.

5.9 Results of Central Assessments

Blood chemistry, serology and urinalysis results will be provided to the site via an investigator portal from the central laboratory. Evaluation of episodes of suspected acute rejection will

require real time assessment of serum creatinine, trough CNI levels and histology from the renal biopsies; these will be evaluated locally to guide patient management. Local laboratory assessments will be reported on the eCRFs.

Central pathology assessment of renal biopsies will not be provided to the sites. These data are not immediately available and will not be used for patient management. These data will be used for analytical purposes only.

[redacted]

Laboratory data 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.)

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 drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

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.

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.

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.

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. 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: See Contact Information list.

SAE Facsimile Number: See Contact Information list.

For studies capturing SAEs/pregnancies 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): See 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 laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the investigational product, it is discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during 56 days after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

The investigator must immediately notify the BMS and/or designee Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours 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 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 administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (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:

1. Serum aminotransferase (ALT or AST) elevations to > 3 times the upper limit of normal (ULN) for the reference laboratory

AND

2. Total serum bilirubin elevations to > 2 times the ULN, without initial findings consistent with cholestasis (elevated serum alkaline phosphatase),

AND

3. Absence of any other readily apparent causes of aminotransferase 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.

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.

The DMC will review accruing unblinded data on key outcomes to include death, graft loss, acute rejection, infections, and malignancies in the overall population as well as relevant subgroups to better assure an appropriate balance between the potential benefits and risks of therapy in the accumulating data set.

A DMC Charter will be prepared, which will include full details on the committee membership, responsibilities and how the Committee will function, to include frequency of meetings and types of data outputs for review and formal early termination criteria. Appropriate updates will be made to the protocol, as well.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

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

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

With a confidence level (one-sided) of 0.975 and assuming the true rates of patient and graft survival by Month 24 in both treatment groups is 93%, the sample size of 220 subjects per arm will afford 90% probability to rule out a difference of 8.3% (sample size based on 1000 simulations per Newcombe methodology).[36]

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

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

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

8.2 Populations for Analyses

The primary efficacy data set will include all randomized subjects (ITT). A secondary efficacy data set will include all randomized subjects who do not violate terms of the protocol that might affect the efficacy outcome (per-protocol). “Per-protocol” analyses will be performed at Month 24 on the primary endpoint and “key” secondary endpoints (Acute Rejection and Renal Function) only if the following occurs:

- More than 10% of the total number of subjects included into the “ITT” data set at Month 24 have significant protocol violations/deviations and consequently would be excluded from the “per-protocol” data set.
- Safety analyses will be based on all randomized and treated subjects.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

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

8.3.2 Secondary Endpoint(s)

- Patient and Functional Graft Survival
  - Proportion of subjects who survive with a functional graft at 12 months post-randomization
- Acute Rejection
  - The incidence and severity of clinically suspected, biopsy proven acute rejection at 12 and 24 months post-randomization
- Renal Function
  - Mean change in cGFR (per 4-variable MDRD equation) from baseline to 12 and 24 months post-randomization (% and absolute)
  - Slopes of cGFR and 1/serum creatinine, respectively from baseline as well as Month 3 to 12 and 24 months post-randomization
  - Proportion of subjects with > 5% and > 10% improvement over baseline in cGFR at 12 and 24 months post-randomization
  - Urine protein/ creatinine ratio (UPCR) at baseline, 3, 6, 12 and 24 months post-randomization
- Hypertension
  - Mean change in systolic and diastolic blood pressure and intensity of treatment regimen (defined as the total number of antihypertensive medications used to control hypertension) from baseline to 12 and 24 months post-randomization
- Donor Specific Antibodies (DSA)
  - Proportion of subjects with DSA at Baseline/Day 1, Months 12 and 24 post-randomization
- The frequency of symptom occurrence and symptom distress as measured with the MTSOSD-59R at baseline, Week 6, and 3, 6, and 12 months post- randomization
- Safety and tolerability of a belatacept in a conversion setting
  - All adverse events
  - Adverse events of special interest
  - Clinically significant changes in vital signs
  - Laboratory test abnormalities
  - Clinical tolerability of the drug

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics of recipients and donors will be summarized descriptively by means and standard deviations for continuous variables, and frequency distribution for categorical variables. Summaries will be performed based on all randomized subjects.

8.4.2 Efficacy Analyses

In the primary analysis of subject and graft survival, and calculated GFR, missing data will be imputed as described in the statistical analysis plan (SAP). Where it is not explicitly stated, analyses will be based upon ITT subjects.

Patient and Functional Graft Survival

The primary composite endpoint of patient and graft survival by 24 months will be summarized within each treatment group using point estimates of the proportion of patients surviving with a functioning graft, and the corresponding 95% CIs. The 95% CIs will also be generated for the difference between the belatacept regimen and CNI to assess the effect of belatacept stratified by baseline cGFR. Month 24 analyses will be performed using ITT subjects as well as per-protocol subjects.

The composite endpoint of patient and functional graft survival by 12 months post-randomization will be summarized using a similar method as for the 24 months analysis.

Acute Rejection

The incidence and severity of clinically suspected, biopsy proven acute rejection up to 12 and 24 months post-randomization will be summarized within each treatment group using point

estimates and 95% CIs. The 95% CIs will also be generated for the difference in rate of the acute rejection by 12 and 24 months between belatacept and CNI stratified by baseline cGFR. Month 24 summaries will be performed using ITT subjects as well as per-protocol subjects.

Additional descriptive sensitivity analyses (for example including borderline events) might be performed as specified in the SAP.

Renal Function

Descriptive summaries of mean calculated GFR (based on the 4-variable MDRD equation) and serum creatinine will be provided for each treatment group at baseline, Months 1, 3, 6, 9, 12, 15, 18, 21, and 24. Changes from baseline and Month 3 to the later time points will be summarized as well. Descriptive summaries of mean percent changes in calculated GFR from baseline to 12 and 24 Months will be provided by treatment group where Month 24 summaries will be based upon ITT subjects as well as per-protocol subjects. In addition 95% CI of the means will be provided.

A point estimate with two-sided 95% CI will be generated for the difference in mean percentage change of cGFR from baseline at Month 12 and Month 24, respectively, between belatacept and CNI.

The proportion of subjects with ≥ 5% and ≥ 10% improvement over baseline at 12 and 24 months will be summarized respectively.

To assess the trend in renal function, a linear mixed model will be used to analyze the mean changes in calculated GFR from multiple time-points (baseline and Month 3) to 12 and 24 months for each regimen with terms for treatment, time, and calculated GFR at baseline and adjusting for important baseline characteristics. A similar analysis in 1/serum creatinine will also be performed.

To diminish the contribution that patients with slower kidney disease progression have on the analysis of change in GFR over time and to further evaluate the treatment effect on renal function over time.[16] The time to cGFR < 15 mL/min/1.73m^2, graft loss or death from baseline and Month 3, respectively, in each treatment group will be summarized using Kaplan-Meier curves.

Urine protein/ creatinine ratio (UPCR) will be summarized descriptively by means and standard deviation by treatment group at baseline, 3, 6, 12, and 24 months post-randomization.

Hypertension

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

[redacted]

New Onset Diabetes Mellitus After Transplantation (NODAT)

Proportion of subjects who develop NODAT at 12 and 24 months post-randomization will be summarized using point estimates and 95% CIs within each treatment group. The 95% CIs will also be generated for the difference between the belatacept regimen and CNI.

8.4.3 Safety Analyses

All AEs and SAEs since randomization will be summarized by treatment group using proportions and incidence rates normalized by patient-years of exposure. Laboratory marked abnormalities will also be descriptively summarized. No statistical tests will be performed for AEs or laboratory marked abnormalities.

[redacted]

[redacted]

8.5 Interim Analyses

At Month 12 following randomization of the last subject, an interim analysis will be performed. The purpose of the interim analysis is to obtain study data to assess the evolving benefit risk profile of belatacept conversion at 12 months post-randomization. All of the above mentioned measures at or up to Month 12 will be assessed. Similar methods as those used for the 24-month analyses will be performed for the 12-month interim analysis. The interim analyses will be descriptive in nature, and no statistical tests will be performed.

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 an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

Representatives of BMS 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 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 (and designee) 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, re-location, 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 is 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

- non-study 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 will provide forms to facilitate inventory control if the 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.

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

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. 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:

- External Principal Investigator designated at protocol development
- Other criteria (as determined by the study team)

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)

11 LIST OF ABBREVIATIONS

Term	Definition
AE	Adverse Event
ALT	Alanine aminotransferase
AM	Morning
ANCOVA	Analysis of covariance
APC	Antigen-Presenting Cell
AR	Acute Rejection
AST	Aspartate aminotransferase
BKV	BK virus
BMS	Bristol-Myers Squibb
BMS-188667	CTLA4Ig (abatacept)
BMS-224818	LEA29Y (belatacept)
BP	Blood Pressure
BPAR	Biopsy-Proven Acute Rejection
BUN	Blood Urea Nitrogen
C_2	Plasma concentration 2 hours post-dose
CAN	Chronic Allograft Nephropathy
cGFR	calculated Glomerular Filtration Rate
CI	Confidence Interval
CMV	*Cytomegalovirus*
CNI	Calcineurin inhibitor
CRF	Case Report Form
CRO	Contract research organization
CsA	Cyclosporine A (cyclosporin)
CSBPAR	Clinically-Suspected, Biopsy-Proven Acute Rejection
CSF	Cerebral spinal fluid
CSR	Clinical study report
CXR	Chest X-ray
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee

Term	Definition
D_5W	Dextrose 5% in water for injection
DSA	Donor Specific Antibodies
EBER	EBV encoded RNA
EBV	Epstein-Barr virus
ECD	Extended Criteria Donors
EC-MPS	Enteric-coated Mycophenolate Sodium
ESR	Expedited Safety Report
ESRD	End-stage renal disease
EVR	Everolimus
FDA	US Food and Drug Administration
FPG	Fasting plasma glucose
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GTT	Glucose Tolerance Test
HbA1c	Hemoglobin A1c
HBV	Hepatitis B virus
HCG	Human Chorionic Gonadotropin
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Imunodeficiency Virus
HLA	Human Leukocyte Antigen
HRT	Hormone Replacement Therapy
HUS	Hemolytic Uremic Syndrome
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Identification
IEC	Independent Ethics Committee

Term	Definition
Ig	Immunoglobulin
IL	Interleukin
IMP	Investigational Medicinal Product
IGRA	Interferon gamma release assay
IRB	Institutional Review Board
IP	Investigational Product
ITT	Intent-To-Treat
IUD	Intrauterine device
i.v.	Intravenous(ly)
IVRS	Interactive Voice Response System
LDL	Low-density lipoprotein
LDT	Lymphocyte depleting therapy
LI	Less intensive
MedDRA	Medical Dictionary of Drug Regulatory Activities
MI	More intensive
MMF	Mycophenolate mofetil
MPA	Mycophenolic acid
MDRD	Modification of Diet in Renal Disease (study)
MFI	Mean Fluorescent Intensity
mRNA	Messenger ribonucleic acid
MRI	Magnetic resonance imaging
MTSOSD-59R	Modified Transplant Symptom Occurrence and Symptom Distress Scale-59R
mTOR	Mammalian target-of rapamycin
NIMP	Non-investigational medicinal product
NKF-K DOQI	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
NODAT	New Onset Diabetes After Transplantation
NSS	0.9% normal saline solution
NULOJIX	Commercial belatacept
OSIF	On-site investigator file

Term	Definition
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics
PG	Plasma Glucose
PK	Pharmacokinetic(s)
PML	Progressive multifocal leukoencephalopathy
PPD	Purified protein derivative
PRA	Panel Reactive Antibodies
PTDM	Post-Transplant Diabetes Mellitus
PTLD	Post-Transplant Lymphoproliferative Disorder
QoL	Quality of Life
RA	Rheumatoid Arthritis
ridit	relative to an identified distribution (analysis)
RO	Receptor occupancy
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SCD	Standard Criteria Donors
SCr	Serum Creatinine
SD	Standard Deviation
[redacted]	[redacted]
SmPc	Summary of Product Characteristics
SOP	Standard Operating Procedure
SRL	Sirolimus
SWFI	Sterile water for injection
TAC	Tacrolimus
TB	Tuberculosis
TG	Triglyceride
[redacted]	[redacted]
UACR	Urinary albumin / creatinine ratio
ULN	Upper limit of normal
UNOS	United Network of Organ Sharing

Term	Definition
UPCR	Urinary protein/creatinine ratio
USPI	US Package Insert
UTI	Urinary tract infection
VNS	Vial needle syringe
VSS	steady-state volume of distribution
WBC	White blood cells
WOCBP	Women of Childbearing Potential

APPENDIX 1 BLOOD PRESSURE MEASUREMENT USING AN ANEROID OR MERCURY SPHYGMOMANOMETER AND HEART RATE MEASUREMENTS REFERENCE

Measurements should be made, whenever possible, by the same certified or trained person throughout the study.

The subject should first rest for at least 10 minutes in the seated position.

1. The accuracy and reliability of blood pressure (BP) measurements will be improved by following these standardized steps:
   a) Situate the individual in a quiet environment with the feet flat on the floor, the back against the chair, and with the arm resting on a table or other support so that the midpoint of the cuff is at the level of the heart (see below).
   b) Place the manometer near eye level (tilted, floor models excepted), sufficiently close to read the calibration markings on the column.
   c) Select an appropriately sized cuff. Bladder width should be at least 40% of arm circumference; bladder length should be at least 80% of arm circumference (see below regarding subjects with large arms).
   d) Locate the brachial artery along the inner upper arm by palpation.
   e) Wrap the cuff smoothly and snugly around the arm, centering the bladder over the brachial artery. The lower margin should be 2.5 cm above the antecubital space. (Do not rely on cuff marking; find the center by folding the bladder in half.)
   f) Determine the level for maximal inflation by observing the pressure at which the radial pulse is no longer palpable as the cuff is rapidly inflated (palpated systolic) and by adding 30 mm Hg.
   g) Rapidly and steadily deflate the cuff. Then wait 15 to 30 seconds before reinflating.
   h) Position the stethoscope over the palpated brachial artery below the cuff at the antecubital fossa. Ear pieces should point forward. The bell head of the stethoscope should be applied with light pressure, ensuring skin contact at all points. Heavy pressure may distort the reading.
   i) Rapidly and steadily inflate the cuff to the maximal inflation level as determined in Step F above.
   j) Release the air in the cuff so that the pressure falls at a rate of 2 mm Hg per second.
   k) Note the systolic pressure at the onset of at least 2 consecutive beats (Phase I of Korotkoff sounds). BP levels should always be recorded in even numbers, and read to the nearest 2 mm Hg mark on the manometer.
   l) Record the diastolic pressure at the cessation of the Korotkoff sounds (Phase V). Listen for 10 to 20 mm Hg below the last sound heard to confirm disappearance, and then deflate the cuff rapidly and completely.
   m) Record the subject's position and the arm used for the measurement.
   n) Wait 1 minute before repeating the BP measurement (steps I-M) in the same arm to permit the release of blood trapped in the arm veins.

Special Pitfalls and Problems:

The Auscultatory Gap

In some subjects, particularly in those with hypertension, the sounds heard over the brachial artery when the cuff pressure is high disappear as the pressure is reduced, and then reappear at some lower level. This early, temporary disappearance of sound is called the 'auscultatory gap,' and occurs during the latter part of Phase 1 and Phase 2. Because this gap may extend over a range as great as 40 mm Hg, one may seriously underestimate the systolic pressure or overestimate the diastolic pressure, unless its presence is excluded by first palpating for disappearance of the radial pulse as the cuff pressure is raised.

Effect of Arm Position

The pressure in the arm increases as the arm is lowered from the level of the heart; conversely, raising the arm above this position lowers the pressure measurement. The effect is largely explained by hydrostatic pressure or by the effect of gravity on the column of blood. Therefore, when measuring indirect blood pressure, the subject's arm should be positioned so that the midpoint of the cuff is at the level of the heart. This location of the heart is arbitrarily taken to be at the junction of the fourth intercostal space and the lower left sternal border. Attention to the position of the cuff in relation to the heart is particularly important when the subject is standing upright.

Subjects with Large Arms

In subjects with large upper arms, a longer and wider cuff is needed for adequate compression of the brachial artery. A cuff with a bladder width of 40% - 50% of the arm circumference should be used in all subjects to assure adequate BP measurements. In subjects with moderately large arms, a 15 cm wide cuff will generally be adequate. Determination of forearm BP should not be used because of the falsely elevated diastolic readings that occur with this technique.