A PILOT RANDOMIZED CONTROLLED TRIAL OF DE NOVO BELATACEPT-BASED IMMUNOSUPPRESSION IN LUNG TRANSPLANTATION

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Study ID: IM103-387

Draft: v 6.0
Date: 8 December 2017

TABLE OF CONTENTS

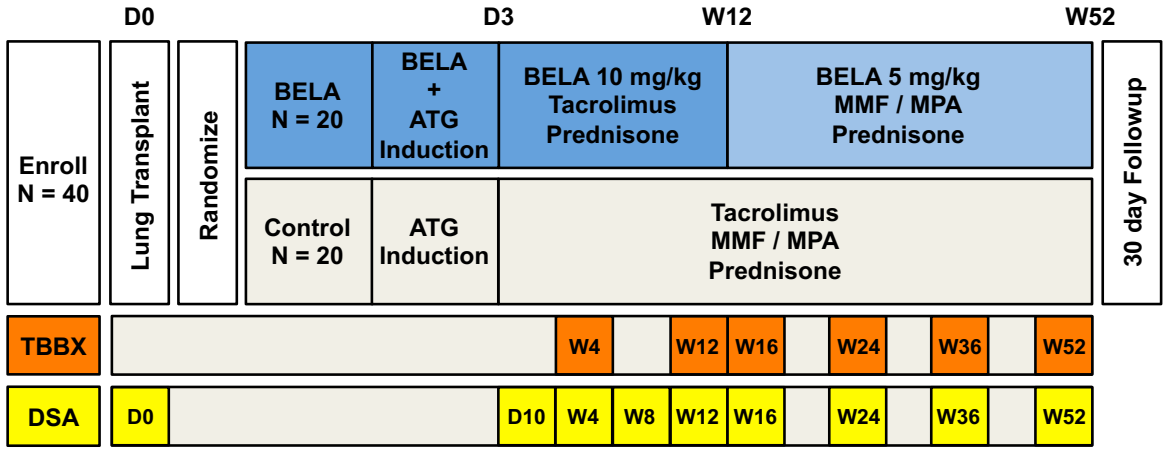
LIST OF ABBREVIATIONS

ACR	Acute Cellular Rejection
AE	Adverse Event
AMR	Antibody-Mediated Rejection
ATG	Anti-Thymocyte Globulin
ATS	American Thoracic Society
BAL	Bronchoalveolar Lavage
BELA	Belatacept
BMS	Bristol-Myers Squibb
BOS	Bronchiolitis Obliterans Syndrome
CARV	Community-Acquired Respiratory Virus/Viral
CBC	Complete Blood Counts
CFR	Code of Federal Regulations
CIP	Cellular Immunophenotyping
CKD	Chronic Kidney Disease
CLAD	Chronic Lung Allograft Dysfunction
CMP	Comprehensive Metabolic Panel
CMV	Cytomegalovirus
CNI	Calcineurin Inhibitor
DCC	Data Coordinating Center
DSA	Donor-Specific HLA Antibodies
DSMB	Data Safety and Monitoring Board
EBV	Epstein-Barr Virus
ECLS	Extra-Corporeal Life Support
ECMO	Extra-Corporeal Membrane Oxygenation
FOB	Fiberoptic Bronchoscopy
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigens
HSV	Herpes Simplex Virus
IgG	Immunoglobulin G
IP	Investigational Product
IRB	Institutional Review Board
IS	Immunosuppression
ISHLT	International Society for Heart and Lung Transplantation
LB	Lymphocytic Bronchiolitis
MMF	Mycophenolate mofetil
MPA	Mycophenolic acid
PCR	Polymerase Chain Reaction
PGD	Primary Graft Dysfunction
PTLD	Post-Transplant Lymphoproliferative Disease
RAS	Restrictive Allograft Syndrome
RCT	Randomized Controlled Trial
SAB	Single Antigen Bead
SAE	Serious Adverse Event
TBBX	Transbronchial lung Biopsy
TMP/SMX	Trimethoprim/sulfamethoxazole
VZV	Varicella Zoster Virus

PROTOCOL SUMMARY

Title	A Pilot Randomized Controlled Trial Of De Novo Belatacept-Based Immunosuppression In Lung Transplantation
Précis	This open-label, pilot, randomized controlled trial (RCT) will compare the combination of Belatacept, mycophenolate mofetil (MMF) and prednisone to tacrolimus, MMF, and prednisone after lung transplantation. The primary endpoint is a composite of the development of donor-specific HLA antibodies (DSA), death, or re-transplantation.
Objectives	The primary objective of this pilot study is to assess the feasibility of conducting a pivotal RCT examining the efficacy and safety of Belatacept-based immunosuppression after lung transplantation.
Endpoints	The primary endpoint of this study is a composite of the development of DSA, death, or re-transplantation. Key secondary endpoints include the individual components of the composite endpoint, antibody-mediated rejection, acute cellular rejection, chronic lung allograft dysfunction, renal function, and infection 1 year after transplantation.
Population	40 adult lung transplant recipients
Phase	II
Number of Sites	2 sites: • Baylor University Medical Center at Dallas • Washington University School of Medicine in St. Louis
Study Agent	Belatacept 10 mg/kg on days 0, 7, 14, 28, 56, 84, then 5 mg/kg on days 112, 140, 168, 196, 224, 252, 280, 308, 336, and 364
Study Duration	3 years
Participant Duration	1 year + 30 day follow-up

STUDY SCHEMATIC



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2. INTRODUCTION

2.1. BACKGROUND INFORMATION

Belatacept is a selective costimulation blocker that prevents T-cell activation. Belatacept is a fusion protein consisting of high-affinity receptor for CD80 and CD86 expressed on the surface of antigen-presenting cells and the Fc portion of human IgG. By binding CD80 and CD86, Belatacept blocks the second signal of T-cell activation thereby promoting anergy.

2.2. RATIONALE

Lung transplantation is the ultimate treatment for patients with end-stage lung disease, and approximately 2000 patients undergo lung transplantation annually in the United States. However, long-term outcomes after transplantation remain disappointing, and the median survival after transplantation is approximately 5.5 years (1). Infection and primary graft dysfunction (PGD) are the most common causes of death in the first year after transplantation, but chronic lung allograft dysfunction (CLAD) is the leading cause of death beyond the first year (1). Different clinical phenotypes of CLAD have been defined including classic bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS), and the incidence of CLAD approaches 50% within 3 years of transplantation (2-4). There is no effective evidence-based treatment for CLAD, and it typically follows a progressive clinical course ultimately resulting in allograft failure and death (4-6). Indeed, the median survival after the diagnosis of CLAD is approximately 3 years, and studies have consistently shown that patients who develop CLAD have a significantly worse quality of life (6, 7). Clearly, lung transplant recipients urgently need strategies to prevent or delay the onset of CLAD to improve survival after transplantation.

The exact pathogenesis of the different phenotypes of CLAD remains unclear. Studies have consistently identified multiple clinical risk factors including primary graft dysfunction (PGD), acute cellular rejection (ACR), lymphocytic bronchiolitis (LB), and the development of donor-specific human leukocyte antigens (HLA) antibodies (DSA) (2, 8-12). DSA appear to play a central role in the development of CLAD. Studies have consistently identified the development of DSA as an independent risk factor for the development of CLAD (11, 12). Furthermore, DSA cause antibody-mediated rejection (AMR) and are associated with an increased risk of high grade and recurrent ACR as well as LB (13, 14). In addition, DSA may mediate the increased risk of CLAD associated with PGD (15). Lastly, experimental data suggest that DSA have a direct pathogenic role in the development of CLAD (16-18). These data are consistent with the experience with DSA in kidney transplantation (19). However, the development of DSA after lung transplantation is significantly more frequent than after kidney transplantation. Indeed, single center studies have reported an incidence of DSA after lung transplantation ranging between 25-50%, and an incidence of 39% over the first 120 days after transplantation was reported in a recent prospective multicenter study (11, 12, 20). Together, these findings demonstrate that DSA are common early after lung transplantation and are associated with an increased risk of ACR, LB, AMR and CLAD.

We hypothesize that Belatacept-based immunosuppression (IS) will result in a lower incidence of DSA development and improved clinical outcomes after lung transplantation.

2.3. POTENTIAL RISKS AND BENEFITS

2.3.1. KNOWN POTENTIAL RISKS

Some studies in kidney transplantation have demonstrated an increased risk of ACR among patients treated with Belatacept in the place of a calcineurin inhibitor (CNI) (21, 22). There have been no controlled studies of Belatacept in lung transplantation, but since the risk of ACR after

lung transplantation is significantly higher than after kidney transplantation, there may be an increased risk of ACR for those randomized to the Belatacept arm of this study. We have designed the study protocol to mitigate this potential risk. First, all study participants will be treated with rabbit anti-thymocyte globulin (ATG, Thymoglobulin®) for induction IS. This is considered a more intensive immunosuppressive induction agent than basiliximab (Simulect®) and clearly more intensive IS than no induction therapy. In addition, participants randomized to the Belatacept arm will be treated with the combination of Belatacept and Tacrolimus for the first 3 months after transplantation. This time period after transplantation carries the highest risk of ACR. Finally, we have implemented 2 additional bronchoscopies with transbronchial lung biopsies at days 120 (week 16) and 270 (week 36) to increase surveillance for ACR.

Another potential risk associated with Belatacept-based immunosuppression is post-transplant lymphoproliferative disease (PTLD) (22). This increased risk has been identified specifically among Epstein-Barr Virus (EBV) seronegative recipients of organs from seropositive donors. To minimize the risk of PTLD, we will exclude EBV seronegative patients from this study.

2.3.2. KNOWN POTENTIAL BENEFITS

Belatacept-based IS has been consistently associated with better kidney function than CNI-based therapy (21-23). We expect participants in this study to derive a similar benefit in kidney function. Furthermore, Belatacept-treated kidney transplant recipients appear to be less likely to develop DSA than CNI-treated recipients (23). The development of DSA after lung transplantation is significantly more frequent than after kidney transplantation, and DSA have been linked to all forms of lung allograft rejection. Thus, this potential benefit of Belatacept-based IS may result in better outcomes after lung transplantation.

3. OBJECTIVES AND PURPOSE

The primary objective of this pilot randomized-controlled trial (RCT) is to assess the feasibility of conducting a large-scale multicenter RCT examining the efficacy of Belatacept-based immunosuppression after lung transplantation. Objective assessments of feasibility include:

- **a.** Enrollment of 50% of eligible patients at the 2 centers
- **b.** Randomization of 80% of eligible patients within 4 hours of completion of transplantation
- **c.** Retention of 75% of randomized patients on the protocol
- **d.** Adherence to the study drug infusion protocol in 90% of those randomized to the Belatacept arm

4. STUDY DESIGN AND ENDPOINTS

4.1. STUDY DESIGN

This is a pilot 2-center open-label RCT comparing Belatacept-based immunosuppression to standard of care immunosuppression consisting of the combination of Tacrolimus, Mycophenolate Mofetil (MMF), and Prednisone.

4.2. STUDY ENDPOINTS

4.2.1. PRIMARY ENDPOINT

The primary endpoint of the study is a composite of the development of DSA, death, or re-transplantation after transplantation. Development of DSA has clearly been associated with all forms of lung allograft rejection (ACR, LB, AMR, and CLAD). This is a highly relevant clinical event and typically develops early after transplantation, making it an appealing surrogate endpoint.

4.2.2. SECONDARY ENDPOINTS

The following secondary endpoints are chosen because of their impact on outcomes after lung transplantation and will be assessed 1 year after transplantation:

- **a.** Individual components of the composite endpoint (DSA, re-transplantation, death).
- **b.** ACR International Society for Heart and Lung Transplantation (ISHLT) grade A1 or higher
- **c.** LB ISHLT grade B1R or higher
- **d.** DSA Immunoglobulin G (IgG) subclasses
- **e.** Complement binding (C1q-positive) and activating (C3-positive) DSA
- **f.** Definite AMR based on the ISHLT definition
- **g.** Probable AMR based on the ISHLT definition
- **h.** CLAD defined as BOS stage 1 or RAS
- **i.** CLAD-free survival
- **j.** Confirmed bacterial infection requiring antibiotic treatment
- **k.** Cytomegalovirus (CMV) infection requiring antiviral treatment
- **l.** Confirmed community-acquired respiratory viral infection (CARV)
- **m.** Chronic kidney disease (CKD) stage 3 as estimated by the Cockcroft-Gault equation
- **n.** Kidney function as estimated by the Cockcroft-Gault equation
- **o.** Malignancy excluding squamous cell and basal cell skin cancer
- **p.** Post-transplant Lymphoproliferative Disease (PTLD)
- **q.** Diabetes mellitus requiring medical treatment
- **r.** Systemic hypertension requiring medical treatment
- **s.** Hypercholesterolemia requiring medical treatment

5. STUDY ENROLLMENT AND WITHDRAWAL

5.1. INCLUSION CRITERIA FOR ENROLLMENT

- **a.** Adult between 18 to 70 years of age
- **b.** On the waiting list for lung transplantation
- **c.** Willingness to participate in this study and sign informed consent
- **d.** For women of child bearing potential, willingness to use highly effective contraception

5.2. EXCLUSION CRITERIA FOR ENROLLMENT

Individuals who meet any of the following exclusion criteria will be excluded from study participation:

- **a.** Requiring invasive mechanical ventilation immediately before transplantation
- **b.** Requiring extracorporeal life support (ECLS) (i.e., ECMO) immediately before transplantation
- **c.** Received treatment to deplete HLA antibodies before transplantation
- **d.** Having DSA immediately before transplantation (i.e., positive virtual crossmatch)
- **e.** Multi-organ transplant recipient (e.g., heart-lung, lung-liver, lung-kidney)
- **f.** Pregnant or breast-feeding
- **g.** Active infection with Hepatitis B virus
- **h.** Active infection with Hepatitis C virus
- **i.** Active infection with human immunodeficiency virus (HIV)
- **j.** Chronic infection with *Burkholderia cepacia* complex before transplantation
- **k.** EBV seronegative status

l. Participation in another interventional clinical trial
m. Any condition that in the opinion of the site PI introduces undue risk by participating in this study

5.3. STRATEGIES FOR RECRUITMENT AND RETENTION

We will recruit study participants from the 2 sites' lung transplant clinics or inpatient services (if appropriate candidates are hospitalized at the time of listing). We will screen and approach potential participants at the time of listing for transplantation. We will explain the study and the potential benefits and risks involved in participation to patients during the informed consent process. The study will not enroll children (< 18 years of age) and will not enroll vulnerable participants (i.e., those who lack the capacity to consent or those who may perceive coercion to participate). We recognize the importance of minorities and women in clinical research, and we will not exclude participants from this study based on race or gender. Race and gender characteristics of patients being listed for transplantation are proportionate to the underlying diagnoses and referral patterns. A targeted/planned enrollment table is shown below:

	Ethnic categories						
Racial categories	Not Hispanic or Latino			Hispanic or Latino			
	Female	Male	Unknown	Female	Male	Unknown	Total
American Indian	0	0	0	0	0	0	0
Asian	1	1	0	0	0	0	2
Pacific Islander	0	0	0	0	0	0	0
Black	2	3	0	0	0	0	5
White	11	14	0	3	4	0	32
More than 1 race	0	0	0	0	1	0	1
Unknown	0	0	0	0	0	0	0
Total	14	18	0	3	5	0	40

We plan to randomize 40 patients at the 2 sites over 15 months. Over the past 3 years, a mean 108 patients have undergone lung transplantation annually at the 2 sites, and in 2016, 123

patients underwent lung transplantation at the 2 sites. Based on these data, we expect that approximately 135 patients will undergo transplantation at the 2 sites over the 15-months study enrollment period. We have planned to enroll a conservative number of patients because we expect that some patients may be ineligible and others may not consent to participate. Nonetheless, we plan to screen all patients listed for transplantation at the 2 sites and approach those who are eligible to consent.

5.4. PARTICIPANT WITHDRAWAL OR TERMINATION

Participants are free to withdraw from study participation at any time upon request. The investigators may terminate study participation if a participant has an adverse event (AE), a serious adverse event (SAE), or any medical condition such that continued participation in the study would not be in the best interest of the participant. The investigators may withdraw participants randomized to the Belatacept arm from the study for any of the indications outlined in **5.4.1.**:

5.4.1. INDIVIDUAL PATIENT-SPECIFIC STOPPING RULES

a. Three episodes of ACR grade A2 or higher
b. Three episodes of LB grade B1R or higher
c. Development of CLAD
d. Development of AMR
e. Serious infectious complication that in the opinion of investigator warrants changing the maintenance immunosuppressive regimen
f. Malignancy including PTLD, but excluding skin cancer

Upon withdrawal from the study protocol, these participants will be treated with a regimen deemed most appropriate by the patient's primary transplant physician.

5.5. STUDY-WIDE STOPPING RULES

Circumstances that may warrant termination or suspension of the study include determination of unexpected, significant, or unacceptable risk to participants. Study-wide stopping rules will be based on the comparison of rates of the following clinical outcomes between the 2 treatment groups:

a. Incidence of DSA
b. Incidence of CLAD
c. Incidence of AMR
d. Incidence of serious infection that in the opinion of the investigator warrants changing the maintenance immunosuppressive regimen

Safety assessments will be made every 12 months after initiation of randomization, and the investigators will terminate or suspend the study if the Belatacept group has a significantly higher incidence of any of the above outcomes (**5.5.**a.-d.) than the standard of care immunosuppression group. In addition, the Data Safety and Monitoring Board (**DSMB**) may develop additional stopping rules for safety concerns. Safety data including AEs, SAEs, laboratory test abnormalities, and treatment failures will be presented by treatment group at each DSMB meeting. Summary statistics and/or plots of the key outcomes will be provided to the DSMB at each meeting to allow appropriate assessment of the relative risks and benefits. We do not plan to include a futility monitoring plan or an efficacy-stopping rule because this is a phase II trial with the potential for collecting valuable information for designing the subsequent clinical trial or identifying potential subgroups of interest.. The investigators will promptly inform

the IRB, Bristol-Myers Squibb (BMS), and the NIH and provide the reasons for temporary suspension or termination. If suspended, the study may resume once concerns about safety, protocol compliance, or data quality are addressed and satisfy the necessary regulatory agencies.

5.6. ETHICAL CONSIDERATIONS

The study will be conducted in the following manner:

a. In accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH), World Health Organization (WHO) and any local directives.
b. In compliance with the protocol.
c. The protocol, any amendments, and the subject informed consent will receive Institutional Review Board / Independent Ethics Committee (IRB/IEC) approval / favorable opinion before initiation of the study.
d. With personnel who are qualified by education, training, and experience to perform their respective tasks and that the study will not use the services of study personnel for whom sanctions have been invoked or where there has been scientific misconduct or fraud.
e. With signed, dated informed consent from each of the participants.
f. 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. The approved informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.
g. Inclusion of relevant safety information regarding dose / schedule of IP and any other drugs / procedures.
h. BMS and health authorities will have direct access to study records.
i. Inclusion of information outlining BMS support of the study (study drug, funding, etc.)

6. STUDY AGENT

Belatacept (Nulojix) will be provided by BMS for use in this study and will be stored and dispensed by the 2 sites' investigational drug service pharmacies. Based on experience in kidney transplantation, Belatacept will be dosed at 10 mg/kg on days 0, 7, 14, 28, 56, 84, then at 5 mg/kg on days 112, 140, 168, 196, 224, 252, 280, 308, 336 and 364, where day 0 is the day of transplant. After the initial 4 doses on days 0, 7, 14 and 28, subsequent doses may be given ± 3 days.

7. STUDY PROCEDURES AND SCHEDULE

7.1. RANDOMIZATION

Participant eligibility for randomization will be determined within 4 hours of completion of transplantation (transfer to the intensive care unit from the operating room).

7.1.1. INCLUSION CRITERIA FOR RANDOMIZATION

a. Provided written informed consent for participation in this study
b. Underwent single or bilateral lung transplant
c. Negative urine pregnancy test for women of child bearing potential

7.1.2. EXCLUSION CRITERIA FOR RANDOMIZATION

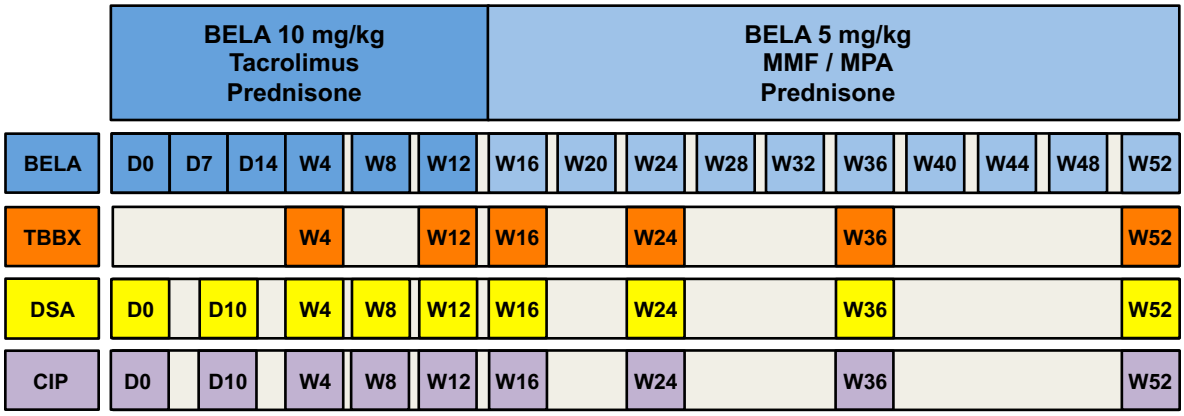
a. Allograft dysfunction requiring ECMO support
b. Delayed chest closure (i.e., primary chest closure not yet performed)
c. Severe coagulopathy and clinically significant bleeding in the opinion of the site PI
d. Any condition that in the opinion of the site PI introduces undue risk by participating in this study

7.1.3. RANDOMIZATION PROCEDURE AND GROUPS

Enrolled participants will be assessed within 4 hours of arriving in the ICU after transplant. Eligible participants will be randomized, within center, and blocked to prevent temporal bias using a computer-generated method with a 1:1 ratio to on one of 2 treatment assignments:

a. Belatacept-based immunosuppression
   i. Belatacept + Tacrolimus + Prednisone from day 0 through day 89, then
   ii. Belatacept + Mycophenolate Mofetil + Prednisone from day 90 through day 365
b. Tacrolimus + Mycophenolate Mofetil + Prednisone

7.1.4. BELATACEPT DOSING AND DIAGNOSTIC TESTING SCHEDULE



7.2. STUDY AND STANDARD OF CARE PROCEDURES

Routine clinical assessment of study participants will be performed according to the sites' clinical protocols. After discharge from the transplant hospitalization, patients are seen in the lung transplant clinic every 1-2 weeks for the first 3 months after transplantation then every 4 weeks through the 1st year after transplantation at both sites. These clinic visits include a medical history, medication history, physical examination, routine lab work, chest x-ray, and spirometry. Certified and trained respiratory therapists will conduct spirometry measurements according to American Thoracic Society (ATS) guidelines. Unscheduled visits are arranged on an as-needed basis if patients develop signs or symptoms of allograft dysfunction or another complicating condition. Participants will undergo fiberoptic bronchoscopy (FOB) with bronchoalveolar lavage (BAL) and transbronchial lung biopsies (TTBX) on days 28, 84, 112, 168, 252, and 365 (± 14 days). In addition, patients will undergo bronchoscopy with BAL and lung biopsies for clinical indications (i.e., if they develop signs or symptoms of allograft dysfunction).

7.3. LABORATORY PROCEDURES AND EVALUATIONS

Routine blood work including complete blood counts (CBC), comprehensive metabolic panels (CMP), blood CMV polymerase chain reaction (PCR), and trough levels of tacrolimus will be done according to the sites' clinical protocols twice weekly during the first 3 months after transplantation then monthly through the 1st year after transplantation. In between these time

points, patients may require unscheduled lab evaluations on an as needed basis. A urine pregnancy test will be performed on all women of child bearing potential at enrollment, at randomization, and before conversion from Tacrolimus to mycophenolate mofetil on day 90 for study participants randomized to Belatacept therapy.

Blood will be drawn for DSA testing on days 0 and 10 (± 3 days), and days 28, 56, 84, 112, 168, 252, and 365 (± 14 days). Samples will be tested for DSA using Luminex Single Antigen Bead (SAB) assay (One Lambda, Canoga Park, CA). If a sample tests positive for DSA, follow up testing will be performed for IgG subclasses (IgG 1, 2, 3 and 4), and markers of complement binding and activation (C1q and C3). The BUMC Transplant Immunology Lab will serve as the study core lab for antibody testing. Specimens from WUSM participants will shipped to the BUMC core lab for processing and analysis. Blood samples will be drawn at the same time points for cellular immunophenotyping (CIP) assays to be performed at both centers using pre-validated DuraClone IM flow cytometry panels (Beckman Coulter, Brea, CA) (24).

7.4. CONCOMITANT AND PROPHYLACTIC MEDICATIONS

All study participants will be treated with ATG (3 mg/kg divided into 3 daily doses starting on day 0) for induction immunosuppression. Tacrolimus will be initiated enterally or sublingually within the first 48 hours after transplantation and dosed to target a trough blood level of 8-15 ng/mL. On day 90, mycophenolate mofetil (MMF) will be substituted for tacrolimus in the Belatacept arm and will be dosed at 1 g twice daily (or converted to enteric coated mycophenolic acid (Myfortic) 720 mg twice daily in the event of gastrointestinal toxicity). In the control arm, MMF will be initiated intravenously at 1 g twice daily on day 0 and will be converted to enteral dosing at 1 g twice daily once the patient can take oral medications or enteric coated mycophenolic acid (Myfortic) 720 mg twice daily in the event of gastrointestinal toxicity. All study participants will be treated with methylprednisolone 500 mg intravenously before perfusion of the allograft during the transplant procedure, then methylprednisolone 0.5 mg/kg intravenously twice daily for 6 doses, then prednisone 0.5 mg/kg orally daily through day 14, then 0.2 mg/kg daily through day 30, then 0.1 mg/kg daily through day 180, then 5 mg daily through day 365.

All study participants will be treated with trimethoprim/sulfamethoxazole (Bactrim), dapsone, inhaled pentamidine, or atovaquone for *Pneumocystis jirovecii* prophylaxis throughout the study period. Recipients at risk for CMV infection (i.e., seronegative recipients of seropositive donors or seropositive recipients) will be treated with valganciclovir for CMV prophylaxis through day 365. Recipients who are not at risk for CMV infection (i.e., seronegative recipients of seronegative donors) will be treated with acyclovir or valacyclovir for herpes simplex virus (HSV) and varicella zoster virus (VZV) prophylaxis throughout the study period. Antifungal prophylaxis will be tailored to culture results from bronchoscopy specimens and pre-transplant cultures.

7.5. SCHEDULE OF EVENTS TABLE

Below is a table illustrating the schedule of study and clinical events. Time windows for each time point are listed above. Unscheduled visits may occur at any time point after randomization, and data from these unscheduled visits will be included in the study analyses as appropriate.

TIME POINTS																
Week		0		4	8	12	16	20	24	28	32	36	40	44	48	52
Day		0	10	28	56	84	112	140	168	196	224	252	280	308	336	365
EVENTS																
Screening	X															
Informed consent	X															
Medical history	X	X														
Pregnancy test	X	X				X										

Physical exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X														
CBC, CMP			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug level			X	X	X	X	X	X	X	X	X	X	X	X	X	X
CMV blood PCR			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest X-ray		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spirometry				X	X	X	X	X	X	X	X	X	X	X	X	X
DSA		X	X	X	X	X	X		X			X				X
CIP		X	X	X	X	X	X		X			X				X
TBBX				X		X	X		X			X				X
AE evaluation			X	X	X	X	X	X	X	X	X	X	X	X	X	X

8. SAFETY CONSIDERATIONS

8.1 SERIOUS ADVERSE EVENT DEFINITION

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

a. Results in death
b. 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)
c. Requires inpatient hospitalization or causes prolongation of existing hospitalization
d. Results in persistent or significant disability or incapacity
e. Results in a congenital anomaly or birth defect
f. 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 medical or surgical intervention to prevent one of the other serious outcomes listed in the definitions above. Examples of such events include, but are not limited to, intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.
g. Results in potential Drug Induced Liver Injury (DILI)
h. Results in suspected transmission of an infectious agent (pathogenic or nonpathogenic) via the study drug
i. Although pregnancy, overdose and cancer are not always considered serious by regulatory definition, these events must be handled as SAEs.

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

a. 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)
b. Elective surgery, planned prior to signing consent
c. Admissions as per protocol for planned medical or surgical procedure
d. Routine health assessment requiring admission for baseline/trending of health status (e.g. routine colonoscopy)
e. Medical / surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
f. Admission encountered for another life circumstance that carries no bearing on health status and requires no medical or surgical intervention (e.g. lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason.

8.2. SERIOUS ADVERSE EVENT REPORTING – Sponsor

Procedures for safety reporting to BMS (Sponsor) are described below:

a. All Serious Adverse Events (SAEs) that occur following a study subject's written consent in the study through 30 days of discontinuation of study drug dosing will be reported to BMS Worldwide Safety: Worldwide.Safety@BMS.com.
b. A MedWatch Form 3500A (Food & Drug Administration) reviewed and approved by BMS will be used to report all SAEs. The BMS protocol ID number will be included on all Form 3500A submitted by the Sponsor or Investigators.
c. Following the study subject's written consent to participate in the study, all SAEs, whether related or not related to the study drug, are collected, including those thought to be associated with protocol-specified procedures. The Investigators will report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure. For drugs with potential for delayed SAEs (e.g. delayed excretion of the parent or active metabolites), a longer follow-up period may be warranted to allow collection of these SAEs, laboratory tests and other assessments.
d. The Sponsor will reconcile the clinical database SAE cases (case level only) transmitted to BMS Global Pharmacovigilance & Epidemiology (GPV&E): Worldwide.Safety@BMS.com. Reconciliation will be performed every 3 months and prior to database lock or final data summary. BMS GPV&E will email, upon request from the Investigators, the GPV&E reconciliation report. Requests for reconciliation should be sent to aebusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigators determine a case was not transmitted to BMS GPV&E, the case will be sent immediately to BMS.
e. In accordance with local regulations, BMS will notify Investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the investigator brochure). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of a SUSAR report.
f. Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (e.g. animal) study, important safety recommendations from a study data monitoring committee, or Sponsor decision to end or temporarily halt a clinical study for safety reasons.
g. Upon receiving an ESR from BMS, the Investigators must review and retain the ESR with the investigator brochure (IB). Where required by local regulations or when there is a central IRB/IEC for the study, the Sponsor will submit the ESR to the appropriate IRB/IEC. The Investigators and IRB/IEC will determine if the informed consent requires revision. The Investigators should also comply with the IRB/IEC procedures for reporting any other safety information.
h. Suspected SAEs (whether expected or unexpected) shall be reported by BMS to the relevant local health authorities (either as expedited and/or in aggregate reports).
i. SAEs, whether related or not related to study drug, and pregnancies will be reported to BMS within 24 hours. SAEs will be recorded on a BMS approved MedWatch Form 3500A; pregnancies will be reported on a Pregnancy Surveillance Form.

SAE Email Address: Worldwide.Safety@BMS.com

SAE FAX Number: 609-818-3804

j. If only limited information is initially available, follow-up reports will be submitted. (Follow-up SAE reports will include the same Investigator term(s) initially reported.)
k. If an ongoing SAE changes in its intensity or relationship to the study drug or if new information becomes available, a follow-up SAE report will be sent within 24 hours to BMS (or designee) using the same procedures used for transmitting the initial SAE report.
l. All SAEs will be followed to resolution or stabilization.

8.3 SERIOUS ADVERSE EVENT REPORTING – FOOD & DRUG ADMINISTRATION (FDA)
Procedures for safety reporting to the FDA are described below:

a. Any event that is both serious and unexpected will be reported to the FDA as soon as possible and no later than 7 days (for a death or life-threatening event) or 15 days (for all other SAEs) after the Investigator or Institution's receipt of the information. BMS will be provided with a simultaneous copy of all adverse events filed with the FDA.
b. SAEs will be reported on MedWatch Form 3500A via electronic submission (http://www.accessdata.fda.gov/scripts/medwatch/). Alternatively, Form 3500A can be sent to the FDA at:

   MEDWATCH
   6500 Fishers Lane
   Rockville, MD 20852-9787
   FAX: 1-800-FDA-0178 (1-800-332-0178)

8.4 ADVERSE EVENT DEFINITION
An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing 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.

Causal relationship to the study drug is determined by a physician and will be used to assess all adverse events. The causal relationship can be one of the following:

a. Related: There is a reasonable causal relationship between study drug administration and the AE.
b. 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 effects 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.

8.5 NONSERIOUS ADVERSE EVENT REPORTING
A ***nonserious adverse event*** is defined as an AE not classified as serious

a. Nonserious adverse events will be provided to BMS in aggregate via interim or final study reports as specified in the agreement or as part of an annual reporting requirement (FDA IND).
b. The collection of nonserious AE information will begin at the initiation of the study drug. All nonserious AE (not only those deemed to be treatment-related) will be collected continuously during the treatment period and for a minimum of 30 days after the last dose of study drug.
c. Nonserious AEs will be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up will also be conducted for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

8.6 LABORATORY TEST ABNORMALITIES

All laboratory test results captured as part of this study will be recorded following institutional procedures and stored in a database maintained by the DCC. Test results that constitute SAEs will be documented and reported.

The following laboratory abnormalities will be documented and reported appropriately:

a. Any laboratory test result that is clinically significant or meets the definition of an SAE
b. Any laboratory abnormality that required the subject to have study drug discontinued or interrupted
c. Any laboratory abnormality that required the subject to receive specific corrective therapy
d. Potential Drug Induced Liver Injury (DILI)
   Whenever 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 will be reported as SAEs. Potential Drug Induced Liver Injury is defined as:

   1. ALT or AST elevation > 3 times upper limit of normal (ULN) AND
   2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
   3. No other immediately apparent possible causes of AST/ALT 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.

8.7 PREGNANCY

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half lives (~ 49 days) after product administration, the investigational product will be permanently discontinued.

Investigators will immediately notify BMS Worldwide Safety: Worldwide.Safety@BMS.com of the event using the Pregnancy Surveillance Form in accordance with SAE reporting procedures

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

8.8 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 will be reported as an SAE.

8.9 OTHER SAFETY CONSIDERATIONS

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate and reported accordingly.

8.10 DATA AND SAFETY MONITORING BOARD

The primary role of the Data and Safety Monitoring Board (DSMB) is to advise on scientific, safety, ethical and other policy issues relating to the study. DSMB members will:

a. Familiarize themselves with the study protocol, communicate by teleconference or email and develop a charter.
b. Propose appropriate analyses and meet periodically to review developing outcome and safety data.
c. Designate a board member to record and maintain minutes for all meetings.
d.

9. STATISTICAL CONSIDERATIONS

9.1. SAMPLE SIZE CALCULATION

All power computations are based on two sided tests with p value ≤ 0.05 considered statistically significant. They reflect a dichotomous composite primary endpoint: the development of DSA, death, or re-transplantation 1 year of transplantation. Power computations are based on various rates of development of the composite primary endpoint in the control group and in the Belatacept group. The incidence of DSA within 1 year of lung transplantation has been shown to be 50-60% in recent studies, and 15% of patients die or undergo re-transplantation within 1 year. However, no data currently exist on the incidence of DSA or survival in lung transplant recipients treated with Belatacept. Data in kidney transplantation suggest that the incidence of DSA among Belatacept-treated patients is approximately 5%. The table below provides sample size estimates for different DSA incidences in the 2 groups. For example, if the incidence of DSA in the Belatacept group is 20% and the incidence in the control group is 50%, the study will have 90% power to detect this difference if 58 subjects are enrolled in each study arm.

	Power	**Primary endpoint in control group**				
Primary endpoint in Belatacept group		35%	40%	45%	50%	60%
10%	90%	65	48	38	30	21
	80%	51	38	30	24	17
15%	90%	106	73	54	41	27
	80%	82	57	42	33	21
20%	90%	198	115	80	58	34
	80%	151	91	62	45	27
25%	90%	459	216	127	85	46
	80%	349	165	98	66	36

We plan to randomize 40 patients in a 1:1 fashion (20 per group); thus, we do not anticipate that this pilot study will be sufficiently powered to detect a statistically significant difference in the incidence of DSA between the 2 groups. However, the primary objective of the pilot study is to assess the feasibility of conducting a large scale pivotal RCT. Nonetheless, this pilot study will generate an estimate and 95% confidence intervals of the incidence of DSA development, death, and re-transplantation among lung transplant recipients treated with Belatacept-based immunosuppression. This will be important in making appropriate power computations and sample size calculations for the pivotal RCT.

9.2. STATISTICAL ANALYSES

We will compare baseline characteristics across groups using t-tests (or Wilcoxon-Rank sum tests if the data are not normally distributed) and chi-square tests. We will use survival models (Kaplan-Meier method using the log rank test and Cox proportional hazards models) to compare freedom from the composite primary endpoint between the 2 groups to enhance the power of the analyses. We will use Cox proportional hazards models to adjust for covariates that include age, gender, race, primary diagnosis, HLA mismatch status, PGD grade, episodes of acute rejection, and CARV infection. Because of the relatively small sample size in this pilot study, we will adjust for only one covariate at a time and will use separate Cox models for each covariate. Thus, we do not plan to develop risk models for the outcome. However, in the larger pivotal trial, we would have an opportunity to use more complex statistical models. Similarly, we will analyze secondary outcomes using the Kaplan-Meier method and the log rank test and Cox models. All of the analyses will be conducted on an intention-to-treat basis that includes all subjects who are randomized. However, we will also conduct secondary analyses on a per protocol basis, recognizing that these can be potentially biased.

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