CAMPath and BELimumab for the Induction of Donor Specific Humoral Transplant Tolerance in Sensitized Kidney Transplant Recipients To Improve Long-Term Allograft Survival

NCT03591380

PI: Arjang Djamali, MD
8/17/2020

CAMPBEL Trial: CAMPath and BELimumab for the Induction of Donor Specific Humoral Transplant Tolerance in Sensitized Kidney Transplant Recipients To Improve Long-Term Allograft Survival

Dated: August 17, 2020
Version 17.0

Principal Investigator:

Arjang Djamali, MD
University of Wisconsin
Department of Medicine
Division of Nephrology
1685 Highland Avenue
5142 MCFB
Madison, Wisconsin 53705
Phone: (608) 262-9306
Fax: (608) 262-6743
E-mail: axd@medicine.wisc.edu

Co-Investigator:

Dixon B. Kaufman, MD
University of Wisconsin
Department of Surgery/ Division of Transplant Surgery
600 Highland Avenue,
Madison, Wisconsin 53792
Phone: (608) 265 - 6471
E-mail: kaufman@surgery.wisc.edu

Revision History

Version Date	Version Number	Detail of Changes
01/21/2018	13.0	Initial approved version
08/02/2018	14.0	Correction of typographical errors and clarifications of text that could be interpreted inconsistently.
10/14/2019	15.0	Removal of Kristi Schneider, RN, MS, ANP as Co-Investigator; Clarification regarding the viral serology tests and the urine sample collection.
03/03/2020	16.0	Revision of sections 1.1, 1.3, 5.1.2 and 7.3
08/17/2020	17.0	Change of Principal Investigator

Table of Contents

Synopsis

Title	CAMPBEL Trial: CAMPath and BELimumab for the Induction of Donor Specific Humoral Transplant Tolerance in Sensitized Kidney Transplant Recipients To Improve Long-Term Allograft Survival
Clinical Phase	Open-label, single-arm, pilot-study
Sponsor	University of Wisconsin
Principal Investigator	Arjang Djamali, MD
Participating Sites	University of Wisconsin Hospital and Clinics
Accrual Objective	Kidney transplant recipients (n=5) will receive standard of care (SOC) therapy consisting of alemtuzumab and steroid induction with mycophenolic acid and tacrolimus maintenance immunosuppression, plus induction and treatment for 6 months with belimumab.

Study Design	This is an open-label pilot-study to evaluate the safety and efficacy of belimumab plus standard of care in the prevention of de novo donor specific antibody in adult subjects after kidney transplantation. We will enroll 5 adult, living donor kidney transplant recipients who are sensitized, evidenced by: Positive sum Donor Specific Antibody (DSA) <1000 MFI and/or Panel of Reactive Antibodies (PRA)>0%. The primary endpoint of this study is *de novo* DSA production. There are two main reasons for selecting this patient population for our proposed study. 1) Sensitized patients are known to have higher rates of *de novo* DSA production and 2) Patients with low levels of DSA (sum DSA<1000 MFI) will enable more fidelity in determining the DSA that is produced *de novo*. Kidney transplant recipients will receive the standard of care (alemtuzumab and steroid induction with mycophenolic acid and tacrolimus maintenance immunosuppression), plus six months of therapy with belimumab. Belimumab 10 mg/kg will be administered IV for 6 months at the following intervals: Day of transplant (Day 0), and then at Weeks 2, 4, 8, 12, 16, and 20 post-transplant.
Study Duration:	Subjects will be treated for 6 months with belimumab and followed for DSA production for 1 year post transplant.
Primary Study Objectives	In this proposal we plan ***to determine (a) whether the addition of belimumab to the standard of care (SOC: alemtuzumab and steroid induction with mycophenolic acid and tacrolimus maintenance immunosuppression) is safe and effective in preventing de novo DSA production at 1, 3, 6, 9, and 12 months post-transplant.*** ***Secondary efficacy endpoints will be 1) graft survival and function as determined by serum creatinine/eGFR and urine protein at 1, 3, 6, 9, and 12 months 2) rates of acute cellular and antibody mediated rejection, at 1, 3, 6, 9, and 12 months.***
Primary Outcomes	To determine whether the addition of belimumab to the standard of care (SOC: alemtuzumab and steroid induction with mycophenolic acid and tacrolimus maintenance immunosuppression) is safe and effective in preventing de novo DSA production 1, 3, 6, 9, and 12 months.
Secondary Outcomes	Secondary endpoints will be 1) graft survival and function as determined by serum creatinine/eGFR and urine protein at 1, 3, 6, 9, and 12 months 2) rates of acute cellular and antibody mediated rejection at 1, 3, 6, 9, and 12 months and 3) the nature, frequency, and severity of serious and non-serious adverse events ≥Grade 2 per Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.
Eligibility Criteria	Subjects 18-60 years of age receiving a living donor kidney transplant who are sensitized: PRA>0 and/or sum DSA<1000 MFI.

Inclusion

- Male or female subjects 18-60 years of age **Criteria**
- Planned to receive a living donor kidney transplant
- Sensitized patients: Positive DSA with sum MFI <1000, and/or PRA>0%
- Subjects must be capable of understanding the purpose and risks of the study and must sign a statement of informed consent.
- Female subjects must be post-menopausal, surgically sterilized, or she and/or sexual partner must be willing to use an acceptable method of birth control with a <1% failure rate as stated in the product label from time of study consent, during study participation, and for 16 weeks after the last dose of the study agent (i.e., contraceptive subdermal implant of levonorgestrel or etonogestrel, intrauterine device or intrauterine system, combined estrogen and progestogen oral contraceptive, Injectable progestogen, contraceptive vaginal ring, percutaneous contraceptive patches, or abstinence) for the duration of the study. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject. The documentation of male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner. Note: Mycophenolate mofetil (MMF) affects the metabolism of oral contraceptives and may reduce their effectiveness. As such, women receiving MMF who are using oral contraceptives for birth control should employ an additional method (e.g., barrier method). Mycophenolate can cause fetal harm when administered to a pregnant female. Use of mycophenolate during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations. Mycophenolate affects the metabolism of oral contraceptives and may reduce their effectiveness. As such, women receiving MMF who are using oral contraceptives for birth control should employ an additional method (e.g., barrier method) resulting in two reliable forms of contraception being used simultaneously before starting study treatments, during therapy, and for 6 weeks after stopping therapy; unless abstinence is the chosen method of contraception
- Female patients of childbearing potential must have a negative serum pregnancy test within 48 hours of transplant. Must be willing to use contraceptives from the time of study consent, during study participation, and for 16 weeks after the last dose of study agent. For sexually active men, condoms should be used during, and for at least 90 days after cessation of mycophenolate treatment. No sperm donation should be made during this period of time. For female partners of male subjects, it is recommended to use highly effective contraception during treatment and for 90 days after the last dose of mycophenolate
- No blood donation should be made by the study subjects during mycophenolate treatment and for at least 6 weeks after stopping mycophenolate treatment
- <u>If stricter female or male contraception requirements are specified in the countryspecific label for any study related therapies, they must be followed.</u>
- Male subjects must agree to use an acceptable method for contraception for the duration of the study.

Female patients of childbearing potential must have a negative serum pregnancy test within 48 hours of transplant. Must be willing to use contraceptives from the time of study consent, during study participation, and for 16 weeks after the last dose of study agent. Reproductive Status: Definition of Women of Child-Bearing Potential (WOCBP). WOCBP comprises women who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or who are not post-menopausal (see definition below). **Post-menopause is defined as**:

- Women who have had amenorrhea for 12 consecutive months (without another cause) and who have a documented serum follicle-stimulating hormone (FSH) level > 35 mIU/mL.
- Women who have irregular menstrual periods and a documented serum FSH level > 35 mIU/mL.
- Women who are taking hormone replacement therapy (HRT). **The following women are WOCBP:**
- Women using the following methods to prevent pregnancy: Oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as intrauterine devices or barrier methods (diaphragm, condoms, spermicides).
- Women who are practicing abstinence from intercourse from 2 weeks prior to administration of the 1st dose of study agent until 16 weeks after the last dose of study agent (Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are <u>not</u> acceptable methods of contraception) Women who have a partner who is sterile (eg, due to vasectomy).

WOCBP must be using an acceptable method of contraception to avoid pregnancy from the time of consent with <1% failure rate as stated in the product label throughout study participation, and for 16 weeks after the last dose of study drug in such a manner that the risk of pregnancy is minimized. Acceptable methods of contraception include: complete abstinence, any form of intra-uterine devices (without hormones), tubal sterilization or your partner has had a vasectomy.

Other acceptable forms of birth control include choosing one hormonal and one barrier method or double-barrier methods. Barrier methods include Essure®, male or female condom, diaphragm with spermicide, shield, cap with spermicide, contraceptive sponge, and spermicidals. Hormonal methods include oral contraceptive pills, transdermal patches, vaginal rings, progesterone-only, and injections. Periodic abstinence (for example, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.
- WOCBP must have a negative serum pregnancy test result (minimum sensitivity 25 IU/L or equivalent units of HCG) within 48 hours prior to transplant (and the first dose of study drug intraoperatively).
- Women must not be breast-feeding

Exclusion Criteria

Subjects are excluded from the study for the following reasons:

- ABO incompatible donor kidney Deceased
- donor
- KDPI□85%
- HLA identical or matched kidney
- Transplant other than kidney: has previously received a hematopoietic stem cell/marrow transplant or an organ transplant other than a kidney (with the exception of corneal transplantation)
- T- and/or B-cell positive crossmatch by complement dependent cytotoxicity or flow cytometry against the recipient
- Currently on any suppressive therapy for a chronic infection (s. uch as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria).
- Hospitalization for treatment of infection within 60 days of Day 0
- Use of parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti parasitic agents) within 60 days of Day 0
- Have a history of a primary immunodeficiency
- Uncontrolled infection or any other unstable medical condition that could interfere with the study
- Seropositive for HIV, HCV or HBV, except for hepatitis B surface antibody positive. If the HIV, HCV or HBV screening virology results are not available prior to transplantation then the most recent historical result (within the last 6 months) will be used.
- Have a significant IgG deficiency (IgG level < 400 mg/dl) Have an IgA deficiency (IgA level < 10 mg/dL)
- Prior therapy at any time: has ever received any of the following: B-cell targeted therapy (e.g., rituximab, other anti-CD20 agents, anti-CD2 [epratuzumab], antiCD52 [alemtuzumab], BLyS-receptor fusion protein [BR3], TACI fragment, crystallizable (Fc), belimumab), or IV cyclophosphamide
- Live vaccines within 30 days
- Have a history of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies
- Patients with a lymphocyte count <500/mm3
- Patients with evidence of current drug or alcohol abuse or dependence.
- Patients with venous access limitations likely to preclude monthly infusions
- Patients whom are unlikely to comply with scheduled study visits based on investigator judgment or has a history of substance abuse, psychiatric disorder or condition that may compromise communication with the investigator
- Myocardial infarction within 6 months prior to enrollment or New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiography evidence of acute ischemia or active conduction system abnormalities
- Diagnosis of liver cirrhosis or chronic viral hepatitis

- Female subject is pregnant or breast-feeding. Confirmation that the subject is not pregnant must be established by a negative serum □-human chorionic gonadotropin (□-hCG) pregnancy test result obtained during screening, and must be within 48 hours prior to transplant. Pregnancy testing is not required for postmenopausal or surgically sterilized women
- Patient has received other investigational drugs within 365 days before enrollment
- Serious medical or psychiatric illness likely to interfere with participation in this clinical study
- Have evidence of serious suicide risk including any history of suicidal behavior in the last 6 months and/or any suicidal ideation in the last 2 months or who in the investigator's judgment, pose a significant suicide risk
- Diagnosed or treated for malignancy within 5 years of enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low-risk prostate cancer after curative therapy.
- Have any other clinically significant abnormal laboratory value in the opinion of the investigator

Enrollment

Treatment Description

Treatment regimen: Alemtuzumab and steroid induction with mycophenolic acid and tacrolimus maintenance immunosuppression per standard of care plus belimumab.
Alemtuzumab: Alemtuzumab 30mg IV at time of induction (Day 0) during kidney transplant.

- □ Standard Steroid Taper: ○ Dexamethasone 100 mg IV on Day 0, ○ Dexamethasone 50 mg IV on Day 1 ○ Dexamethasone 18 mg IV on Day 2 ○ Dexamethasone 12 mg IV on Day 3 ○ Prednisone 30 mg on Day 4, and then taper per standard of care.

- Mycophenolic Acid (Myfortic): Mycophenolic acid 720 mg administered orally twice-daily starting post operatively on Day 0. Mycophenolate mofetil may be substituted per SOC. Dose may be adjusted as clinically indicated.
- Tacrolimus: Tacrolimus will be administered orally twice-daily starting post operatively on Day 0. Dosing at discretion of PI.
- Belimumab therapy. 10 mg/kg/dose will be administered IV for 6 months at the following intervals: at time of transplant (Day 0), then post-transplant at 2, 4, 8, 12, 16, and 20 weeks.

Study Procedures Potential subjects will be identified prior to kidney transplantation. Potential subjects will be approached about the study by the principal, co-investigators, or research staff.

Informed consent will be obtained before any study specific procedures are performed.

Belimumab: 10 mg/kg/dose will be administered IV for 6 months at the following intervals: at time of transplant (Day 0), then post transplant at 2, 4, 8, 12, 16, and 20 weeks.

Anti-HLA Antibody Levels: Anti-HLA antibody levels will be monitored prior to transplant and at 1, 3, 6, 9, and 12 months post-transplant per standard of care, using Luminex® microbeads to determine if treatment is effective in down-regulating *HLA class I and II DSA*.

Kidney Transplant Biopsy: A transplant kidney biopsy will be performed at time of transplant, and at 1 year post transplant per standard of care. Results will be collected and recorded from the electronic medical record.

Peripheral blood: will be collected prior to transplant, and at 1, 3, 6, 9 and 12 months and stored for future studies (if consented to) as described below.

- **Serum BAFF/APRIL levels:** If the subject agrees, we will obtain a sample for future BAFF/APRIL levels analysis in the serum collected at baseline, 1, 3, 6, 9, 12 months.

- **Immunoglobulin Analysis:** Quantification of total serum levels of Immunoglobulin levels (IgM, IgA, and IgG) will be performed prior to transplant and at 1, 3, 6, 9 and 12 months post transplant.
- **B Lymphocyte Analysis:** B-cell FACS panels will be used to measure changes over the course of therapy in the transitional, naïve, memory and plasma cell compartments. For the subsets of interest, absolute numbers of cells and proportions relative to all B cells for the individual subsets will be determined, as will activation status. Specifically we will address peripheral transitional, naive, memory and plasma cell populations prior to transplant and at 1, 3, 6, 9, and 12 months post-transplant. Further exploratory analyses will include the expression of BLyS receptors (BR3, TACI and BCMA) on B cells, frequency of alloreactive B cells (using tetramers) and an analysis of the effect of belimumab on IL-10 secreting B regulatory cells. Again these assessments may be performed prior to transplant and at 1, 3, 6, 9, and 12 months post-transplant.
- **T Lymphocyte Analysis:** Similar assessments will be made of T cell subsets prior to transplant and at 1, 3, 6, 9, and 12 months post-transplant. Specifically we will evaluate activated T cell and T regulatory cell populations.
- **Cytokine Analysis:** Quantification of serum BLyS and APRIL levels and cytokines/chemokines associated with T-helper skewing or activation will be performed prior to transplant and at 1, 3, 6, 9, and 12 months post-transplant

1. Background Information and Scientific Rationale

1.1 Background

Alloantibody directed against graft MHC antigens is a significant barrier to improving long-term kidney allograft survival. **It is estimated that greater than 50% of kidney allograft failures can be attributed to alloantibody** [1]. The source of alloantibody production are B-lymphocytes. ***BLyS*** (B lymphocyte stimulator)***, is a B cell survival factor that is required for B cell survival and differentiation***. *De novo* donor specific antibody (DSA) post kidney transplant is thought to occur in 20-50% of patients at 2 years and are associated with inferior graft survival [2-6]. A major unmet need in the kidney transplant field are safe and effective therapies to prevent the emergence of *de novo* MHC donor-specific alloantibody.

Belimumab (GSK1550188) is a recombinant, fully human IgG1λ monoclonal antibody that binds soluble BLyS with high affinity and inhibits its biological activity. In vivo, neutralization of BLyS blocks the differentiation of transitional B cells to naïve B cells and the survival of these B cell subsets, thus reducing the number of B cells in the mature resting stage [7]. Clinical efficacy of belimumab in SLE has been demonstrated through improvements in disease activity, steroid use, and risk of severe flare; autoantibody levels decreased with treatment [8]. Belimumab has been approved under the trade name BENLYSTA™ in the United States, Canada, and the European Union. We propose a clinical study whereby BLyS is inhibited with belimumab at the time of kidney transplantation in order to prevent the production of *de novo* DSA.

Support for this hypothesis currently exist in the literature. **1)** Preclinical studies in murine islet and cardiac transplantation have demonstrated efficacy of murine antiBLyS antibody in improving graft survival [9], and an increase in transitional B cells with BLyS blockade has been postulated as a potential mechanism for this improved graft survival [7,10]. **2)** Additionally, this transitional B-cell signature has been implicated in additional clinical tolerance studies [7,11] and **3)** elevated BLyS levels have been associated with the development of *de novo* DSA **4)** Additionally, BLyS levels were greatest in patients with poorly functioning grafts. It has also been reported that BLyS staining on kidney allograft biopsies correlates with staining for complement deposition, and that peripheral BLyS levels correlate with HLA-specific antibody levels and poor graft outcome. Elevated BLyS levels pre-transplantation have also correlated with an increased risk of AMR post-transplantation.[2,12,13,15, 16, 17, 18, 19]

Post kidney transplant, the incidence of *de novo* DSA has been estimated to occur in 20-50% of patients by 2 years [2-6]. Thus, while these patients have an induced level of relative T cell quiescence on current immunosuppressive regimens, B cell quiescence, as measured by the production of DSA, is not achieved in a large number of kidney transplant recipients. This suggests that current therapies are inadequate to control the humoral immune response. The addition of BLyS inhibition at the time of kidney transplant may prove to be a paradigm shift for our transplant recipients and the prevention of detrimental *de novo* DSA.

We therefore propose a clinical study where we will inhibit the B cell survival factor BLyS at the time of kidney transplantation, which we hypothesize will prevent the differentiation of alloreactive B cells, increase the transitional B cell population, and thus prevent the generation of *de novo* DSA.

Belimumab (GlaxoSmithKline, Inc.) The common name of the investigational product is BENLYSTA. The generic United States Adopted Name / International

NonProprietary Name (USAN/INN) is belimumab; the GlaxoSmithKline (GSK) code for the drug is GSK1550188. Belimumab is reconstituted in 4.8 mL sterile water and diluted in normal saline (250 mL). After reconstitution and dilution in normal saline, the material is stable for up to 8 hours at 2-8°C, or at room temperature.

The calculated dose (mg) of investigational product to be administered to the subject is determined by the subject's body weight (kg) within 24 hours prior to transplant (Day -1 or Day 0). If a subject's weight increases or decreases by more than 5% from their baseline (Day -1 or Day 0) weight, the current weight should be used to calculate the dose of investigational product administered. The first dose of investigational product will be administered on Day 0, intra-operatively. Where possible, the study drug infusion should be completed before reperfusion of the allograft. The dose of investigational product administered may not be altered. The rate of infusion may be slowed or interrupted if the subject appears to develop signs of adverse reactions or infusion-related symptoms. At subsequent visits, if a subject's weight increases or decreases by more than 5% from their baseline weight measured at their previous visit, the current weight should be used to calculate the dose of investigational product administered and it will be used as the subject's new baseline weight for their next visit. At later visits, these subjects may continue to be infused over a longer infusion period at the investigator's clinical discretion. The rate of infusion should not be increased above the recommended rate.

Investigational product should be administered by the investigator/site personnel prepared to manage infusion reactions and anaphylaxis. Investigators/site personnel should be aware of the risk of hypersensitivity reactions, which may present as an infusion reaction, and monitor subjects closely. Subjects will be monitored during and after each infusion according to study site guidelines or standard operating procedure for any untoward reactions. Trained rescue personnel and rescue medications/equipment should be available for a minimum of the first 3 doses, and subjects should be observed for a minimum of 3 hours after the completion of the infusion for the first 3 doses.

Subjects should also be informed of the signs and symptoms of a hypersensitivity reaction, the possibility of a delayed reaction, and be instructed to seek medical care should a reaction occur. Delayed-type, non-acute hypersensitivity reactions have also been observed and included symptoms such as rash, nausea, fatigue, myalgia, headache, and facial edema.

For subjects who have previously received IV immunoglobulin (IVIG) or subjects with a history of allergies (allergic responses to food, drugs, insects, or a history of urticaria), diphenhydramine (12.5 to 50 mg based on clinical judgment) or equivalent and acetaminophen may be administered prophylactically prior to dosing. Antihistamine H2-receptor antagonists (e.g., ranitidine) are also permitted. Sites are encouraged to follow their standard practices to manage any untoward infusion reactions noted during or after the infusion period.

1.2 Dose Rationale

In this study, belimumab will be administered as 10 mg/kg IV infusions dosed at the same frequency as in the current labeling for SLE.

The selection of belimumab dose was based on review of pooled analyses of safety, efficacy and pharmacokinetic (PK) data from Phase 3 SLE studies. In those studies,

not only for the primary endpoint, but also for some disease activity and flare indices, and for certain critical biomarkers (anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies, complement levels and B-cell subsets), a dose response relationship was seen, with greater differences from placebo for the belimumab 10 mg/kg group than the belimumab 1 mg/kg group. The differences were more marked when only data from subjects with low complement and anti-dsDNA at baseline were analyzed [14].

In transplantation, unlike SLE or other autoimmune diseases, the event (reperfusion of the allograft) that triggers the pathogenic process is easily identified. In this study, to maximize BLyS binding at the time of this triggering event, the first dose of investigational product will be administered on the day of transplantation intraoperatively. Where possible, study drug infusion should be completed before reperfusion of the allograft.

This study will focus on examining the impact of belimumab during the first 6 months after transplantation, when episodes of rejection are most likely to occur; investigational product will be administered at Day 0, Week 2, Week 4 and then every 4 weeks through Week 20. Subjects will then be observed through the 1-year study period with no further belimumab dosing.

For detailed information of the safety and efficacy of belimumab at each of the doses studied, refer to the IB GlaxoSmithKline Document Number 2011N128591_01 (Investigator's Brochure: Belimumab. Version 11: 20-JUN-2013: always refer to the most recent version).

1.3 Summary of Known and Potential Risks and Benefits to Human Subjects

Belimumab: Belimumab has been generally well tolerated in the Phase 2 and Phase 3 SLE studies. The majority of subjects in the SLE studies were receiving concomitant corticosteroids and/or other immunosuppressants including azathioprine and mycophenolate mofetil (MMF). Precautions will be taken to mitigate the risk of infections, infusion and hypersensitivity reactions, and the potential risk of malignancy. These precautions will include the use of the ICTR Data Monitoring Committee (DMC), which will review subject safety and efficacy data.

Common adverse reactions (≥5%) in clinical trials were: nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, and pharyngitis. Serious adverse reactions have included: infections, Progressive Multifocal Leukoencephalopathy (PML), Hypersensitivity reactions; including anaphylaxis, depression. .

PML
Progressive multifocal leukoencephalopathy (PML) resulting in neurological deficits, including fatal cases, has been reported in SLE patients receiving immunosuppressant pharmacotherapy, including belimumab. A diagnosis of PML should be considered in any subject presenting with new-onset or deteriorating neurological signs and symptoms. The subject should be referred to a neurologist or other appropriate specialist for evaluation. If PML is confirmed, study agent should be discontinued and consideration should be given to stopping immunosuppressant therapy.

If PML is suspected, this should be immediately reported to the Medical Monitor. The appropriateness of continuing study agent, while the case is being assessed, should be discussed.

Suicidality

Some autoimmune diseases have an increased risk of suicidal behavior and/or ideation [Bachen, 2009; Timonen, 2003; Stenager, 1992]. For this reason in studies of patients with autoimmune disease, patients should be clinically assessed for suicidal ideation and/or behavior at each visit, but not for study purposes. If patient exhibits suicidal ideations or it is verbally expressed, the PI will enter a note and refer the patient to a psychiatrist.

Dosing

Infusion reactions occurred more frequently on the first two infusion days and tended to decrease with subsequent infusions. Delay in the onset of acute hypersensitivity reactions has been observed and recurrence of clinically significant reactions after initial resolution of symptoms following appropriate treatment, have been observed. Therefore, patients should remain under clinical supervision for 3 hours after completion of the first 2 IV infusions. Should symptoms of acute hypersensitivity occur, an extended period of monitoring may be appropriate, based on clinical judgment. This may include, but is not limited to, monitoring vital signs and observing any untoward reactions. Beyond the first 2 IV infusions, subjects should be monitored during and for an appropriate period of time after administration according to the study sites' guidelines or standard operating procedure for IV infusions. Patients treated with belimumab should be made aware of the potential risk, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention. Delayed-type, non-acute hypersensitivity reactions have also been observed and included symptoms such as rash, nausea, fatigue, myalgia, headache, and facial oedema.

For additional information on the risks associated with belimumab, refer to the package insert for Benlysta® (GlaskoSmithKlein) at:
https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Benlysta/pdf/BENLYSTA-PI-MG.PDF

In this study, belimumab will be administered in combination with standard of care immunosuppressants, which will include alemtuzumab, tacrolimus, mycophenolic acid and corticosteroids (standard taper) for all study subjects. There has been no experience with the use of alemtuzumab or tacrolimus in combination with belimumab, while there are data on the use of belimumab in combination with MMF and/or corticosteroids. As with all immunosuppressants, each of these agents has the potential to be associated with infections and/or malignancy.

Alemtuzumab: The most common adverse events associated with alemtuzumab are:

- Infusion reactions including moderate fever and chills
- Leukopenia

As with all immunosuppression, administration of alemtuzumab may be associated with an increased risk of infection and the development of malignancy (especially of the skin and lymphoid system). Alemtuzumab (30 mg IV x 1) is standard induction immunosuppression for both cadaveric and living-donor renal transplants at many centers.

In 251 kidney-transplant recipients receiving alemtuzumab induction (30 mg IV x 1), the adverse events did not differ significantly between patients treated with alemtuzumab, anti-thymocyte globulin and basiliximab. The principal side effects were leucopenia (57%) and infection (32%). CMV infection occurred in 13% of the recipients and PTLD in two of the recipients.

The carcinogenic effects and the effect of alemtuzumab on fertility have not been established. Alemtuzumab is contraindicated in patients who have active acute or chronic infections that contraindicate any additional immunosuppression.

For additional information on the risks associated with alemtuzumab, refer to the package insert for Campath® (Genzyme Corporation) at the following website: http://www.campath.com/pdfs/2009-08-Campath%20US%20PI.pdf

Tacrolimus: The following risks are associated with the administration of tacrolimus:

- Hypertension.
- Hyperkalemia.
- Nephrotoxicity.
- Neurotoxicity.
- Post-transplant insulin-independent diabetes mellitus.
- Myocardial hypertrophy (in most cases reversible upon dose reduction).
- Increased risk of renal insufficiency in patients with hepatic impairment.
- Increased susceptibility to infection.

For additional information on the risks of tacrolimus, refer to the Prograf® package insert at the following website: http://www.astellas.us/docs/prograf.pdf.

Mycophenolic Acid: The following risks are associated with the use of mycophenolic acid are:

- Increased risk of developing lymphomas, lymphoproliferative diseases and other malignancies especially of the skin in patients receiving MMF as part of an immunosuppressive regimen. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.
- Increased susceptibility to infection, including opportunistic infections, fatal infections and sepsis.
- Increased risk of developing latent viral infections including Progressive Multifocal Leukoencephalopathy (PML) and BK virus- associated nephropathy.
- Increased risk of first trimester pregnancy loss and congenital malformations, especially of the external ear, face, limbs, heart esophagus and kidneys. • Increased risk of neutropenia and leukopenia
- Increased risk of gastrointestinal bleeding.

Common side effects associated with use of MMF include diarrhea, abdominal pain, nausea and vomiting, headache and drug induced fever.

For additional information about the risks of mycophenolic acid, refer to the Myfortic® package insert at the following website:
http://www.pharma.us.novartis.com/product/pi/pdf/myfortic.pdf

Dexamethasone: Side effects of dexamethasone include convulsions, headache, vertigo, mood swings, psychosis, congestive heart failure (CHF), hypertension, salt and water retention, increased potassium excretion, Cushing syndrome, menstrual irregularities, hyperglycemia, GI irritation, peptic ulcer, weight gain. Dermatologic effects may include thin skin, petechiae, ecchymosis, facial erythema, poor wound healing, hirsutism and urticaria. Muscle weakness, loss of muscle mass and osteoporosis may also occur. Ophthalmologic complications may include increased intraocular pressure, glaucoma, exophthalmos and cataracts. Other complications may include immunosuppression and increased susceptibility to infection.
For further information about the risks associated with dexamethasone, please refer to the package insert at the following website:
http://www.americanregent.com/documents/Product15PrescribingInformation.pdf

2. Objectives

We propose an open-label, single-arm, pilot study to test whether the addition of belimumab, to inhibit the B cell survival factor BLyS at the time of kidney transplantation, to standard or care therapy (alemtuzumab and steroid induction with mycophenolic acid and tacrolimus maintenance immunosuppression) will prevent the prevent the generation of de novo DSA.

3. Study Design

3.1 Description

We propose an open-label, single-arm pilot study to examine the addition of belimumab at induction to our standard of care regimen of alemtuzumab and steroid induction followed by tacrolimus and mycophenolic acid maintenance immunosuppression in adult living donor kidney transplant recipients to assess its ability to induce functional B-cell transplant tolerance: prevent the generation of de novo DSA. Significant support for this hypothesis exists in the literature including 1) the successful induction of transplant tolerance in a preclinical model [9], 2) the transitional B cell tolerance signature [11] 3) the association of elevated BLyS levels with the development of de novo DSA post kidney transplant [2, 12, 13]. Our study population will consist of sensitized adult kidney transplant recipients: PRA>0 and/or sum DSA<1000 MFI. The primary endpoint of this study is de novo DSA production.

There are two main reasons for selecting this patient population for our proposed study. 1) Sensitized patients are known to have higher rates of de novo DSA production and 2) excluding patients with lower levels of DSA (sum DSA<1000 MFI) will enable more fidelity in determining the DSA that is produced *de novo*.

Additionally, we contend that alemtuzumab should be the induction agent of choice for this study instead of Thymoglobulin for three reasons. 1) In the United States it is provided at no cost and is easy to administer (a single 30mg dose is given

intravenously with no central venous access required). This cuts down significantly on cost as opposed to Thymoglobulin. 2) Mechanistically, more support exists in the literature for the use of alemtuzumab rather than Thymoglobulin. BLyS levels have been shown to significantly increase after alemtuzumab induction as opposed to Thymoglobulin induction, and lastly, 3) de novo DSA production appears to be ~50% at 2 years with alemtuzumab (potentially due to the increase BLyS levels). Therefore, we are potentially more likely to show a reduction in DSA levels (the primary endpoint) compared to our control cohort.

We will collect blood samples prior to transplant, then 1, 3, 6, 9 and 12 months to measure anti-HLA antibodies and BAFF/APRIL levels. In addition, we will collect protocol kidney biopsies at time of transplant and at 1-year post transplant.

3.2 Study Endpoints

3.2.1 Primary Endpoints

The primary endpoint of this study is *de novo* DSA production at 1, 3, 6, 9, and 12 months.

3.2.2 Secondary Endpoints

Secondary endpoints will be 1) graft survival and function as determined by serum creatinine/eGFR and urine protein at 1, 3, 6, 9, and 12 months 2) rates of acute cellular and antibody mediated rejection at 1, 3, 6, 9, and 12 months and 3) the nature, frequency, and severity of serious and non-serious adverse events ≥Grade 2.

3.3 Study Population

Subjects 18-60 years of age receiving a living donor kidney transplant who are sensitized by pregnancy, transfusions, or prior transplant: PRA>0% and/or sum DSA<1000 MFI.

3.4 Screening and Enrollment

This research study will be explained in lay language to each potential research participant. The participant will sign an informed consent prior to any screening study procedures. After written consent is obtained, subjects who are deemed to qualify for the study will be enrolled. Potential subjects will be invited to participate initially via phone or in person by study personnel to briefly explain the study. If the potential subject agrees, the study personnel will go through the consent form and answer questions. The study personnel will ask the potential subject if they would like to be in the study. If the subject agrees to participate, they will be informed about signing the consent and setting up study visits.

3.5 Criteria for Discontinuation

It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of subjects should be avoided.

In addition to the reasons for withdrawal provided below, subjects are free to withdraw from treatment or from the study at any time for any reason or may be withdrawn if necessary to protect their health.

Subjects who withdraw from the study or study treatment after receiving at least one dose of investigational product will continue to be followed up until the end of the study.

Reasons for withdrawal may include the following:

- Prohibited concurrent medication or therapy
- **Prior therapy at any time**: has ever received any of the following: B-cell targeted therapy (e.g., rituximab, other anti-CD20 agents, anti-CD2 [epratuzumab], anti-CD52 [alemtuzumab], BLyS-receptor fusion protein [BR3], TACI fragment, crystallizable (Fc), or belimumab)
- Live vaccines within 30 days
- Unacceptable toxicity as assessed by the PI

Study drug must be discontinued if the investigator determines that continuing it would result in a significant safety risk for that patient. Subjects MUST discontinue investigational product for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason).
- Any clinical adverse event, clinically stignificant laboratory abnormality, or concurrent 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 - Instruct WOCBP (Women of Child Bearing Potential) to contact the investigator or study staff immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation. The investigator must immediately notify GlaxoSmithKline if a study subject becomes pregnant. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be reported to GSK within 24 hours.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness.
- AE(s) (including infections, abnormal laboratory value(s), abnormal test procedure result(s) including ECG abnormalities, unsatisfactory death, significant protocol deviation, withdrawal of consent, or lost to follow-up, according to the criteria specified above.
- Malignancy (except non-melanoma skin cancer)

In addition to these requirements for study drug discontinuation, the investigator should discontinue study drug for a given patient if, in his/her professional judgment, it is felt that continuation would be detrimental to the patient's well-being.

Patients may withdraw from the study for any reason at any time.

All subjects who discontinue should comply with any protocol-specified follow-up procedures. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned

or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). If a subject withdraws before completing the study, the reason for withdrawal must be documented appropriately.

3.5.1 Discontinuation of study treatment and premature patient withdrawal

Patients may voluntarily withdraw from the study treatment or from the study for any reason at any time. They may be considered withdrawn from the study if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason. If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study. The investigator should discontinue study treatment for a given patient or withdraw the patient from study if, on balance, he/she believes that continuation would be detrimental to the patient's well-being. Patients who discontinue study treatment should NOT be considered withdrawn from the study and should continue to be followed until the end of the study, unless consent is withdrawn. Patients who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled patients.

3.6 Criteria for Terminating the Study

The Principal Investigator will review safety and efficacy criteria on an ongoing basis. The study enrollment will be halted and data reviewed by the Data Safety Monitoring Committee and the University of Wisconsin Health Sciences Institutional Review Board for any of the following:

1) If greater than two patients are discontinued from study treatment due to elevated liver function tests as described in the protocol.
2) If greater than two patients develop hypogammaglobulinermia and infectious complications resulting in discontinuation of study treatment 3) Death of one or more patients.

After this review, the Investigator, Data Safety Monitoring Committee and the IRB will jointly make a final determination regarding continuation, modification, or termination of the study. The study can be terminated at any time for any reason by the Principle Investigator or GlaxoSmithKline, Inc. Should this be necessary, the patient should be seen as soon as possible. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the DMC, IRB and the FDA of the early termination of the trial.

See Section 7.3 for information on the ICTR Data Monitoring Committee (DMC) for this study.

4. Selection of Subjects

Potential subjects will be identified prior to kidney transplant based on the following inclusion and exclusion criteria.

4.1 Inclusion Criteria

- Male or female subjects 18-60 years of age
- Planned to receive a living donor kidney transplant
- Sensitized patients: Positive sum DSA <1000, and/or PRA>0%.
- Subjects must be capable of understanding the purpose and risks of the study and must sign a statement of informed consent.
- Female subjects must be post-menopausal, surgically sterilized, or she and/or sexual partner must be willing to use an acceptable method of birth control with a <1% failure rate as stated in the product label from time of study consent, during study participation, and for 16 weeks after the last dose of the study agent (i.e., contraceptive subdermal implant of levonorgestrel or etonogestrel, intrauterine device or intrauterine system, combined estrogen and progestogen oral contraceptive, Injectable progestogen, contraceptive vaginal ring, percutaneous contraceptive patches, or abstinence) for the duration of the study. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject. The documentation of male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner. Note: Mycophenolate mofetil (MMF) affects the metabolism of oral contraceptives and may reduce their effectiveness. As such, women receiving MMF who are using oral contraceptives for birth control should employ an additional method (e.g., barrier method). Mycophenolate can cause fetal harm when administered to a pregnant female. Use of mycophenolate during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations. Mycophenolate affects the metabolism of oral contraceptives and may reduce their effectiveness. As such, women receiving MMF who are using oral contraceptives for birth control should employ an additional method (e.g., barrier method) resulting in two reliable forms of contraception being used simultaneously before starting study treatments, during therapy, and for 6 weeks after stopping therapy; unless abstinence is the chosen method of contraception
- Female patients of childbearing potential must have a negative serum pregnancy test within 48 hours of transplant. Must be willing to use contraceptives from the time of study consent, during study participation, and for 16 weeks after the last dose of study agent. For sexually active men, condoms should be used during, and for at least 90 days after cessation of mycophenolate treatment. No sperm donation should be made during this period of time. For female partners of male subjects, it is recommended to use highly effective contraception during treatment and for 90 days after the last dose of mycophenolate
- No blood donation should be made by the study subjects during mycophenolate treatment and for at least 6 weeks after stopping mycophenolate treatment

- <u>If stricter female or male contraception requirements are specified in the countryspecific label for any study related therapies, they must be followed.</u>

- Male subjects must agree to use an acceptable method for contraception for the duration of the study.

Female patients of childbearing potential must have a negative serum pregnancy test within 48 hours of transplant. Must be willing to use contraceptives from the time of study consent, during study participation, and for 16 weeks after the last dose of study agent. Reproductive Status: Definition of Women of Child-Bearing Potential (WOCBP). WOCBP comprises women who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or who are not post-menopausal (see definition below).

Post-menopause is defined as:

- Women who have had amenorrhea for 12 consecutive months (without another cause) and who have a documented serum follicle-stimulating hormone (FSH) level > 35 mIU/mL.
- Women who have irregular menstrual periods and a documented serum FSH level > 35 mIU/mL.
- Women who are taking hormone replacement therapy (HRT).

The following women are WOCBP:

- Women using the following methods to prevent pregnancy: Oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as intrauterine devices or barrier methods (diaphragm, condoms, spermicides).
- Women who are practicing abstinence from intercourse from 2 weeks prior to administration of the 1st dose of study agent until 16 weeks after the last dose of study agent (Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are <u>not</u> acceptable methods of contraception) Women who have a partner who is sterile (e.g., due to vasectomy).

WOCBP must be using an acceptable method of contraception to avoid pregnancy from the time of consent with <1% failure rate as stated in the product label throughout study participation, and for 16 weeks after the last dose of study drug in such a manner that the risk of pregnancy is minimized. Acceptable methods of contraception include: complete abstinence, any form of intra-uterine devices (without hormones), tubal sterilization or your partner has had a vasectomy.

Other acceptable forms of birth control include choosing one hormonal and one barrier method or double-barrier methods. Barrier methods include Essure®, male or female condom, diaphragm with spermicide, shield, cap with spermicide, contraceptive sponge, and spermicidals. Hormonal methods include oral contraceptive pills, transdermal patches, vaginal rings, progesterone-only, and injections. Periodic abstinence (for example, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

- WOCBP must have a negative serum pregnancy test result (minimum sensitivity 25 IU/L or equivalent units of HCG) within 48 hours prior to transplant (and the first dose of study drug intraoperatively).Women must not be breast-feeding

4.2 Exclusion Criteria

- ABO incompatible donor kidney
- Deceased donor
- KDPI□85%
- HLA identical or matched kidney
- Transplant other than kidney: has previously received a hematopoietic stem cell/marrow transplant or an organ transplant other than a kidney (with the exception of corneal transplantation)
- T- and/or B-cell positive crossmatch by complement dependent cytotoxicity or flow cytometry against the recipient
- Currently on any suppressive therapy for a chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria).
- Hospitalization for treatment of infection within 60 days of Day 0
- Use of parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti parasitic agents) within 60 days of Day 0
- Have a history of a primary immunodeficiency
- Uncontrolled infection or any other unstable medical condition that could interfere with the study
- Seropositive for HIV, HCV or HBV, except for hepatitis B surface antibody positive If the HIV, HCV or HBV screening virology results are not available prior to transplantation then the most recent historical result (within the last 6 months) will be used.
- Have a significant IgG deficiency (IgG level < 400 mg/dl) Have an IgA deficiency (IgA level < 10 mg/dL)
- Prior therapy at any time: has ever received any of the following: a) B-cell targeted therapy (e.g., rituximab, other anti-CD20 agents, anti-CD2 [epratuzumab], antiCD52 [alemtuzumab], BLyS-receptor fusion protein [BR3], TACI fragment, crystallizable (Fc), belimumab), or IV cyclophosphamide
- Live vaccines within 30 days
- Have a history of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies
- Patients with a lymphocyte count <500/mm3
- Patients with evidence of current drug or alcohol abuse or dependence.
- Patients with venous access limitations likely to preclude monthly infusions
- Patients whom are unlikely to comply with scheduled study visits based on investigator judgment or has a history of substance abuse, psychiatric disorder or condition that may compromise communication with the investigator
- Myocardial infarction within 6 months prior to enrollment or New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiography evidence of acute ischemia or active conduction system abnormalities
- Diagnosis of liver cirrhosis or chronic viral hepatitis

- Female subject is pregnant or breast-feeding. Confirmation that the subject is not pregnant must be established by a negative serum □-human chorionic gonadotropin (□-hCG) pregnancy test result obtained during screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women
- Patient has received other investigational drugs within 365 days before enrollment
- Serious medical or psychiatric illness likely to interfere with participation in this clinical study
- Have evidence of serious suicide risk including any history of suicidal behavior in the last 6 months and/or any suicidal ideation in the last 2 months or who in the investigator's judgment, pose a significant suicide risk
- Diagnosed or treated for malignancy within 5 years of enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low-risk prostate cancer after curative therapy.
- Have any other clinically significant abnormal laboratory value in the opinion of the investigator

5. Treatment

5.1 Immunosuppression Protocol

The immunosuppressive therapy will consist of the standard of care (SOC) alemtuzumab and steroid induction with mycophenolic acid and tacrolimus maintenance immunosuppression and belimumab 10 mg/kg IV administered for 6 months at the following intervals: at time of transplant (Day 0), then post-transplant at 2, 4, 8, 12, 16, and 20 weeks.

5.1.1 Antibacterial, antiviral, and antifungal prophylaxis

Antibacterial, antiviral for CMV prophylaxis, and antifungal prophylaxis therapy will be administered and adjusted per institutional standard of care. Recommended prophylaxis per current institutional standard of care includes:

- Antibacterial prophylaxis: Sulfa-Trimethoprim Double Strength (Bactrim DS) 800-160 MG per tablet daily for one year
- Antiviral CMV prophylaxis per donor/recipient CMV risk profile:
    - High or moderate CMV risk: Donor seropositive/Recipient seronegative [D+/R-], Donor seropositive/Recipient seropositive [D+/R+], or Donor seronegative/Recipient seropositive [D-/R+]:
        - Valganciclovir 900 mg orally daily for 6 months. Dosing adjusted for renal function.
    - Low CMV risk: Donor seronegative/Recipient seronegative [D-/R-]:
        - Acyclovir 400 mg twice daily orally for 3 months. Dosing adjusted for renal function.
- Antifungal prophylaxis:
    - Nystatin 5 mL swish and swallow for one month

5.1.2 Treatment monitoring and dose modifying strategies

The following AEs, laboratory assessment results or changes in concurrent medications require evaluation and discussion with the GSK medical monitor within 24 hours of the investigator becoming aware of the event.

Dose Adjustment and Discontinuation

If a subject experiences a clinically significant AE and this AE continues at the next scheduled dose, or could potentially be exacerbated by the next dose, the investigator may delay the next dose by up to 2 weeks or withhold 1 dose, per physician discretion. As a result, any subsequent study visits will be adjusted. If a similar concern is present at the time of the next scheduled dose, any decision made to discontinue treatment will be driven by the Investigator's clinical judgment. Laboratory tests will be repeated per Investigator's discretion.

If it is determined that investigational product should be discontinued, the subject should be followed at regularly scheduled monthly study visits as required until resolution of the AE, and return for follow-up visits as described in Subject Withdrawal Criteria.

For a full listing of the discontinuation criteria, please see section 3.5 of the protocol.

Hypogammaglobulinemia

Benlysta should be discontinued in subjects with IgG levels <250 mg/dL associated with a severe or serious infection. For IgG concentrations < 250 mg/dl that are not associated with a severe or serious infection, increased vigilance for infection is required. Clinical judgment should be applied with respect to the appropriateness of continuing study therapy in these subjects. If a subject experiences any IgG levels < 250 mg/dL, the dose of study agent must be withheld and the Medical Monitor and GlaxoSmithKlein must be consulted before administering any subsequent dose of study agent. If a subject experiences a clinically significant, potentially life-threatening (Grade 4) AE that the investigator believes may be definitely, possibly or probably related to study agent, then treatment with study agent will be discontinued. The subject should be withdrawn from study agent, and followed at regularly scheduled study visits as specified by protocol and also until resolution of the AE(s) (whichever is longer).

Liver Chemistry Stopping Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the US Food and Drug Administration premarketing clinical liver safety guidance).

Study treatment will be stopped if any of the following liver chemistry stopping criteria is met:

1. Alanine aminotransferase (ALT) □ 3x upper limit of normal (ULN) and total bilirubin □ 2xULN (>35% direct bilirubin); or ALT □ 3xULN and international normalized ratio

(INR) > 1.5. NOTE: serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).

2. ALT □ 5xULN.

3. ALT □ 3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).

4. ALT □ 3xULN persists for □ 4 weeks.

5. ALT □ 3xULN and cannot be monitored weekly for 4 weeks.

6. ALT □5xULN but <8xULN and labs cannot be monitored weekly for □ 2 weeks

Subjects with ALT □ 3xULN and < 5xULN and bilirubin < 2xULN, who do not exhibit hepatitis symptoms or rash, can continue study treatment as long as they can be monitored weekly for 4 weeks.

Concurrent Medication- Prohibited

Subjects who receive concurrent medication or treatment that is prohibited for safety reasons (e.g. live vaccines, cyclophosphamide or B-cell agents such as rituximab) should be withdrawn from study treatment and should not receive additional investigational product without the explicit approval of the Medical Monitor (Funding Sponsor).

Required Actions, Monitoring, and Follow up Assessments following ANY Liver Stopping Event

Actions:

- Immediately discontinue study treatment
- Report the event to GSK within 24 hours
- Complete the liver event CRF and complete SAE data collection tool if the event also meets the criteria for an SAE (All events of ALT □ 3xULN and bilirubin □ 2xULN (>35% direct bilirubin) or ALT □ 3xULN and INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants)
- Perform liver event follow up assessments
- Monitor the subject until liver chemistries resolve , stabilize, or return to within baseline (see MONITORING below)
- Do not restart/rechallenge subject with study treatment unless allowed per protocol and GSK Medical Governance approval is granted **Monitoring:**

For bilirubin or INR criteria:

- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs**

- Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline
- A specialist or hepatology consultation is recommended □ For All other criteria:
- Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24-72 hrs
- Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline

Follow Up Assessments:

- Viral hepatitis serology (Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody) □ Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin□2xULN
- Obtain complete blood count with differential to assess eosinophilia
- Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
- Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications
- Record alcohol use on the liver event case report form □ For bilirubin or INR criteria:
- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).
- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). NOTE: not required in China
- Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver event case report form

Increased Monitoring Criteria with Continued Therapy

Criteria

- If ALT □5xULN and <8xULN and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 2 weeks **OR**
- ALT □3xULN and <5xULN and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks

Required Actions

- Notify the GSK medical monitor within 24 hours of learning of the abnormality to discuss subject safety.
- Subject can continue study treatment
- Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline

- If at any time subject meets the liver chemistry stopping criteria, proceed as described above for Required Actions and Follow up Assessments following ANY Liver Stopping Event
- If ALT decreases from ALT □5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly.
- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

5.1.3 Duration of Treatment and Follow-up.

The above treatment protocol is investigational. However all patients will be treated and monitored according to our standard of care for kidney transplant patients. DSA will be monitored pre-transplant and at 1, 3, 6, 9, and 12 months. We will perform a protocol biopsy at 1 year post-transplant per standard of care.

Data for the study will be collected for 1 year post transplant via REDCap. We will collect medical health information generated as part of post-transplant standard of care clinic visits, lab analysis and procedures done within the year. If the kidney fails and patient returns to dialysis the study coordinator or the PI will contact the patient's dialysis unit and local nephrologists every three months for one year post transplant to collect the necessary safety monitoring information including infectious (such as herpes simplex virus) and hematological complications, and lab results.

6. Study Procedures

The following assessments will be obtained for all subjects, as outlined in the Study Visit Schedule of Events (Appendix A).

6.1 Screening Visit

Prior to any screening procedures, informed consent will be obtained. Once consent is obtained, the following assessments will be completed and information collected for study participants within 30 days of transplant. If any screening procedure has been performed within the 30-day screening window per standard of care, results can be used for the screening visit and procedure does not need to be repeated.

- Document informed Consent
- Demographics
- Medical history
- Physical exam including vital signs and weight
- Medications
- Obtain standard of care lab results, including:
- Hematology panel-CBC and differential
- Liver Function-AST, ALT, total bilirubin
- Electrolytes
- BUN/Creatinine
- cPRA (HLA alloantibodies)
- Serum pregnancy test for women of child bearing potential

- Urine protein/creatinine except when the study subject is anuric or oliguric, and/or unable to provide a urine sample.
- Perform ECG, abnormalities must be documented as not medically relevant
- Review of medical history collected at most recent standard of care pretransplant clinic visit and primary care/specialists care visits. Determine eligibility based on inclusion/exclusion criteria

6.2 Day of Transplant (Day 0)

The first dose of investigational product will be administered on Day 0 intra-operatively. The dose of investigational product administered may not be altered. The rate of infusion may be slowed or interrupted if the subject appears to develop signs of adverse reactions or infusion-related symptoms. At later visits, these subjects may continue to be infused over a longer infusion period at the investigator's clinical discretion. The rate of infusion should not be increased above the recommended rate.

Blood pressure and heart rate will be recorded within 15 minutes prior to belimumab infusion, at 15± 5 minutes after the beginning of the infusion, and 15± 5 minutes following completion of the infusion.

Biopsy will be obtained at transplant per standard of care.

6.3 Post-Transplant Study Visits: Week 1, Week 2, Month 1, 2, 3, 4, 5, 6, 9, 12

Study visits will occur at Week 1 +/- 3 days (while in the hospital recovering from surgery), Week 2, and Months 1, 2, 3, 4, 5, 6, 9, and 12, after transplant in conjunction with standard of care. With the exception of the Week 2 visit that will take 3 hours, visits that include a belimumab infusion (Months 1, 2, 3, 4, 5) will take about 2 hours to complete. The remainder of study visits will only take about an hour. Many of the procedures required for the study are the same as those done at standard of care clinic visits and will not require additional procedures/tests. At these visits, the following procedures and tests will occur:

- Collection of vital signs (including temperature, blood pressure, heart and breathing rate, and weight), at all visits
- A brief physical exam
- Blood and urine sample collections for standard laboratory tests (all visits), except when the study subject is anuric or oliguric, and/or unable to provide a urine sample.
- Review of medications (on day of study visit.)
- Research blood sample collection at Months 1, 3, 6, 9, 12 (if consented)
- Any changes to health or medical history will be recorded and assessed

6.3.1 Study Treatment

 Belimumab: 10 mg/kg/dose will be administered IV for 6 months at the following intervals: at time of **transplant (Day 0)**, then post -transplant at Weeks **2, 4, 8, 12, 16, and 20.**

6.3.2 Study Related Clinical Assessments

- Physical examination to include patient weight and vital signs prior to each infusion and at each study visit . Physical exam will include standard neurologic assessments to monitor for the presence of any drug related toxicities as outlined in section 5.1.2.
- Adverse events recorded prior to each belimumab dose. Subjects will be asked to report any changes in sleep patterns, anxiety or mental status, suicidal ideation.
- Concomitant medications collected and reviewed at each visit

6.3.3 Laboratory Assessments

Laboratory assessments will be performed according to the schedule of events in Appendix A.

Post-transplant follow-up standard of care labs results will be collected via the Transplant Data System every month for the first year post-transplant for safety monitoring.
Subjects who do not receive a transplant, following belimumab injection, will have their labs and clinical care monitored quarterly by the study coordinators, or the PI who will collect the data from UWHC electronic records or request records from the subject's provider if not within the UWHC system.

Subjects will also have a kidney biopsy at 1 year post-transplant per standard of care.

6.3.4 Mechanistic Assessments

We will measure anti-HLA antibodies using the Single Antigen Bead Luminex assay (One Lambda, Inc., CA, USA) prior to treatment and 1, 3, 6, 9, and 12 months.

The following standard of care assays will be done and data analyzed as part of this protocol:

Single antigen Bead Luminex Antibody screening. This state of the art flow cytometry based assay is performed routinely in our HLA laboratory at the UWHC. It allows us to determine both anti HLA antibody and PRA measurements. Blood samples are analyzed for HLA antibodies by LabScreen® Single Antigen Class I and II beads LXFC kits from One Lambda, Inc (OLI, Canoga Park, CA, USA). The method is followed as described in the package insert, using 3µL of HLA antigen coated beads.

Kidney Transplant Biopsy: A donor biopsy will be collected intra-operatively per standard of care at the time of transplant, and percutaneously with ultrasound guidance as per standard protocol at 1 year post-transplant. Results will be collected and recorded from the electronic medical record.

6.3.5 Banking of Samples for Future Studies

If the subject agrees to allow their blood cells/plasma to be used for future research related to kidney transplantation by indicating such on the informed consent, the samples and all the coded data associated including standard of care kidney function

and study related lab results, medication and adverse event logs, and physical exam notes will be maintained by key personnel. Samples will be coded with a subject number and stored a -80° C freezer or in liquid nitrogen storage in Dr. Djamali's Research Laboratory at the University of Wisconsin Hospital and Clinics, 600 Highland Ave Madison, Wisconsin. Subjects will not be re-consented and the results of any future testing will not be provided to the subjects nor will they be used in making any clinical decisions regarding their care. The risks to the subjects are limited to breach of confidentiality and release of information to individuals not involved in this research. We will do everything possible to keep the subjects information confidential. No identifiable information will be shared. Any electronic files pertaining to health information and samples will only be accessible to the investigators and study personnel. Computers are password protected and the files will be stored on a Department of Surgery secure password protected network server. No portable electronic devices will be used for data collection or storage. No future research (with the exception of mechanistic assays identified in this protocol) or sharing of samples will be done without an IRB approved protocol.

If the subject agrees **peripheral blood will be collected prior to transplant and at 1, 3, 6, 9, and 12** months and stored for the below future studies.

- **BAFF and APRIL measurements*:*** Serum BAFF and APRIL levels will be measured as described previously using the Quantikine ELISA Immunoassay (R&D Systems, Minneapolis, MN) [(17).] Briefly, samples are collected in tubes without anticoagulant and spun at 2000 rpm for 10 min. Serum is collected and frozen in liquid nitrogen for long term. Standards and sera are assayed in duplicate wells. This will occur on samples prior to treatment and 1, 3, 6, 9, and 12 months.

- **B Lymphocyte Analysis:** B-cell FACS panels will be used to measure changes over the course of therapy in the transitional, naïve, memory and plasma cell compartments. For the subsets of interest, absolute numbers of cells and proportions relative to all B cells for the individual subsets will be determined, as will activation status. Specifically we will address peripheral transitional, naive, memory and plasma cell populations prior to transplant and at 1, 3, 6, 9, and 12 months post-transplant. Further exploratory analyses will include the expression of BLyS receptors (BR3, TACI and BCMA) on B cells, frequency of alloreactive B cells (using tetramers) and an analysis of the effect of belimumab on IL-10 secreting B regulatory cells. Again these assessments will be performed prior to transplant and at 1, 3, 6, 9, and 12 months post transplant

- **T Lymphocyte Analysis:** Similar assessments will be made of T cell subsets prior to transplant and at 1, 3, 6, 9, and 12 months post-transplant. Specifically we will evaluate activated T cell and T regulatory cell populations.

- **Cytokine Analysis:** Quantification of serum BLyS and APRIL levels and cytokines/chemokines associated with T-helper skewing or activation will be performed prior to transplant and at 1, 3, 6, 9, and 12, months posttransplant

- **Immunoglobulin Analysis:** Quantification of total serum levels of Immunoglobulin levels (IgM, IgA, and IgG) will be performed prior to transplant and at 1, 3, 6, 9, and 12 months post-transplant.

7. Safety Assessments

The patient will be evaluated for safety, and adverse events will be documented according to the procedures of the investigational site. The investigator will determine the relationship of the events to the administration of belimumab.

Patients will be clinically assessed for suicidal ideation and/or behavior at each visit. If patient exhibits suicidal ideations or it is verbally expressed, the PI will enter a note and refer the patient to a psychiatrist.

Expected Adverse Events (AEs) ≥ Grade 2, and <u>all unexpected</u> adverse events will be documented, graded, and assessed for causality to belimumab by the Principal Investigator.

All Serious Adverse Events (SAEs) will be reported to GlaxoSmithKline within 24 hours. SAEs that meet the FDA and IRB reporting criteria will be reported within the specified timeframe. Serious Adverse Events will be documented, graded, and assessed for causality to belimumab by the Sponsor-Investigator.

If the patient is a WOCBP, pregnancy tests (blood; minimum sensitivity 25 IU/L of HCG) must be performed within 48 hours before the first dose and the beginning of each cycle. If the patient becomes pregnant, she must be discontinued from treatment.

Laboratory tests may be performed as part of routine standard of care as directed by subject's nephrologist. Results of these standard of care tests will be monitored as part of this study. Additional tests including a hematology profile will be done prior to each study drug cycle and hepatic function labs will be done prior to each treatment cycle for monitoring the subject's for potential drug related toxicities.

Physical exams will be performed prior to each cycle, and will include the monitoring of specific known study drug related toxicities including neuropathy and edema.

Subjects will continue to have health information collected from standard of care clinic visits, or nephrology/dialysis unit visits, and monitored for safety for 12 months from the time of discontinuation of study treatment. If subjects transplant fails prior to the 6 month time point, they will continue to have health information collected from standard of care post-transplant follow up clinic visits, or nephrology/dialysis unit visits, and monitored for safety for 12 months from the time of transplant.

<u>MMF</u>

Mycophenolate can cause fetal harm when administered to a pregnant female. Use of mycophenolate during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations.
Mycophenolate affects the metabolism of oral contraceptives and may reduce their effectiveness. As such, women receiving MMF who are using oral contraceptives for birth control should employ an additional method (e.g., barrier method) resulting in two reliable forms of contraception being used simultaneously before starting study treatments, during therapy, and for 6 weeks after stopping therapy; unless abstinence is the chosen method of contraception

• For women of childbearing potential, a serum pregnancy test is required within 48 hours prior to transplant.

• For sexually active men, condoms should be used during, and for at least 90 days after cessation of mycophenolate treatment. No sperm donation should be made during this period of time. For female partners of male subjects, it is recommended to use highly effective contraception during treatment and for 90 days after the last dose of mycophenolate

• No blood donation should be made by the study subjects during mycophenolate treatment and for at least 6 weeks after stopping mycophenolate treatment

<u>If stricter female or male contraception requirements are specified in the countryspecific label for any study related therapies, they must be followed.</u>

7.1 Adverse Events

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or 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 (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

Adverse events are defined as any signs (including abnormal diagnostic test result) or medical diagnoses noted by medical personnel, or symptoms reported by the subject, regardless of relationship to study drug, that:

1. have onset anytime after the start of study drug treatment, or

2. increase in severity during drug treatment or procedures (pre-existing signs, symptoms or diagnoses).

Subjects will be interviewed in a non-directed manner to identify potential adverse events. This occurrence of an adverse event will be based on changes in the subject's physical examination, laboratory results, and/or signs and symptoms. Only those abnormal laboratory results that are considered clinically significant will be evaluated as a potential adverse event. All adverse events ≥Grade 2 per CTCAE, including observed or volunteered problems, complaints, or symptoms are to be recorded, if they are thought to be related to the study drug or study procedures. All documented adverse events will be monitored until they are resolved or are clearly determined to

be due to a subject's stable or chronic disease condition or intercurrent illness(es). Each adverse event is to be evaluated for duration, intensity and causal relationship with the study medication or other factors.

Adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.
Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting ageappropriate instrumental ADL.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

7.2 Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at <u>any dose</u>:

- Is fatal
- Is life-threatening
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

The inpatient stay following the transplantation procedure will be considered SAE only if prolonged for more than 14 days.

A medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent a serious outcome, may also be considered serious (e.g. intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse). Medical and scientific judgment must be exercised when classifying events as serious. The Investigator must determine both the intensity of the serious adverse event and the relationship of the event to the administration of study medications.

7.2.1 Reporting

It is the responsibility of the Investigator to promptly notify the Institutional Review Board of all unanticipated problems involving risk to human research subjects. All serious adverse events including fatal or life-threatening events experienced by study participants in the study will be reported to GlaxoSmithKline, Inc., to ICTR DMC, the FDA per applicable regulations, and the UW IRB according to current IRB guidelines.

Adverse Events that are:	**Notify:**
Serious Suspected/Related* Unexpected	**GSK Medical Monitor:** Within 24 hours **DMC:** Within 14 business days **HSIRB:** Within 14 *business* days **FDA** and all participating institutions as soon as possible, but no later than 15 *calendar* days after learning of the event
Life threatening or Fatal Suspected/Related* Unexpected	**GSK Medical Monitor:** Within 24 hours **DMC:** Within 24 hours **HSIRB:** Within 1 *business* day of learning of the event. **FDA:** Within 7 *calendar* days of learning of the event
*Events that are possibly, probably, or definitely related meet the criteria for "Suspected/Related"	

7.3 ICTR Data Monitoring Committee (DMC)

We plan to utilize the UW ICTR Data Monitoring Committee (DMC) to oversee the study. The UW ICTR DMC is comprised of experienced members (core plus ad hoc) with expertise required to oversee this study. The DMC members will review protocol-specific reports created by statisticians using data pulled from the ICTR OnCore clinical research management system and Research Electronic Data Capture (REDCap) data management tool. These standard reports will include an overview of study objectives, a review of actual and projected accrual rates, an evaluation of patient demographics for balance of randomization, and a summary of the number and seriousness of adverse events. An interim analysis of study results may be performed and source documents may be reviewed to allow the DMC to independently judge whether the overall integrity and conduct of the protocol remain acceptable based on data provided and reported by the Principal Investigator. The DMC will make recommendations to the Principal Investigator that could include actions of continuation, modification, suspension, or termination.

In providing oversight for the conduct of this study, the ICTR DMC will meet biannually during the study to review all adverse events. Additional meetings may be scheduled as determined by the DMC or as requested by the PI. The predefined stopping points for this study are described in section 3.6 of this protocol. We will submit all reportable events to the DMC and the Health Sciences IRB in accordance with their reporting guidelines.

8. Ethical Considerations and Compliance in Good Clinical Practice

8.1 Statement of Compliance

This trial will be conducted in compliance with the protocol, current Good Clinical Practices (GCP), adopting the principles of the Declaration of Helsinki, and all applicable regulatory requirements.

Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate ethics review committee or Institutional Review Board (IRB). Any amendments to the protocol or consent materials must also be approved before they are implemented.

8.2 Informed Consent

The informed consent form is a means of providing information regarding the trial to a prospective participant and allows for an informed decision about participation in the study. All participants must read, sign and date a consent form prior to participation in the study, taking study drug and/or undergoing any study-specific procedures.

The informed consent form must be updated or revised whenever important new safety information is available, whenever the protocol is amended, and/or whenever any new information becomes available that may affect a patients' participation in the trial.

A copy of the informed consent will be given to a prospective participant for review. The Study Investigator or a designee of the Investigator will review the consent and answer any questions that the potential participant may have. The participant will be informed that their participation is voluntary and they may withdraw from the study at any time, for any reason.

8.3 Recruitment Methods

Patients being evaluated for a living donor kidney transplant who meet the selection criteria will be contacted by study personnel. The potential subjects will be contacted to briefly explain the study and ask if they would mind to review a consent form. If the potential subject agrees, the study personnel go through the consent form and answer questions. At the end, the study personnel will ask the potential subject if they would like to be in the study. If a potential subject replies yes, study personnel will have them review and sign the consent form. Study personnel will meet them prior to any study related procedures to obtain consent.

8.4 Privacy and Confidentiality

A patient's privacy and confidentiality will be respected throughout the study. Each study participant will be assigned a sequential identification number and these numbers rather than names will be used to collect, store and report participant information.

All data collected for this study from subjects will be done in a private patient exam room. Data may be extracted from the subject's medical record (paper/electronic) by the Publications and Clinical Research Service (PACRS), study coordinators and the PIs. Data necessary to achieve the aims of the research will be the only data collected from the subjects or the medical records. Source documents for data, including signed ICF and Research Authorization forms, will be maintained in subject study specific binders. Subjects are identified on all documents and samples by a study specific identifier and study assigned number. These binders are stored in the locked office of the Office of Clinical Trials coordinator.

All paper files and computers are located in an office that is staffed during the day, and locked when staff is not present. Electronic source documents and data analysis will be created and stored on the Department of Surgery secure password protected network server.

Study personnel will have access to the OnCore registration log that links identifiable subject information to the assigned subject study code. Only key personnel assigned to the study will have access to this information.

Data including treatments, eGFR, AEs, deaths, infections (bacterial/viral/fungal), or sepsis may be included in REDCap for Data Safety Monitoring.

No data or subject information will be released to the funding institution as this is an investigator initiated study and all data belongs solely to the investigator. No data will be stored on laptops or portable devices.

8.5 Records Retention

The investigator will retain, in a confidential manner, all data pertinent to the study for all treated subjects. The investigator will retain source documents and accurate case histories that record all observations and other data pertinent to the investigation (e.g., the medical record) for the maximum period (7 years) or 2 years after completion/termination of the IND with the FDA, as required by applicable regulations and guidelines or following institutional procedures.

9. Statistical Section

A biostatistician in the UW Madison Department of Surgery or the Division of Nephrology will perform the statistical analyses. The primary outcome and secondary outcomes will be assessed using descriptive statistics. Specifically, we will describe the rate of de novo DSA development, graft survival and function as determined by serum creatinine/eGFR and urine protein, rates of acute cellular and antibody

mediated rejection, and the nature, frequency, and severity of serious and non-serious adverse events ≥Grade 2.

10. References

1. Sellares J, de Freitas DG, Mengel M, et al. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. *American Journal of Transplantation.* 2012;12(2):388399.
2. Todeschini M, Cortinovis M, Perico N, et al. In kidney transplant patients, alemtuzumab but not basiliximab/low-dose rabbit anti-thymocyte globulin induces B cell depletion and regeneration, which associates with a high incidence of de novo donor-specific anti-HLA antibody development. *Journal of Immunology.* 2013;191(5):2818-2828.
3. DeVos JM, Patel SJ, Burns KM, et al. De novo donor specific antibodies and patient outcomes in renal transplantation. *Clinical Transplants.* 2011:351-358.
4. DeVos JM, Gaber AO, Knight RJ, et al. Donor-specific HLA-DQ antibodies may contribute to poor graft outcome after renal transplantation. *Kidney International.* 2012;82(5):598-604.
5. Terasaki PI, Cai J. Humoral theory of transplantation: further evidence. *Current Opinion in Immunology.* 2005;17(5):541-545.
6. Mihaylova A, Baltadjieva D, Boneva P, et al. Clinical relevance of anti-HLA antibodies detected by flow-cytometry bead-based assays--single-center experience. *Human Immunology.* 2006;67(10):787-794.
7. Redfield RR, 3rd, Rodriguez E, Parsons R, et al. Essential role for B cells in transplantation tolerance. *Current Opinion in Immunology.* 2011;23(5):685-691.
8. Hahn BH. Belimumab for systemic lupus erythematosus. *The New England Journal of Medicine.* 2013;368(16):1528-1535.
9. Parsons RF, Yu M, Vivek K, et al. Murine islet allograft tolerance upon blockade of the B-lymphocyte stimulator, BLyS/BAFF. *Transplantation.* 2012;93(7):676-685.
10. Parsons RF, Vivek K, Rostami SY, et al. Acquisition of humoral transplantation tolerance upon de novo emergence of B lymphocytes. *Journal of Immunology.* 2011;186(1):614-620.
11. Newell KA, Asare A, Kirk AD, et al. Identification of a B cell signature associated with renal transplant tolerance in humans. *The Journal of Clinical Investigation.* 2010;120(6):1836-1847.
12. Zarkhin V, Li L, Sarwal MM. BAFF may modulate the rate of B-cell repopulation after rituximab therapy for acute renal transplant rejection. *Transplantation.* 2009;88(10):1229-1230.
13. Thibault-Espitia A, Foucher Y, Danger R, et al. BAFF and BAFF-R levels are associated with risk of long-term kidney graft dysfunction and

development of donor-specific antibodies. *American Journal of Transplantation.* 2012;12(10):2754-2762.
14. van Vollenhoven RF, Petri MA, Cervera R, et al. Belimumab in the treatment of systemic lupus erythematosus: high disease activity predictors of response. *Annals of the Rheumatic Diseases.* 2012;71(8):1343-1349.
15. Parsons RF, Yu M, Vivek K, Zekavat G, Rostami SY, Ziaie AS, Luo Y, Koeberlein B,Redfield RR, Ward CD, Migone TS, Cancro MP, Naji A, Noorchashm H. Murine islet allograft tolerance upon blockade of the Blymphocyte stimulator, BLyS/BAFF.*Transplantation* 2012;93(7):676-85.
16. Lehnhardt A, Dunst F, Koch M, Kemper MJ. BAFF/BAFF-R axis is dysregulated in patients after pediatric renal transplantation. *Pediatr Nephrol* 2011. 26;9:1613-1614.
17. Xu H, He X, Liu Q, Shi D, Chen Y, Zhu Y, Zhang X. Abnormal High Expression of BCell Activating Factor Belonging to the TNF Superfamily (BAFF) Associated With Long-Term Outcome in Kidney Transplant Recipients. *Transplant Proc* 2009a.41;5:1552-1556.
18. Xu H, He X, Sun J, Shi D, Zhu Y, Zhang X. The Expression of B-Cell Activating Factor Belonging to Tumor Necrosis Factor Superfamily (BAFF) Significantly Correlated With C4D in Kidney Allograft Rejection. *Transplant Proc* 2009b. 41;1:112-116.
19. Banham G, Prezzi D, Harford S, Taylor CJ, Hamer R, Higgins R, Bradley JA, ClatworthyMR. Elevated pretransplantation soluble BAFF is associated with an increased risk of acute antibody-mediated rejection. *Transplantation*. 2013 Aug 27;96(4):413-20

11.0 Appendix A (Schedule of Events)

	CAMPBEL Trial											
		Hospitalization	Outpatient Visit									
	Screen	Day of Transplant (Day 0)	1 Week	2 Weeks	4 Weeks Month 1	8 Weeks	Weeks Month 3	Weeks	Weeks	Weeks Month 6	Weeks Month 9	Weeks Month 12
	≤30 days prior to transplant	May be same day as screening	◻ 3d	◻ 3d	◻ 3d	◻ 3d	◻ 3d	◻ 3d	◻ 3d	◻ 7d	◻ 7d	◻ 7d
Informed Consent	X											
Demographics	X											
Medical History	X											
Physical Exam	X		X	X	X	X	X	R	R	X	X	X
Vital Signs (+ weight)[1]	X	XΔ	X	X	X	X	X	R	R	X	X	X
Hematology[2*]	X	X	X	X	X	X	X	R	R	X	X	X
Comprehensive Metabolic Panel*	X	X	X	X	X	X	X	R	R	X	X	X
Urine Protein/ Creatinine*	X	X	X	X	X	X	X	R	R	X	X	X
Serum pregnancy test[8*]	X	X		R[8]	R[8]	R[8]	R[8]	R[8]	R[8]			
PRA*	X	X			X		X			X	X	X
Anti HLA antibodies by Luminex*	X	X			X		X			X	X	X
ECG*	X											
Viral Serology[3*]	X	X										
Immunoglobulin Panel: IgG, IgA, IgM by clinical lab*	X				X	X	X	X	X	X	X	X
Tacrolimus Trough			X	X	X	X	X	X	X	X	X	X
Steroid Taper		X										
Alemtuzumab		X										
Tacrolimus/ Mycophenolic Acid[9]		X	X	X	X	X	X	X	X	X	X	X
Belimumab[4]		R[4]		R[4]	R[4]	R[4]	R[4]	R[4]	R[4]			
Kidney biopsy[5]		X										X
Adverse Events[6]		R[6]	R[6]	R[6]	R[6]	R[6]	R[6]	R[6]	R[6]	R[6]	R[6]	R[6]
Con Meds	R		R	R	R	R	R	R	R	R	R	R
Cytokine Analysis[7]	R	R			R		R			R	R	R
T Lymphocyte Analysis[7]	R	R			R		R			R	R	R
B Lymphocyte Analysis[7]	R	R			R		R			R	R	R
Immunoglobulin Analysis (IgM, IgA, IgG)[7]	R	R			R		R			R	R	R
BAFF/APRIL Analysis[7]	R	R			R		R			R	R	R

[1] Vital signs include temperature, blood pressure, pulse and respiratory rate recorded prior to each study drug dose.

[2] Hematology: CBC and differential

[3] HIV, HBsAg, anti-HBc, anti-HBs antibodies, hepatitis C antibody, herpes simplex virus, CMV, Epstein Barr virus, and varicella zoster virus per standard of care. For eligibility assessment, if the screening virology results for HIV, HCV and HBV are not available prior to transplantation then the most recent historical result (within the last 6 months) will be used. Per standard of care, the viral serology tests for CMV, Epstein Barr Virus, and varicella are not to be repeated once found positive.

[4] Belimumab infusion [5] Kidney biopsy will be performed at time of transplant per standard of care, and at 1 year to assess histologic response per standard of care.

[6] Adverse events recorded prior to each study drug dose and will include subject reports of changes in sleep patterns, anxiety and suicidality

[7] If subject consents: Blood collected for future research lab processing and analysis by transplant research lab [8] For Women of Child-bearing potential, within 48 hours prior to transplant and prior to each dose of belimumab. [9] Tacrolimus and Mycophenolic Acid start date and dosing may be adjusted per physician discretion

*Clinical labs drawn on the day prior to transplant (day -1) do not need to be repeated unless clinically indicated

X=Standard of Care R= Procedure for Research Purposes

Δ Blood pressure and Heart rate will be recorded within 15 minutes prior to infusion, 15±5 minutes after beginning infusion and 15±5 after completion of infusion