A Pilot Study of Belimumab (Benlysta) for Prevention of Chronic Graft-versus-Host Disease Following Allogeneic Hematopoietic Cell Transplantation

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Study Drug: Belimumab (Benlysta)

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Protocol Revision History

Initial Approval Version	**08/24/17**
Amendment #1 Version	**02/22/18**
Amendment #2 Version	**01/14/19**
Amendment #3 Version	**01/08/20**
Amendment #4 Version	**05/29/20**
Amendment #5 Version	**08/01/22**

SYNOPSIS

Background:

- Chronic graft-versus-host disease (GvHD) is the leading cause of late morbidity and non-relapse mortality following allogeneic hematopoietic stem cell transplantation (alloHSCT), occurring in 40-60% long-term survivors
- Chronic GvHD occurs due to the dysfunctional peripheral tolerance during post-transplant hematopoietic reconstitution that allows the development and persistence of alloreactive donor-derived T and B cells
- Prednisone is the front-line therapy, however about 50% of persons have steroid-refractory disease and there is no standard second line therapy
- The most attractive approach for controlling chronic GvHD would be the prevention of the most severe and irreversible clinical manifestations while maintaining Graft-versus-Leukemia effect

Objectives:

- Primary: To evaluate safety and tolerability of belimumab as prophylaxis of chronic GvHD in subjects following alloHCT.

- Secondary:
  - To evaluate the impact of prophylactic belimumab on the incidence and severity of chronic GvHD at 6, 12 and 24 months after alloHCT
  - To evaluate the impact of prophylactic belimumab on the incidence and severity of acute GvHD at 3 and 6 months after alloHCT
  - To evaluate the impact of prophylactic belimumab on overall survival at 6, 12 and 24 months after alloHCT
  - To evaluate the impact of prophylactic belimumab on relapse rate at 6, 12 and 24 months after alloHCT
  - To evaluate the impact of prophylactic belimumab on overall corticosteroid requirement (dose and duration) for treatment of chronic GvHD at 6, 12 and 24 months after alloHCT
  - To evaluate the impact of prophylactic belimumab on the necessity to use alternative treatment modalities for chronic GvHD at 6, 12 and 24 months after alloHCT

- Exploratory:
  - To evaluate the effect of prophylactic belimumab on post-transplant immune cell reconstitution.
  - To explore candidate biomarkers (i.e. BAFF level, BAFF:B cell ratio; B cell subpopulation frequency) that could predict subjects who may benefit from prophylactic administration of belimumab to prevent chronic GvHD.

Eligibility:

<u>Key Inclusion criteria:</u>

1. At least 18 years of age
2. ECOG performance status ≤ 2
3. Diagnosis of hematologic malignancy (i.e. acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, myelodysplastic syndrome, chronic myelogenous leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma)
4. Use of myeloablative or non-myeloablative conditioning regimen
5. Use of mobilized peripheral blood stem cells from fully HLA-matched related or unrelated donor as a graft source

6. Acute GvHD prophylaxis with methotrexate and tacrolimus
7. Documented complete remission with full donor engraftment (by STR identity testing) on Day +30 bone marrow biopsy
8. Adequate end organ function:
   - Serum bilirubin ≤ 1.5 x ULN
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN
   - Creatinine clearance ≥ 40 mL/min/1.73 m^2 by the Cockcroft-Gault formula
9. Women of childbearing potential must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry, for the duration of study participation, and for 16 weeks after the last dose of study drug. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.
10. Able to understand and willing to sign an IRB-approved written informed consent

Key Exclusion Criteria:

1. Active grade III-IV classic acute GvHD; subjects with prior resolved acute GvHD on stable doses of immunosuppression at time of enrollment will be permitted
2. Evidence of classic chronic GvHD or overlap chronic GvHD at time of enrollment
3. Subjects who participated in a clinical trial of acute GvHD prophylaxis in which chronic GvHD was a secondary end point
4. Donor lymphocyte infusion administered to treat relapse or loss of donor chimerism
5. Treatment with rituximab or other anti-B cell specific antibodies within previous 3 months
6. History of other malignancy ≤5 years previous with the exception of basal cell or squamous cell carcinoma of the skin which were treated with local resection only or carcinoma *in situ* of the cervix
7. Currently receiving any other investigational agents
8. Known allergy or intolerance to any component of belimumab, including human or murine proteins or monoclonal antibodies
9. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations (including current drug or alcohol abuse or dependence, or history of drug or alcohol abuse or dependence within the last year) that would limit compliance with study requirements
10. Use of parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti-parasitic agents) within 14 days prior to planned start of therapy
11. 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 and/or poses a significant suicide risk in the judgment of the investigator
12. History of pre-existing immunodeficiency disorder, autoimmune condition, or chronic infection
13. Known HIV positivity
14. Serologic evidence of current or past hepatitis B infection based on the results of testing for HBsAg and anti-HBc – Patients positive for HBsAg or HBcAb are excluded
15. Positive test for hepatitis C antibody (patients with documented clearance of hepatitis C by PCR following treatment will be permitted)
16. Currently on therapy for active chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria). Prophylactic therapy is allowed.
17. Has any other clinically significant abnormal laboratory value in the opinion of the investigator

Design:
This is a single center, open-label pilot and feasibility study of prophylactic belimumab for the prevention of chronic GvHD following alloHCT at Washington University School of Medicine in St. Louis.

The study will include Screening Phase, Treatment Phase, and Follow-up Phase. Subjects will be screened for the study after obtaining the results from their standard-of-care Day +30 bone marrow biopsy. Those subjects meeting the Inclusion and Exclusion Criteria will be enrolled in the study and start treatment between Day +30 and Day +80 after alloHCT. The study population will include 10 subjects. Planned duration of treatment is 7 cycles (6 months; see study schema). Subjects will be followed for 24 months.

Subjects may be on steroids that were used to treat acute GvHD and then developed chronic GvHD before completing a taper. At the time of enrollment subject should be responding to therapy with severity of acute GvHD grade II or less, and the dose of steroid should be ≤0.5 mg/kg/day of prednisone equivalent with no dose increase in the preceding 1 week. Subjects may also remain on other systemic immunosuppressive drugs that were used to prevent acute GvHD. Subjects diagnosed with or treated for chronic GvHD prior to study enrollment will be excluded from the study.

The subjects who develop chronic GvHD while receiving treatment with the study drug, belimumab, may continue on the study with the careful documentation of their GvHD severity and treatments used for it.

The primary endpoint is safety and tolerability of belimumab. Subjects who receive at least one dose of belimumab will be eligible for primary endpoint analysis and it will be performed according to the CTCAE v4.03.

Documentation of chronic GvHD will be per NIH criteria (**Appendix B**). Those subjects diagnosed with chronic GvHD will have organ specific staging and global scoring according to the NIH criteria (**Appendix D** and **Appendix E**).

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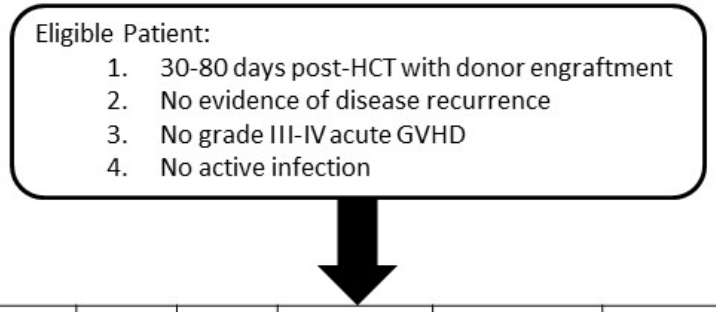
SCHEMA



	Screening/ Enrollment	Cycle 1	Cycle 2	Cycle 3	Cycles 4-7	Follow-up #1	Follow-up #2-6	Follow-up #7-9
Day	Day 30 – 80 post-transplant		+2 wk	+4 wk	+8,+12,+16,+20 wks	+6 mo post-C1D1 Belimumab	+9,+12,+15,+18,+21,+24 mo post-C1D1 Belimumab	+3,+4,+5 yr post-C1D1 Belimumab
Belimumab Administration	X		X	X	X			
Safety Assessment	X		X	X	X		X	
GvHD Assessment	X			X	X	X	X	
Serum collection (research)	X			X		X	X	X*
PBMC collection (research)	X			X		X	X	X*

*(optional) Study lab draws will continue yearly, up to 5 years post-HCT, to continue to monitor immune reconstitution post-Belimumab

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1 BACKGROUND AND RATIONALE

Allogeneic hematopoietic cell transplantation (alloHCT) is a potentially curative therapy for subjects with aggressive or relapsed/refractory hematologic malignancies. In 2013, the Center for International Blood and Marrow Transplant Research (CIBMTR) estimated approximately 8,000 alloHCT were performed in the US (www.cibmtr.org). Unfortunately, the high non-relapse mortality (NRM) associated with alloHCT significantly limits the number of subjects who undergo this treatment modality.

1.1 Graft-versus-Host Disease

Chronic graft-versus-host disease (GvHD) is the most common cause of late morbidity and non-relapse mortality following alloHCT, occurring in roughly 40-60% of long-term survivors [1-3]. Risk factors for developing chronic GvHD include older patient age, use of peripheral blood stem cells versus bone marrow, and lack of T-cell depletion [4, 5]. Chronic GvHD is a multisystem, debilitating, immune-mediated disorder characterized by immunosuppression and immune dysregulation, resulting in increased risk of infections, impaired organ function and reduced quality of life (QOL). Importantly, the incidence of GvHD is on the rise due to multiple factors, including more transplantation of older adults, increased use of mobilized peripheral blood as a stem cell source, increased use of alternative donors (i.e., unrelated or haploidentical donors), and improved early post-transplant survival. Symptoms of chronic GvHD occur gradually, starting on average at 6 months after transplantation. Chronic GvHD targets skin, mouth, eyes, gut, liver, lungs, joints, and genitourinary system; it may be restricted to a single site, but more frequently several organ-sites are included.

1.1.1 Chronic GVHD diagnosis and classification

One of the major obstacles to clinical research in chronic GvHD has been the lack of standardized criteria for the diagnosis, staging, and measurements of response to therapy. In 2005 the National Institutes of Health (NIH) Consensus Conference consolidated expert opinions and standardized recommendations for diagnosis and staging, histopathology, biomarkers, response criteria, ancillary therapy and supportive care, and design of clinical trials. The Chronic GvHD Consortium was subsequently established to conduct multicenter studies on chronic GvHD and many retrospective and prospective longitudinal studies have been published over the last nine years further validating the NIH Consensus Conference criteria [6-15]. In 2014, now with 9-years of experience, the experts met again to update and improve on the original recommendations and clarify controversies [16-21]. The 2014 NIH criteria provide greater specificity and more accurate measures of the disease burden. According to the NIH criteria, the diagnosis of chronic GvHD requires at least one *diagnostic* manifestation (establish the diagnosis of chronic GvHD without the need for further testing) or at least one *distinctive (*highly suggestive of chronic GvHD but insufficient alone to establish the diagnosis) confirmed by biopsy, laboratory test, or by radiology in the same or another organ. *Other features* can be recognized as part of chronic GvHD only if the diagnosis is confirmed and *common features* are found in both acute and chronic GvHD and cannot be used to distinguish between the two disorders. Chronic GvHD is separated from acute GvHD not by time since HCT, but by the presence of diagnostic and distinctive clinical manifestations. The NIH Consensus Conference recognizes two major categories of GvHD - acute and chronic, each one with 2

subcategories: (1) “classic” acute GvHD, (2) “persistent, recurrent or late” acute GvHD, (3) “classic” chronic GvHD and (4) an “overlap syndrome” **(Appendix A)**. Early diagnosis is important because the goal of treatment is control of symptoms and the prevention of irreversible organ damage.

1.1.2 Pathophysiology of chronic GvHD

Although the precise pathophysiology of chronic GvHD is not known, recent advances have been made in understanding the disease process [22]. In contrast to acute GvHD, which results from activation of adoptively transferred host-reactive donor T cells, chronic GvHD occurs due to dysfunctional peripheral tolerance during post-transplant hematopoietic reconstitution that allows the development and persistence of autoreactive donor-derived T and B cells. Though a pathologic role for T cells in both acute and chronic GvHD has long been recognized [23, 24], a significant role of B cells in the pathogenesis of chronic GvHD has more recently been appreciated [2, 25]. Augmented B-cell responses in chronic GvHD result in marked abnormalities in B-cell homeostasis and signaling pathways, but the mechanisms responsible for aberrant B-cell homeostasis and the inability to establish B-cell tolerance in patients with chronic GvHD have not been fully elucidated [26]. Alloreactive B-cells are associated with chronic GvHD, in particular, antibodies against minor histocompatibility antigens (mHAs) correlated with chronic GVHD incidence. HY antibodies develop in male patients who receive their alloHCT from a female donor [27]. HY antigens are mHAs found on the Y chromosome with homologous proteins on the X chromosome, and by looking at the HY antigens in sex-mismatched transplants an allo-immune response representing chronic GVHD was studied. The rationale is that lymphocytes from the female donor graft, which lack a Y chromosome, recognize the HY mHAs as foreign, thus producing HY specific antibodies. In support of this hypothesis, rituximab, a monoclonal antibody targeting CD20-expressing cells such as B cells, infused 2-3 months after alloHCT in male patients with female donors prevented development of HY antigen-specific alloreactive B-cells and IgM antibodies. Rituximab has been used both for prevention and treatment of established chronic GvHD supporting the role of B cell-directed therapy as a plausible treatment strategy [28, 29]. Another potential mechanism to impair abnormal B cell function is through the inhibition of B-cell activating factor (BAFF), which is a homeostatic cytokine important for survival of autoreactive B cells and has been shown to be elevated in serum of patients after alloHCT [30, 31]. Moreover, prolonged elevation of BAFF serum levels in the post-transplant environment has been implicated in the development of chronic GvHD. As such, patients with chronic GvHD have delayed normal B-cell reconstitution associated with elevated BAFF:B-cell ratios compared to patients without chronic GvHD. In contrast, chronic GvHD patients who demonstrate clinical improvement and positive response to treatment have robust recovery of the peripheral naive B-cell pool, though it is unclear what role BAFF has on this clinical scenario.

1.1.3 Treatment and Prevention of Chronic GvHD

Approaches to the treatment of chronic GvHD are complex and the field is rapidly advancing. While there have been a number of effective strategies to prevent and treat acute GvHD, prophylactic and treatment options for chronic GvHD remain limited. Currently there is no FDA-approved therapy for chronic GvHD, and

development of well-designed prospective therapeutic studies for chronic GvHD is an urgent unmet clinical need. Successful management and supportive care of patients with chronic GvHD require close follow-up to identify complications before they limit organ function or threaten mortality. Chronic GvHD and its treatment further results in increased risk of infection, impaired organ function, and reduced QOL. The goal of therapy is to stop destructive immunological processes, improve symptoms, and eventually establish immunological tolerance with ultimate withdrawal of immunosuppressive therapy. Approximately 85% of patients who survive beyond five years after diagnosis are able to stop systemic therapy [32].

The most attractive approach for controlling chronic GvHD would be the prevention of the most severe and irreversible clinical manifestations [33, 34]. Selective modulation of alloreactive response and inflammation, rather than general immunosuppression, might be a promising mechanism for reducing GvHD while preserving GvL effect. Inhibitors of specific B-cell signaling pathways, both small molecules and monoclonal antibodies, are now available for clinical use and are being applied in the treatment of B-cell malignancies. These new agents can also be used to identify and potentially modify specific abnormalities of B-cell homeostasis. Development of clinical trials using these agents in patients undergoing allogeneic HCT will enable the development of new strategies to target B-cell responses for prevention and treatment of chronic GvHD.

1.2 Belimumab

1.2.1 Clinical Pharmacology

Belimumab (Benlysta) is a recombinant, human immunoglobulin G 1 lambda (IgG1λ) monoclonal antibody that blocks the binding of soluble human B lymphocyte stimulator protein (BLyS, also referred to as BAFF and TNFSF13B) to its receptors on B cells [35]. Belimumab does not bind B cells directly, but by binding BLyS it inhibits the survival of B cells and reduces the differentiation of B cells into immunoglobulin-producing plasma cells. Belimumab has a molecular weight of approximately 147 kDa and is produced by recombinant DNA technology in a mammalian cell expression system [36]. In humans with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), elevated BLyS levels have been found to be positively correlated with elevated autoantibody levels, immunoglobulin IgG, and disease activity [37]. By neutralizing the activity of BLyS, belimumab inhibits survival of B cells.

1.2.2 Preclinical Experience

Please refer to Investigators Brochure for experience in preclinical studies.

1.2.3 Clinical Experience and Toxicology

Over 3,000 individuals with SLE have been treated with belimumab in clinical studies. Two Phase 3 studies of belimumab in SLE were completed in 2009. Results of these studies showed that belimumab treatment (10 mg/kg IV every 2 weeks for 3 doses and every 4 weeks thereafter) was effective in reducing disease activity as measured by the SLE responder index (SRI) at Week 52, the primary efficacy endpoint of both trials [38, 39]. The data suggested that belimumab

treatment may be associated with reduced steroid use and risk of severe flare. Belimumab is currently FDA approved for the treatment of systemic lupus erythematosus and another trial assessing the efficacy in rheumatoid arthritis has recently been completed. Furthermore, clinical trials in other rheumatologic conditions, such as scleroderma and Sjögren's syndrome [40] are underway [www.clinicaltrials.gov]. Treatment with belimumab plus standard of care was generally well tolerated with no apparent dose response in the safety profile. Rates of adverse events (AEs), severe AEs, serious adverse events (SAEs), AEs leading to discontinuation, and serious/severe infections were generally comparable to the rates observed in the placebo plus standard of care group. When used as a single agent there were rare grade ≥3 adverse events with the most common grade 1 or 2 adverse events involving infectious complications (i.e., upper respiratory infections, gastroenteritis, urinary tract infection), headaches, and neutropenia [37, 40]. Moreover, when belimumab was combined with standard of care immunosuppressive therapy in subjects with lupus, there was no increased rate of adverse events of any grade compared to standard of care plus placebo suggesting an acceptable benefit/risk balance of belimumab when combined with additional immune modulating agents [38, 39]. Psychiatric events, including depression and suicide, were observed more frequently with belimumab, although it is unknown if belimumab treatment is associated with increased risk for these events. Although no increase in the rate of serious infections or malignancies was observed, as with other immunomodulating therapies the mechanism of action of belimumab could increase the risk for these events. Hypersensitivity and infusion reactions were observed more frequently with belimumab, with anaphylaxis observed ≤ 1% of subjects. The most commonly-reported adverse reactions, occurring in ≥ 3% of patients receiving 10 mg/kg belimumab in clinical trials (and at a ≥ 1% greater rate than placebo) were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, pharyngitis, cystitis, leucopenia, and gastroenteritis viral. Experience from open-label, long-term continuation trials of belimumab in SLE patients confirms prolonged treatment with belimumab remains generally well tolerated, with no apparent increase in the incidence rate of AEs or SAEs over time, including important events such as infections and malignancies [37, 41]. Long term belimumab treatment appears to provide sustained improvement in SLE disease activity and reduction of flares. Please refer to the investigator's brochure for summaries of clinical trials of belimumab.

The observation that antagonism of BLyS by treatment with belimumab results in reductions of B cells, serum immunoglobulins and in particular, reduction of a variety of serum autoantibodies suggests that belimumab may have therapeutic benefit in other B cell-mediated autoimmune diseases in which BLyS may have a role [42]. Diseases which are characterized by autoantibody production or excess antibody levels in which elevated levels of BLyS have been observed, and in some cases, shown to be correlated with disease activity include: Sjogren's Syndrome, idiopathic thrombocytopenic purpura (ITP), anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides, chronic graft versus host disease (GvHD), chronic antibody-mediated allograft rejection, and Waldenstrom's macroglobulinemia.

1.2.4 Pharmacokinetics and Drug Metabolism

Pharmacokinetic Parameter	Population Estimates (n = 563)
Peak concentration (C_{max}, mcg/mL)	313
Area under the curve (AUC, day · mcg/mL)	3,083
Distribution half-life ($t_{½}$, days)	1.75
Terminal half-life ($t_{½}$, days)	19.4
Systemic clearance (CL, mL/day)	215
Volume of distribution (Vss, L)	5.29

1.3 Study Rationale

Given the role of B cells in the pathophysiology of chronic GvHD, the association between elevated BAFF levels post-transplant in abnormal B-cell homeostasis and chronic GvHD, and the efficacy of belimumab in the inhibition of BAFF signaling, these proof-of-principle findings support the rational for use of belimumab as prophylaxis of chronic GvHD. We propose a pilot and feasibility study to assess the safety and tolerability, as well as preliminary efficacy, of belimumab as prophylaxis of chronic GvHD following alloHCT. Our *central hypothesis* is that belimumab will be well tolerated and have a favorable effect on incidence and severity of chronic GvHD.

2 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate safety and tolerability of belimumab as prophylaxis of chronic GvHD in subjects following alloHCT. This will be assessed by CTCAE v. 4.03.

2.2 Secondary Objectives

1. To evaluate the impact of prophylactic belimumab on the incidence and severity of chronic GvHD at 6, 12 and 24 months after alloHCT
2. To evaluate the impact of prophylactic belimumab on the incidence and severity of acute GvHD at 3 and 6 months after alloHCT
3. To evaluate the impact of prophylactic belimumab on overall survival at 6, 12 and 24 months after alloHCT
4. To evaluate the impact of prophylactic belimumab on relapse rate at 6, 12 and 24 months after alloHCT
5. To evaluate the impact of prophylactic belimumab on overall corticosteroid requirement (dose and duration) for treatment of chronic GvHD at 6, 12 and 24 months after alloHCT
6. To evaluate the impact of prophylactic belimumab on the necessity to use alternative treatment modalities for chronic GvHD at 6, 12 and 24 months after alloHCT

2.3 Exploratory Objectives

1. To evaluate the effect of prophylactic belimumab on post-transplant immune cell reconstitution.
2. To explore candidate biomarkers (i.e. BAFF level, BAFF:B cell ratio; B cell subpopulation frequency) that could predict subjects who may benefit from prophylactic administration of belimumab to prevent chronic GvHD.

3 PATIENT SELECTION AND ENROLLMENT

3.1 Inclusion Criteria

1. At least 18 years of age
2. ECOG performance status ≤ 2
3. Diagnosis of hematologic malignancy (i.e. acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, myelodysplastic syndrome, chronic myelomonocytic leukemia)
4. Use of myeloablative or non-myeloablative conditioning regimen
5. Use of mobilized peripheral blood stem cells from fully HLA-matched related or unrelated donor as a graft source
6. Acute GvHD prophylaxis with methotrexate and tacrolimus
7. Documented complete remission and full donor engraftment (by STR identity testing) on Day +30 bone marrow biopsy
    a. Complete remission: less than 5% blasts in an aspirate bone marrow sample with a count of at least 200 nucleated cells, no blasts with Auer rods or persistence of extramedullary disease PLUS absolute neutrophil count (ANC) > 1,500/μL, platelet count ≥ 50,000/μL and no leukemic blasts in the peripheral blood.
    b. Negative minimal residual disease
    c. Full donor engraftment by STR testing (either by bone marrow or peripheral blood testing)
8. Adequate end organ function:
    a. Serum bilirubin ≤ 1.5 x ULN
    b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN
    c. Creatinine clearance ≥ 40 mL/min/1.73 m^2 by the Cockcroft-Gault formula
9. Women of childbearing potential must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry, for the duration of study participation, and for 16 weeks after the last dose of study drug. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.
10. Able to understand and willing to sign an IRB-approved written informed consent.

3.2 Exclusion Criteria

1. Active grade III-IV classic acute GvHD; subjects with prior resolved acute GvHD on stable doses of immunosuppression at time of enrollment will be permitted
2. Evidence of classic chronic GvHD or overlap chronic GvHD at time of enrollment
3. Subjects who participated in a clinical trial of acute GvHD prophylaxis in which chronic GvHD was a secondary end point
4. Donor lymphocyte infusion administered to treat relapse or loss of donor chimerism
5. Treatment with rituximab or other anti-B cell specific antibodies within previous 3 months
6. History of other malignancy ≤ 5 years previous with the exception of basal cell or squamous cell carcinoma of the skin which were treated with local resection only or carcinoma *in situ* of the cervix
7. Currently receiving any other investigational agents
8. Known allergy or intolerance to any component of belimumab, including human or murine proteins or monoclonal antibodies
9. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations (including current drug or alcohol abuse or dependence, or history of drug or alcohol abuse or dependence within the last year) that would limit compliance with study requirements
10. Use of parenteral (IV or IM) antibiotics (antibacterials, antivirals, anti-fungals, or anti-parasitic agents) within 14 days prior to planned start of therapy
11. 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 and/or poses a significant suicide risk in the judgment of the investigator
12. History of pre-existing immunodeficiency disorder, autoimmune condition, or chronic infection
13. Known HIV positivity
14. Serologic evidence of current or past hepatitis B infection based on the results of testing for HBsAg and anti-HBc – Patients positive for HBsAg or HBcAb are excluded
15. Positive test for hepatitis C antibody (patients with documented clearance of hepatitis C by PCR following treatment will be permitted)
16. Currently on therapy for active chronic infection (such as tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster and atypical mycobacteria). Prophylactic therapy is allowed.
17. Has any other clinically significant abnormal laboratory value in the opinion of the investigator

3.3 Inclusion of Women and Minorities

Men and women as well as members of all races and ethnic groups are eligible for this trial.

4 REGISTRATION PROCEDURES

Subject must not start any protocol intervention prior to registration through the Siteman Cancer Center. The subject must read, understand and sign the Institutional Review Board approved consent form. The following steps must be taken before registering subjects to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center OnCore database

3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

All necessary procedures and evaluations must be performed to document that the subject meets all of the inclusion criteria and none of the exclusion criteria prior to first dose on Day 1. Adult subjects must read, understand, and sign the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) approved informed consent form (ICF) confirming his or her willingness to participate in this study before any study-specific screening procedures are performed. Subjects less than 18 years of age will not be enrolled on this study. Subjects must also grant permission to use protected health information per the Health Insurance Portability and Accountability Act (HIPAA).

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed informed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All subjects must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a UPN for this study. All data will be recorded with this identification number on the appropriate CRFs.

5 TREATMENT OF SUBJECTS AND STUDY DESIGN

This is a single center, open-label pilot and feasibility study of prophylactic belimumab for the prevention of chronic GvHD following alloHCT at Washington University School of Medicine in St. Louis. The study will include Screening Phase, Treatment Phase, and Follow-up Phase.

Subjects will be screened for the study after obtaining the results from their standard-of-care Day +30 bone marrow biopsy. Those subjects meeting the Inclusion and Exclusion Criteria will be enrolled in the study and start treatment between Day +30 and Day +80 after alloHCT. At enrollment, subjects may continue on steroids that were used to treat acute GvHD. At the time of enrollment, however, subjects should be responding to therapy and the dose of steroid should be ≤0.5 mg/kg/day of prednisone equivalent with no dose increase in the preceding 1 week. Subjects may also remain on other systemic immunosuppressive drugs that were used to prevent or treat acute GvHD. At the time of enrollment, acute GvHD should be grade II or less. Subjects diagnosed with or treated for chronic GvHD will be excluded from the study. The study population will include 10 subjects. Planned duration of treatment is for 7 cycles (6 months; see study schema). Subjects will be followed for 24 months. One of the secondary endpoints is to evaluate the impact of

belimumab on incidence and severity of chronic GvHD. The subjects who develop chronic GvHD while receiving treatment with the study drug, belimumab, may continue on the study at the discretion of treating transplant physician with careful documentation of their GvHD severity and treatments used for it. If at any point it is considered that the study drug may be contributing to chronic GvHD it will be discontinued.

The primary endpoint is safety and tolerability of belimumab. Subjects who receive at least one dose of belimumab will be eligible for primary endpoint analysis and it will be performed according to the CTCAE v4.03.

Diagnosis of chronic GvHD will be per NIH criteria (**Appendix B**). Those patients diagnosed with chronic GvHD will have organ specific staging and global scoring according to the NIH criteria (**Appendices D** and **E**).

5.1 Baseline Evaluations

5.1.1 Medical History and Demographics

The subject's relevant medical history through review of medical records and by interview will be collected and recorded. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history and the date of initial diagnosis will be recorded.

5.1.2 Prior and Concomitant Medications

All active medications from 30 days prior to signing of ICF through 30 days after the last dose of study drug will be documented. All prior and current treatments for acute and chronic GvHD will be documented.

5.1.3 History and physical neurological, and psychiatric exam, vital signs and ECOG performance score

The physical examination will include the general appearance of the subject, height (Screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system. Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature. ECOG performance score will be recorded (Appendix C).

5.1.4 Laboratory

5.1.4.1 Bone Marrow Biopsy

Remission will be assessed as defined in the Inclusion Criteria. It will be evaluated using a local laboratory and include pathology review, minimal residual disease and engraftment testing.

5.1.4.2 Hematology

Hematology will be evaluated using a local laboratory and parameters will include a complete blood count: white blood cells, red blood cells, hemoglobin, hematocrit, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils.

5.1.4.3 Chemistry

Serum chemistry will be evaluated using a local laboratory and parameters will include sodium, potassium, chloride, blood urea nitrogen (BUN)/Urea, creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, LDH, phosphate, uric acid, magnesium and bicarbonate.

5.1.4.4 Hepatitis Serologies

Hepatitis serologies will be evaluated using a local laboratory and include hepatitis C antibody, hepatitis B surface antigen, and hepatitis B core antibody. If hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody is positive, then PCR to quantitate hepatitis B DNA or hepatitis C RNA must be performed.

5.1.4.5 Serum Immunoglobulins

Serum immunoglobulins will be evaluated using a local laboratory and include IgA, IgG and IgM levels.

5.1.4.6 Pregnancy test

Serum pregnancy test is required at Screening using a local laboratory and only for women of childbearing potential.

5.1.5 ECG

At Screening, 12-lead ECG is required and will be done in triplicate (≥1 minute apart). Any clinically significant abnormalities noted at Screening should be included in the medical history.

ECGs should be performed at the investigator's discretion, particularly in subjects with arrhythmic symptoms (e.g. palpitations, lightheadedness) or new onset of dyspnea.

5.1.6 Chronic GvHD Assessment

Patients should be assessed for chronic GvHD and no active chronic GvHD should be present. Please see Diagnostic Criteria for Chronic GvHD (Appendix B).

5.1.7 Correlative pharmacodynamics and immunology studies

Refer to Section 9.0.

5.2 Study Drug Administration

Belimumab will be administered intravenously at 10 mg/kg over 1 hour. Enrollment and the first dose of belimumab (Cycle 1) will be administered between Day +30 and Day +80 after alloHCT, after reviewing bone marrow biopsy results and confirming eligibility. Subjects will receive belimumab every 2 weeks for 3 cycles and then every 4 weeks for a total of 7 cycles (6 months of therapy).

Therefore: Cycle 1 of belimumab will be administered between Day +30 and +60 after alloHCT, Cycle 2 will be administered 2 weeks later (+/- 3 days), Cycle 3 will be administered two weeks after Cycle 2 (+/- 3 days), and each subsequent cycle will be given every 4 weeks thereafter (+/- 1 week) for total of 7 cycles (6 months of therapy). This dosing and schedule of belimumab administration is similar to prior phase III studies for systemic lupus erythematous [38, 39]. Subjects will continue to adjust their standard of care immunosuppressive medications at the discretion of treating physician.

5.3 Premedication

Premedication with an oral antihistamine, with or without an antipyretic, may be administered before the infusion of belimumab.

5.4 Duration of Therapy

Treatment may continue for six months, or until one of the following criteria applies:

- Documented and confirmed original hematologic disease relapse
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unable to receive further treatment in the judgment of the investigator
- Grade III-IV acute GvHD not responding to therapy after 2 weeks
- Serious noncompliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms. Subjects who prematurely discontinue treatment for any reason will be followed as indicated in the study calendar.

5.5 Duration of Follow-up

Subjects will be followed after discontinuation of treatment every 3 months during the first 2 years post-C1D1 and then annually for 5 years post-C1D1 or until death, whichever occurs first. Subjects removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.6 Concomitant Medication and Supportive Care Guidelines

5.6.1 Permitted Concomitant Medications

All systemic immunosuppressive medications with exact doses and additional treatment modalities for chronic GvHD will be recorded at time of every visit. Adjustment to immunosuppressive medications or initiation of additional treatment modalities for treatment of chronic GvHD will be at the discretion of the treating transplant oncologist. Systemic immune suppressive medications that the patient is already receiving at the time of enrollment will be tapered at the discretion of the treating transplant oncologist.

Infectious prophylaxis should follow institutional guidelines. All patients should continue on prophylaxis against viral, fungal and pneumocystis infections.

5.6.2 Prohibited Medications

After prior B-cell therapy, there must be a wash-out of 5 therapeutic half-lives, when pharmacodynamic effect would be minimal (e.g., one year following rituximab).

From the time of initiation of conditioning regimen subjects must not have received any biologic investigational agent (i.e. any drug not approved for sale in the country in which it is being used).

For 30 days prior to administration of belimumab (or 5 half-lives, whichever is greater) subjects must not have received any non-biologic investigational agent (i.e. any drug not approved for sale in the country in which it is being used).

Live vaccines should not be given within 30 days prior to administration of belimumab or concurrently with belimumab.

5.6.3 Supportive Care Guidelines

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Use of neutrophil growth factors and red blood cell growth factors is permitted per institutional policy and in accordance with the ASCO guidelines. Transfusions may be given in accordance with institutional policy.

5.7 Management of Adverse Clinical Events and Dose Modification Guidelines

Belimumab is generally a well-tolerated agent. Most common adverse reactions are: nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, depression, migraine. Management guidelines for some potential events are outlined below. Further details are available in the Investigator's Brochure. All serious AEs, including AEs of Special Interest, i.e., serious hypersensitivity or infusion reactions; serious infections, including herpes zoster and opportunistic infections; malignancy; and/or Suicidal thought, intent or behaviour must be reported to GSK within 24 hours of awareness.

Hypersensitivity and Infusion Reactions

Site personnel will be aware of the risk of hypersensitivity reactions, which may present as infusion reactions, and monitor subjects closely. Subjects should remain under clinical supervision for 3 hours after completion of the first 2 infusions. The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. 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 infusions, subjects should be monitored during infusion and for 30 minutes after infusion according to standard operating procedure for IV infusions. 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 with recurrence of clinically significant reactions after initial resolution of symptoms following appropriate treatment. Therefore, subjects should be monitored during and for an appropriate period of time after administration of belimumab. Delayed-type, non-acute hypersensitivity reactions have also been observed and included symptoms such as rash, nausea, fatigue, myalgia, headache, and facial edema.

Serious infections

Serious infections, including herpes zoster and opportunistic infections are rare, but possible. Infection prophylaxis should follow institutional guidelines. If patient develops infection requiring intravenous or intramuscular antibiotics, belimumab may be held for up to two weeks and will then be administered. If a patient needs a dose held for more than two weeks, the PI will be contacted to determine suitability for further study participation.

Rash with or without pruritus

Rash should be managed symptomatically according to standard medical practice. Patient should be evaluated for presence of acute GvHD (see guidelines below).

Elevation of liver enzymes

Elevation of liver enzymes is not listed as an expected adverse event with belimumab. However, elevated liver enzymes can occur in the context of acute GvHD and such patients should be evaluated for presence of acute GvHD.

Nausea and/or vomiting

Standard anti-emetics may be used for prophylaxis and treatment of nausea or vomiting.

Diarrhea

Diarrhea should be managed according to clinical practice. Patient should be evaluated for presence of acute GvHD (see guidelines below).

Depression and suicidality

Some autoimmune diseases have an increased risk of depression and suicidal behavior and/or ideation [Bachen, 2009; Timonen, 2003; Stenager, 1992]. For this reason, in studies of subjects with autoimmune disease, subjects should be assessed for depression, suicidal ideation and/or behavior at each visit by the treating physician (to be recorded in a physician note).

Progressive Multifocal Leukoencephalopathy (PML)

PML resulting in neurological deficits, including fatal cases, has been reported in SLE subjects 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, belimumab should be discontinued and consideration should be given to stopping immunosuppressant therapy.

5.8 Acute GvHD

Any patient with new rash, diarrhea or elevated liver enzymes should be evaluated for presence of acute GvHD. In the event a study participant were to develop acute GvHD grade III-IV after initiating belimumab therapy, belimumab treatment will be held. Belimumab administration can be delayed for up to two weeks, however, if the grade of acute GvHD does not improve to grade II or less by that time, belimumab will be discontinued indefinitely and patient will be taken off study.

5.9 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative pregnancy test within 7 days prior to the first dose of belimumab.

Women of childbearing potential must agree to one of the following:

- Complete abstinence from intercourse from 2 weeks prior to administration of the first dose of belimumab until 16 weeks after the last dose of belimumab (if consistent with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are <u>not</u> acceptable methods of contraception.
- Consistent and correct use of one of the following acceptable methods of birth control for one month prior to the start of the study agent, during the study, and 16 weeks after the last dose of study agent:
- Oral contraceptive, either combined or progestogen alone
- Injectable progestogen
- Implants of levonorgestrel or etonogestrel
- Estrogenic vaginal ring
- Percutaneous contraceptive patches
- Intrauterine device (IUD) or intrauterine system (IUS) with < 1% failure rate as stated in the product label
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, "documented" refers to the outcome of the investigator's/designee's medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject's medical records.
- Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository)

If a patient is suspected to be pregnant, belimumab should be immediately discontinued. In addition, a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing. If a female

patient or female partner of a male patient becomes pregnant during therapy or within one month after the last dose of belimumab, the investigator must be notified in order to facilitate outcome follow-up.

5.10 Study Stopping Rule

As this is a pilot study enrolling 10 eligible participants, the study will be suspended if any death considered at least possibly related to study treatment occurs during participation. The suspension may be lifted only if review of the event by the PI and QASMC results in a recommendation to permit further study enrollments.

6 PHARMACEUTICAL INFORMATION

6.1 Belimumab (Benlysta) Description

Benlysta (belimumab) is a human IgG1λ monoclonal antibody specific for soluble human B lymphocyte stimulator protein (BLyS, also referred to as BAFF and TNFSF13B). Belimumab has a molecular weight of approximately 147 kDa. Belimumab is produced by recombinant DNA technology in a mammalian cell expression system.

6.2 Clinical Pharmacology

Please refer to Section 1.2.

6.3 Pharmacokinetics and Drug Metabolism

Please refer to Section 1.2.

6.4 Supplier(s)

Belimumab will be provided free of charge by GSK.

6.5 Dosage Form and Preparation

Belimumab will be supplied as a sterile, white to off-white, preservative-free, lyophilized powder for intravenous infusion. It will be provided in single-use glass vials with a rubber stopper and a flip-off seal. Each 5-mL vial contains 120 mg of belimumab and each 20-mL vial contains 400 mg of belimumab. Upon reconstitution with Sterile Water for Injection, USP, each single-use vial delivers 80 mg/mL belimumab in 0.16 mg/mL citric acid, 0.4 mg/mL polysorbate 80, 2.7 mg/mL sodium citrate, and 80 mg/mL sucrose, with a pH of 6.5.

Dilution Instructions:

1. Dextrose intravenous solutions are incompatible with BENLYSTA. BENLYSTA should only be diluted in 0.9% Sodium Chloride Injection, USP. Dilute the reconstituted product to 250 mL in 0.9% Sodium Chloride Injection, USP (normal saline) for intravenous infusion. From a 250-mL infusion bag or bottle of normal saline, withdraw and discard a volume equal to the volume of the reconstituted solution of BENLYSTA required for the patient's dose. Then add the required volume of the reconstituted

solution of BENLYSTA into the infusion bag or bottle. Gently invert the bag or bottle to mix the solution. Any unused solution in the vials must be discarded.
2. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard the solution if any particulate matter or discoloration is observed.
3. The reconstituted solution of BENLYSTA, if not used immediately, should be stored protected from direct sunlight and refrigerated at 2° to 8°C (36° to 46°F). Solutions of BENLYSTA diluted in normal saline may be stored at 2° to 8°C (36° to 46°F) or room temperature. The total time from reconstitution of BENLYSTA to completion of infusion should not exceed 8 hours.
4. No incompatibilities between BENLYSTA and polyvinylchloride or polyolefin bags have been observed.

6.6 Storage and Stability

Vials of belimumab should be stored refrigerated between 2° and 8°C (36° to 46°F). Vials should be protected from light and stored in the original carton until use; it should not be frozen; exposure to heat should be avoided. It should not be used beyond the expiration date.

6.7 Administration

Belimumab will be given intravenously at a dose of 10 mg/kg over the course of one hour. Refer to the package insert for reconstitution instructions.

6.8 Special Handling Instructions

None.

7 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix G for definitions and Appendix H for a grid of reporting timelines.

Adverse events will be tracked from C1D1, as soon as the infusion of Belimumab, through 30 days following the last day of study treatment. All adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF
- Adverse events that are less than CTCAE grade 3
- AEs not of special interest as defined in Section 7.1.4.1 (special interest AEs will be recorded regardless of grade, including those thought to be related to chronic GvHD)

Refer to the data submission schedule in Section 12 for instructions on the collection of AEs in the EDC.

Reporting requirements for Washington University study team may be found in Section 7.1.

7.1 Sponsor-Investigator Reporting Requirements

7.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change. The PI is required to promptly notify the IRB of the following events:

7.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The Sponsor investigator is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

7.1.3 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the Washington University principal investigator to report to the FDA as follows:

- Report any unexpected fatal or life-threatening suspected adverse reaction (refer to Appendix G for definitions) no later than **7 calendar days** after initial receipt of the information.
- Report a suspected adverse reaction that is both serious and unexpected (SUSAR, refer to Appendix G) no later than **15 calendar days** it is determined that the information qualifies for reporting. Report an adverse event (Appendix G) as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:
    - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
    - One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug

    - An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group
- Report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies that suggest a significant risk in humans exposed to the drug no later than 15 calendar days after it is determined that the information qualifies for reporting.
- Report any findings from animal or in vitro testing that suggest significant risk in humans exposed to the drug no later than 15 calendar days after it is determined that the information qualifies for reporting.
- Report any clinically important increase in the rate of a serious suspected adverse reaction of that listed in the protocol or IB within 15 calendar days after it is determined that the information qualifies for reporting.

Submit each report as an IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. Study teams must notify the Siteman Cancer Center Protocol Development team of each potentially reportable event within 1 business day after initial receipt of the information, and must bring the signed 1571 and FDA Form 3500A to the Siteman Cancer Center Protocol Development team no later than 1 business day prior to the due date for reporting to the FDA.

Each notification to FDA must bear prominent identification of its contents ("IND Safety Report") and must be transmitted to the review division in the Center for Drug Evaluation and Research (CDER) or in the Center for Biologics Evaluation and Research (CBER) that has responsibility for review of the IND. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such ("Follow-up IND Safety Report").

7.1.4 Reporting to GSK

In addition to events described in Section 7.4 as reportable, all events of possible drug-induced liver injury with hyperbilirubinemia defined as ALT ≥ 3x ULN **and** bilirubin ≥ 2x ULN (>35% direct) (or ALT ≥ 3x ULN and INR > 1.5, if the INR is measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants) should be reported.

Any pregnancy that occurs during study participation must be reported. To ensure subject safety, each pregnancy must be reported within 2 weeks of learning of its occurrence. 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 promptly reported to GSK.

Safety information should be sent via email notification **within 24 hours of awareness** for all SAEs and AEs of Interest, and within 60 days for any other reportable non-serious events to oax37649@gsk.com (backup fax number +44 208 754 7822).

7.1.4.1 Adverse Events of Special Interest:

The frequency of all (both serious and non-serious) of the following Adverse Events of Special Interest will be assessed and included in the final report:

- Serious Hypersensitivity or Infusion Reactions
- Serious infections, including herpes zoster and opportunistic infections
- Malignancy
- Suicidal thought, intent or behaviour

7.2 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 7.1

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

8 MEASUREMENT OF EFFECT

8.1 Primary Endpoint: Safety and Tolerability

All subjects who receive any study treatment are evaluable for safety and tolerability. Subjects are followed for primary endpoint from first receiving study treatment until a 30-day follow-up after the last dose. Adverse events will be diagnosed and graded according to CTCAE v4.03 as described above.

8.2 Secondary Endpoints

Subjects who receive at least 2 cycles of belimumab are evaluable for secondary and explorative endpoints.

1. **Incidence and severity of chronic GvHD at 6, 12 and 24 months after alloHCT**
   The presence of chronic GvHD will be determined according to the 2014 NIH Criteria (**Appendix B**). If chronic GvHD is diagnosed, each organ will be scored 0-3 and graded, according to the 2014 NIH criteria for Diagnosing and Staging of Chronic GvHD (**Appendix D**). These data will allow calculation of the NIH global severity score of mild, moderate or severe (**Appendix E**). Data will be collected on forms capturing chronic GvHD diagnosis and activity according to the 2014 NIH Criteria for chronic GvHD.

2. **Incidence and severity of acute GvHD at 3 and 6 months after alloHCT**
   Acute GvHD will be graded according to modified Minnesota CIBMTR (**Appendix F**).

3. **Overall survival at 6, 12 and 24 months after alloHCT**
   Overall survival will be determined from date of belimumab initiation, with death from any cause as the event of interest, and censoring at last follow up date for those with incomplete observations.

4. **Relapse rate at 6, 12 and 24 months after alloHCT**
   Relapse rate will be determined from date of belimumab initiation and censoring at last follow up date for those with incomplete observations.

5. **Overall corticosteroid requirement (dose and duration) for treatment of chronic GvHD at 6, 12 and 24 months after alloHCT**
   The dose of corticosteroids will be captured at each study visit.

6. **Use of alternative treatment modalities for chronic GvHD at 6, 12 and 24 months after alloHCT**
   The use of additional systemic immune suppressive agents will be captured at each study visit.

8.3 Exploratory Endpoints/Correlative Studies

Subjects who receive at least 2 cycles of belimumab are evaluable for explorative endpoints/correlative studies.

Age- and disease-matched controls with matched conditioning regimens and donor source/mismatch status will be obtained from the Bone Marrow Transplant Tissue Bank at Siteman Cancer Center at Washington University in St. Louis. These patients have had peripheral blood samples stored at time of transplant, 30 days post-transplant, 100 days post-transplant, 180 days post-transplant, and 360 days post-transplant. Immune competence and B cell phenotype subset panels will be performed on these samples. Additionally, BAFF levels will be measured and correlated with development of GvHD similarly to study cohort. The clinical outcomes including survival, recurrence rate, engraftment, incidence of acute and chronic GvHD, and medications list are readily available in institutional computerized database.

9 CORRELATIVE STUDIES

All subjects will have blood drawn for correlative studies. Serum will be removed from a serum separator tube (SST) containing 10 mL patient blood, and peripheral mononuclear cells (PBMC) will be isolated from a 10 mL CPT tube at baseline and first follow-up post-belimumab (+24 wk), then every three months thereafter to assess BAFF levels and immune cell reconstitution. An additional serum sample will be collected prior to cycle 3 (+4 wk) to assess efficacy of belimumab in suppressing BAFF levels. BAFF levels will be quantitated by ELISA and immune cell reconstitution will be quantitated by whole blood flow cytometry.

Once there is evidence of B cell reconstitution (anticipate between 18-24 months post-transplant), serum (1 x 10 mL SST) and PBMC (5 x 10 mL CPT tubes) will be collected for isolation of the

mononuclear cell layer, or buffy coat, by Ficoll-based density separation for additional B cell phenotyping by flow cytometry. Similar blood collections will be performed at 1 and 2 years post-C1D1. Additional optional correlative lab draws will continue to be collected for similar analysis yearly thereafter up to 5 years post-C1D1. All samples will be processed and stored in the Dunn Lab (7408 BJCIH, 660 S Euclid Ave, St. Louis, Missouri) or Tissue Procurement Center until time of analysis.

The following variables will be assessed:

- Immune competence panel to quantify the relative frequency and absolute number of T cells, B cells, and NK cells which will determine impact of belimumab on immune reconstitution following transplantation.
- BAFF levels at baseline and following treatment to assess the efficacy of belimumab in suppressing this target cytokine as well as to correlate development of chronic GvHD with circulating BAFF levels (i.e. degree of inhibition).
- A B cell phenotype panel will be performed to assess the effect of belimumab on reconstitution and homeostasis of B cell subsets after transplant.
- Immunoglobulin subset quantification will be performed to determine the effect of belimumab on the functional competency of B cells after transplant.

10 STUDY CALENDAR

10.1 Screening and Treatment Calendar

	Screening[1]	Baseline[2]	C1	C2	C3	C4	C5	C6	C7
				+2wk	+4wk	+8wk	+12wk	+16wk	+20wk
Informed consent	X								
H&P, ECOG PS	X		X	X	X	X	X	X	X
VS	X		X	X	X	X	X	X	X
CBC	X		X	X	X	X	X	X	X
CMP, LDH, phosphate, uric acid, magnesium	X		X	X	X	X	X	X	X
Pregnancy test[7]	X		X[8]	X	X	X	X	X	X
IgG and IgA		X							
Hepatitis serologies	X								
ECG (triplicate)	X		As clinically indicated						
Belimumab			X[5]	X[5]	X[5]	X[6]	X[6]	X[6]	X[6]
Research blood		X[2]			X[4]				
Acute GvHD assessment		X			X	X	X	X	X
Chronic GvHD assessment					X	X	X	X	X
Immunosuppressive medication assessment	X	X	X	X	X	X	X	X	X
Medication reconciliation		Monthly							
AE assessment		X ---------- X[9]							

1. Screening assessments must take place between 30 and 80 days post-transplant
2. pre-treatment
3. Every 3 months starting at F/U #1 (+24wk)
4. Prior to treatment
5. Dosing window is +/- 3 days
6. Dosing window is +/- 1 week
7. Women of childbearing potential only
8. Pregnancy test need not be repeated on Cycle 1 if conducted within 7 days of Cycle 1 dose
9. AE assessment continues for 30 days post-EOT

10.2 Follow-Up Calendar

Follow-up visits start 4 weeks after the end of protocol treatment (6-month follow-up is 6 months post-C1D1 and 4 weeks post-C7D1).

	+6mo	+9mo	+12mo	+15mo	+18mo	+21mo	+24 mo	+3 yr	+4 yr	+5 yr
CBC	X									
CMP, LDH, phosphate, uric acid, magnesium	X									
Pregnancy test[1]	X									
Research blood[2]	X	X	X	X	X	X	X	X[2]	X[2]	X[2]
Acute GVHD assessment	X									
Chronic GVHD assessment	X	X	X	X	X	X	X			
Immunosuppressive medication assessment	X	X	X	X	X	X	X			
AE assessment	X									

1. Women of childbearing potential only
2. Once there is evidence of B cell reconstitution, additional blood will be drawn (refer to Section 9), and will continue on an optional basis at 3, 4, and 5 years post-C1D1

11 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least 1 patient has been enrolled) or one year after accrual has opened (if no patients have been enrolled at the six-month mark).

For phase I dose escalation studies, the Principal Investigator will review all patient data at least monthly (or before each dose-escalation if occurring sooner than monthly), and provide a semi-annual report to the Quality Assurance and Safety Monitoring Committee (QASMC). For phase II or dose expansion cohorts of a phase I study, the Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy (phase I studies only if efficacy is objective of the protocol)
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Power analysis and/or interim analysis (if described in the protocol)
- Summary of toxicities separated by cohorts with the number of dose-limiting toxicities indicated
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

12 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	**Submission Schedule**
On-Study Form	Prior to start of study treatment
Treatment Form Medical History Form	At the end of each cycle

Correlatives Form	Baseline Cycle 3 pre-treatment 6 mos post-C1D1 9 mos post-C1D1 1 yr post-C1D1 15 mos post-C1D1 18 mos post-C1D1 21 mos post-C1D1 Evidence of B-cell reconstitution 2 yrs post-C1D1 3 yrs post-C1D1 4 yrs post-C1D1 5 yrs post-C1D1
Treatment Summary Form	End of treatment
Acute GvHD Form	Baseline Cycle 3 Cycle 4 Cycle 5 Cycle 6 Cycle 7 6 mo f/u
Chronic GvHD Form	Cycle 3 Cycle 4 Cycle 5 Cycle 6 Cycle 7 6 mo f/u 9 mo f/u 12 mo f/u 15 mo f/u 18 mo f/u 21 mo f/u 24 mo f/u
Follow-Up Form	6 mos 9 mos 12 mos 15 mos 18 mos 21 mos 24 mos
Adverse Event Form Immunosuppressive Meds Form	Continuous
Progression Form	Time of progression
Death Form	Time of death

12.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 7.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

13 STATISTICAL ANALYSIS

This trial is designed to allow preliminary assessments of safety/tolerability and efficacy of belimumab in the post-allogeneic stem cell transplant setting. No pre-specified hypothesis testing will be performed. All analyses of demographics, biological activity, and safety will be descriptive. A 90% exact binomial confidence interval will be constructed for preliminary efficacy information. Data obtained from correlative studies will be used to identify parameters associated with efficacy from belimumab treatment that will guide design of subsequent larger clinical trials. Age-, disease-, and donor-matched subjects will be used as an institutional control. These control subjects will be identified within the Bone Marrow Transplant and Lymphoma Tissue Bank (HRPO# 201103349). Presently, there are roughly 100 subjects with banked specimens and associated clinical outcomes data that will serve as the comparator in this study in assessing preliminary efficacy. The data from this study will be used for sample size calculation estimates of an expansion cohort in a subsequent phase II study. A total of N=10 patients will be enrolled for this study. Though the sample size was not determined based on statistical power, this would provide us reasonable precision on both safety and feasibility. Based on intensive simulation studies regarding the sample size for pilot and translational studies, Piantadosi (2005) recommends that a sample size of 10 to 20 patients be adequate to provide preliminary information. For safety assessment, for example, there would be 90% chance of observing at least 1 serious adverse event if the true rate is at least 20%. Conversely, there would be less than 10% chance that we would observe 2 or more serious adverse events if the true rate is less than 5%.

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APPENDIX A. Clinical Differentiation of Acute and Chronic GvHD

Category	Time of Symptoms After alloHSCT or DLI	Presence of Acute GvHD Features	Presence of Chronic GvHD Features
Acute GvHD			
Classic acute GvHD	≤ 100 days	Yes	No
Persistent, recurrent, or late-onset acute GvHD	> 100 days	Yes	No
Chronic GvHD			
Classic chronic GvHD	No time limit	No	Yes
Overlap chronic GvHD	No time limit	Yes	Yes

DLI- donor lymphocyte infusion

APPENDIX B. Diagnostic Criteria for Chronic GvHD

Organ or Site	Diagnostic Features[1]	Distinctive Features[2]	Others[3]	Common Features[4]
Skin	Poilkiloderma Lichen planus-like features Sclerotic features Morphea-like features Lichen sclerosis-like features	Depigmentation Papulosquamous lesions	Sweat impairment Ichthyosis Keratosis pilaris Hypopigmentation Hyperpigmentation	Erythema Maculopapular rash Pruritus
Nails		Dystrophy Longitudinal ridging, splitting, or brittle features Onycholysis Pterygium unguis Nail loss		
Scalp and body hair		New onset of scarring or nonscarring scalp alopecia Loss of body hair Scaling	Thinning scalp hair, typically patchy, coarse, or dull Premature grey hair	
Mouth	Lichen-type features	Xerostomia Mucocele Mucosal atrophy Pseudomembranes Ulcers		Gingivitis Mucositis Erythema Pain

Organ or Site	Diagnostic Features[1]	Distinctive Features[2]	Others[3]	Common Features[4]
Eyes		New onset dry, gritty, or painful eyes Cicatricial conjunctivitis Keratoconjunctivitis sicca Confluent areas of punctuate keratopathy	Photophobia Periorbital hyperpigmentation Blepharitis	
Genitalia	Lichen planus-like features Lichen sclerosis-like features	Erosions Fissures Ulcers		
Females	Vaginal scarring or clitoral/labial agglutination			
Males	Phimosis or urethral/meatus scarring or stenosis			
GI Tract	Esophageal web Strictures or stenosis in the upper to mid-third of the esophagus		Exocrine pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea Weight loss

Organ or Site	Diagnostic Features[1]	Distinctive Features[2]	Others[3]	Common Features[4]
Lung	Bronchiolitis obliterans diagnosed with lung biopsy BOS [5]	Air trapping and bronchiectasis on chest CT	Cryptogenic organizing pneumonia Restrictive lung disease[6]	
Muscle, Fascia, joints	Fasciitis Joint stiffness or contractures secondary to sclerosis	Myositis or polymyositis[7]	Edema Muscle cramps Arthralgia or arthritis	
Hematopoietic and immune			Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hypergammaglobilinemia Autoantibodies (AIHA and ITP) Raynaud's phenomenon	
Other			Pericardial or pleural effusions Ascites Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality or cardiomyopathy	

1. Sufficient to establish the diagnosis of chronic GvHD
2. Seen in chronic GvHD, but insufficient alone to establish a diagnosis of chronic GvHD; In all cases, infection, drug effect, malignancy, or other causes must be excluded

3. Can be acknowledged as part of the chronic GvHD symptomatology if the diagnosis is confirmed
4. Shared features by both acute and chronic GvHD
5. BOS can be diagnostic for lung chronic GvHD only if distinctive sign or symptom present in another organ
6. Pulmonary entities under investigation or unclassified
7. Diagnosis of chronic GvHD requires biopsy

APPENDIX C. Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX D. Organ Specific Staging of Chronic GvHD

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capabl of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† **SCORE % BSA** ☐ *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ **S**uperficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Poikiloderma ☐ Severe or generalized pruritus ☐ Hair involvement ☐ Nail involvement ☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GI Tract ***Check all that apply:*** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5%* ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LIVER	☐ Normal total bilirubin and ALT or AP < 3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	☐ Elevated total bilirubin > 3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LUNGS**				
Symptom score:	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: **%** FEV1 ☐	☐ FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%
Pulmonary function tests ☐ Not performed				
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

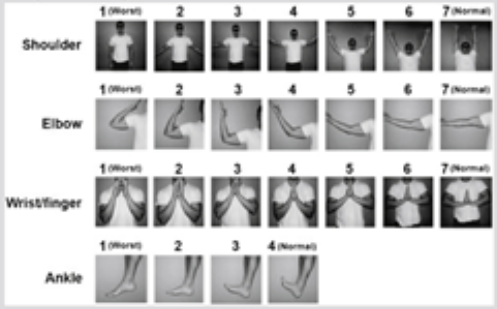
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
GENITAL TRACT (*See Supplemental figure*‡) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs‡ and females with or without discomfort on exam	☐ Moderate signs‡ and may have symptoms with discomfort on exam	☐ Severe signs‡ with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms ___	☐ Others (specify):_____

Overall GVHD Severity *(Opinion of the evaluator)* ❑ **No GVHD** ❑ **Mild** ❑ **Moderate** ❑ **Severe**

Photographic Range of Motion (P-ROM)



APPENDIX E. Global Scoring of Chronic GvHD

Stage	Definition
Mild	1 or 2 organs involved with no more than score 1 *plus* Lung score 0
Moderate	At least 1 organ (not lung) with a score of 2 or 3 or more organs involved with no more than score 1 or Lung score 1
Severe	At least 1 organ with a score of 3 or Lung score of 2 or 3

In skin: higher of the 2 scores to be used for calculating global severity

In lung: FEV1 is used instead of clinical score for calculating global severity

If the entire abnormality in an organ is noted to be unequivocally explained by a non-cGVHD documented cause, that organ is not included for calculation of the global severity

If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the score organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

APPENDIX F. Minnesota-CIBMTR Staging and Grading for Acute GVHD

Acute GVHD Staging

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Skin (% BSA)	No rash	< 25%	25%-50%	> 50%	Generalized erythroderma with bullae
Gut (diarrhea, mL/day)	< 500	> 500	> 1000	> 1500	Severe abdominal pain +/- ileus
Upper GI		Persistent, severe nausea			
Liver (bilirubin, mg/dL)	≤ 2	2.1-3	3.1-6	6.1-15	> 15

BSA = body surface area; GI = gastrointestinal.

Acute GVHD Grading, MN-CIBMTR Criteria

Grade	Skin	Liver	Lower GI	Upper GI
Minnesota				
I	1-2	0	0	0
II	3	1	1	1
III	-	2-4	2-3	-
IV	4	-	4	-
CIBMTR				
A	1	0	0	0
B	2	1-2	1-2	1
C	3	3	3	-
D	4	4	4	-

APPENDIX G: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website: http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse event

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX H: Reporting Timelines

Expedited Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Drug/Device Manufacturer**
Serious AND unexpected suspected adverse reaction			Report no later than 15 calendar days after it is determined that the information qualifies for reporting	
Unexpected fatal or life-threatening suspected adverse reaction			Report no later than 7 calendar days after initial receipt of the information	
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment		
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.			
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.			
Protocol exception	Approval must be obtained prior to implementing the change			
Clinically important increase in the rate of a serious suspected adverse reaction			Report no later than 15 calendar days after it is determined that the	

Event	HRPO	QASMC	FDA	Drug/Device Manufacturer
of that list in the protocol or IB			information qualifies for reporting	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.			
Breach of confidentiality	Within 10 working days.			
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.			

Routine Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Drug/Device Manufacturer**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.	The most current toxicity table from the DSM report is provided to the FDA with the IND's annual report.	
Minor deviation	Report summary information at the time of continuing review.			
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.			
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue			

and the patient will be withdrawn, report at continuing review.