Abbreviated Title: Baricitinib in cGVHD

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Title: A Phase 1/2 study of baricitinib, a JAK1/2 inhibitor, in chronic graft-versus-host disease (cGVHD) after allogeneic hematopoietic stem cell transplantation (SCT)

NCI Principal Investigator: Steven Z. Pavletic, MD, MS,
Immune Deficiency Cellular Therapy Program (IDCTP)
National Cancer Institute
Building 10, Room 4-3130
10 Center Drive
Bethesda, MD 20892
Phone: 240-760-6174
E-mail: pavletis@mail.nih.gov

Drug Name:	Baricitinib
IND Number:	129360
Sponsor:	Center for Cancer Research
Manufacturer:	Eli Lilly and Company
Supplier:	Eli Lilly and Company

Commercial Agents: None

PRÉCIS

Background:

Chronic graft-versus-host disease (cGVHD) is the leading cause of non-relapse morbidity and mortality in persons after allogeneic hematopoietic stem cell transplantation (SCT).

Approximately 50% of patients with cGVHD have disease refractory to systemic corticosteroids; currently, there is no standard second-line therapy.

The JAK-STAT pathway relays the signaling function of several inflammatory cytokines that have a role in GVHD (IFN-γ, IL-2, IL-6, IL-12).

Murine models have demonstrated activity of JAK inhibitors in graft-versus-host disease.

Baricitinib is a potent and selective inhibitor of JAK1 and JAK2 that has demonstrated anti-inflammatory effects and a good safety profile in patients with rheumatoid arthritis, but has not been evaluated in GVHD.

Objectives:

To determine the safety and tolerability of baricitinib in patients with cGVHD that is refractory to steroids

To determine the efficacy of baricitinib in patients with cGVHD that is refractory to steroids

Eligibility:

Inclusion:

Age ≥18 years

Moderate or severe cGVHD per NIH consensus criteria

Karnofsky performance status ≥ 50%

cGVHD that did not respond to high-dose corticosteroids (prednisone at 1.0 mg/kg/day for at least 1 week or prednisone at 0.5 mg/kg/day or 1 mg/kg every other day for at least 4 weeks), or second-line therapy (any)

Receiving stable or tapering doses of systemic therapy in the preceding 4 weeks if taking systemic therapy for cGVHD

Exclusion:

Neutrophils <1.0x10^9/L, platelets <50X10^9/L, creatinine ≥ 1.5 times the upper limit of normal ***or*** estimated creatinine clearance <50mL/min/1.73m^2 (Cockroft-Gault formula), serum aspartate aminotransferase or alanine aminotransferase concentration >3x ULN or total bilirubin ≥1.5x ULN

Progressive malignancy, uncontrolled infection or any major organ dysfunction as defined by the protocol

Design:

This is a Phase 1/2 trial to determine the safety and efficacy of baricitinib in patients with cGVHD that is refractory to steroids.

Patients will initially be treated with baricitinib at 2mg daily for 12 weeks. If the response at 12 weeks is a CR and there has not been a DLT, the dose will remain at 2mg daily for an additional 12 weeks, with the primary response assessment at 24 weeks of total treatment. If the response is a PR or stable disease, the dose will be increased to 4mg daily for an additional 12 weeks, with the primary response assessment at 24 weeks of total treatment. If there is progression of disease at any time within the first 12 weeks, the dose can be increased to 4mg daily at that time, and patients will continue for a total of 24 weeks of treatment. Patients will have the option to continue baricitinib for an additional 6 months as tolerated if they have stable or responding disease.

The co-primary endpoint of safety will be determined by rate, severity, and duration of adverse events based on CTCAE v4 criteria. Assessment for DLTs will occur every 2 weeks during the first 4 weeks of each dose level. Safety monitoring will occur every 4 weeks thereafter.

The co-primary endpoint of efficacy will be defined as rate of overall response at 24 weeks per NIH consensus criteria (CR or PR).

Peripheral blood samples will be collected prior to treatment, at 2 weeks, at 12 weeks and every 12 weeks thereafter to evaluate cytokine and cellular profiles, STAT phosphorylation, candidate chronic GVHD biomarkers. Pharmacokinetic studies will also be performed at each dose level.

In an initial futility analysis, if 0 of the first 7 patients enrolled in cohort 1 have responded at 12 weeks, then a 2nd cohort of patients will be accrued to start treatment at the higher dose (4mg daily). Otherwise, if 1 or more of the first 7 patients respond in cohort 1, then 21 evaluable patients will be treated in cohort 1. Similarly, if the second cohort is used, and if 0 of the 7 patients enrolled in this second cohort have responded at 12 weeks, then no further patients will be accrued. Otherwise, if 1 or more of the first 7 patients respond in cohort 2, then 21 evaluable patients will be treated in cohort 2.

A total of 21 evaluable patients will be enrolled in either cohort 1 or 2 as appropriate, in order to have 80% power to detect a response rate consistent with 30% and ruling out 10%, with a one-sided significance level of 0.10 for the cohort. As an early stopping rule for safety, if 2/3 or greater patients at any given dose level experiences a dose limiting toxicity requiring dose reduction or discontinuation, that dose will not be subsequently used and no further dose escalation will take place.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objectives:

- To determine the safety and tolerability of baricitinib in patients with cGVHD that is refractory to steroids
- To determine the efficacy of baricitinib in patients with cGVHD that is refractory to steroids

1.1.2 Secondary Objectives:

- To determine the efficacy of baricitinib on patient reported outcomes in patients with steroid-refractory cGVHD
- To determine impact of baricitinib on the immune system and inflammatory markers
- To describe pharmacokinetics and pharmacodynamics of baricitinib in patients with cGVHD

1.2 BACKGROUND AND RATIONALE

1.2.1 Chronic graft-versus-host disease

Chronic graft-versus-host disease (cGVHD) is an important late complication of allogeneic hematopoietic cell transplantation. It is a leading cause of mortality in patients who are more than 2 years after allogeneic hematopoietic stem cell transplantation (SCT).[1,2] Symptoms of cGVHD usually appear within 2 years post-SCT. Reported incidences have been in the range of 36% in recent years, and has been significantly rising compared to previous time periods,[3] and can depend on recipient age, donor type, graft type, graft manipulation or donor lymphocyte infusions.[4] Chronic GVHD is strongly associated with prior acute GVHD (aGVHD).[5,6] Traditionally, the cutoff point between aGVHD and cGVHD was day 100 post-SCT. In 2005, an NIH consensus project proposed two main GVHD categories, each with two subcategories: (1)

"classic" aGVHD occurring within 100 days after SCT and (2) "persistent, recurrent or late" aGVHD. The broad category of cGVHD includes: (1) "classic" cGVHD (without features or characteristics of aGVHD), and (2) an "overlap syndrome" with concordant features of cGVHD and aGVHD.[4] Chronic GVHD is a multi-organ alloimmune and autoimmune disorder characterized by immune dysregulation, immunodeficiency, impaired organ function and decreased survival. It requires prolonged ongoing immunosuppression and inter-disciplinary management. Moreover, studies of long term survivors of SCT have shown the chronic GVHD is a key risk factor for mortality and leading cause of death in patients who survive 2-5 years after SCT.[7,8]

Pathophysiology

The pathophysiology of cGVHD is poorly understood. T- (Th1, Th17, Thf) and B-cells play a role in the pathogenesis of cGVHD, suggesting a general loss of tolerance, including abnormalities in the function of regulatory T-cells (Tregs) [9,10]. Natural Tregs (CD4+,CD25+,FoxP3+) maintain self-tolerance.[10,11] Studies in mice indicate Tregs can suppress GVHD and that a deficiency of Tregs worsens GVHD.[12] There are conflicting data in humans concerning role of Tregs in the development of cGVHD.[13] A recent study suggested *in vivo* administration of low-dose IL-2 as a potential Treg-mediated therapeutic approach for severe cGVHD.[14]

Chronic GVHD is associated with T-cell dysregulation, which consequently leads to cytokine dysregulation. In persons with cGVHD, higher levels of tumor necrosis factor-α, IL- 6, transforming growth factor-β, and IL-1β are reported.[15-19]

Autoimmunity and autoreactive T-cells have an important role in cGVHD. Some studies have shown that host thymus is not required for induction of cGVHD and that quiescent autoreactive T- and B-cells in transplants from non-autoimmune donors may be activated and expanded to cause cGVHD.[20] In contrast, involvement of thymus-dependent pathways in cGVHD development begins with injury to the thymus from a chemotherapy-conditioning regimen or aGVHD. Loss of B-cells with the ability to produce antibodies and to present antigen is also involved in the pathophysiology and may enhance development of cGVHD. Autoantibodies like anti-nuclear, anti-mitochondrial, anti-parietal, anti–smooth muscle and anti–parotid are present in persons with cGVHD.[21,22] Also, persons with autoantibodies had more cGVHD-associated symptoms than persons without autoantibodies.[22] Autoantibodies against platelet-derived growth factor receptor (PDGFR) may play a role in cGVHD.[23] These PDGFR-α autoantibodies stimulate thyrosine phosphorylation in a cascade of events contributing inflammation and fibrosis.

There are studies that also report elevated levels of BAFF (B-cell activating factor of the TNF family), which is produced by T-cells and granulocytes. BAFF supports differentiation and survival of normal B-cells in persons with cGVHD and autoimmune diseases.[12,24] Fujii et al. showed that in early-onset cGVHD, there are elevated sBAFF, sIL-2Rα, sCD13, and anti-dsDNA levels. In late-onset cGVHD, sBAFF, anti-dsDNA and ANA are higher, suggesting that the B-cell activation is predominant.[25] These observations create rationale for treatments with anti-CD20 antibodies in cGVHD.[26] All of these pathways are potential targets for cGVHD therapy. However, to date, no laboratory parameter is considered a reliable biomarker for the diagnosis, measurement of severity, prognosis or therapeutic effect in cGVHD.[27]

Clinical manifestations

The usually affected organs in cGVHD are the skin, eyes, mouth, gut, liver, lungs, joints and genitourinary tract. Examples of diagnostic skin manifestations are sclerotic features and poikiloderma, lichen-type and hyperkeratotic plaques in the mouth or bronchiolitis obliterans in lung biopsy.[4] The clinical manifestations of the disease are reminiscent of the autoimmune diseases such as systemic sclerosis, systemic lupus erythematosus or Sjögren syndrome. According to the NIH consensus global scoring system, cGVHD is categorized as mild, moderate or severe. Systemic immune-suppressive therapy is usually indicated in persons with cGVHD involving 3 or more organs or with a severity score of 2 or higher in any organ. Systemic therapy is also to be considered in persons with thrombocytopenia (platelets $<100x10^9/L$) or progressive onset during prednisone treatment.[5] Chronic GVHD eventually leads to impaired functional performance, deteriorating quality of life, increased risk of infections and death.[28-31]

Treatment

Initial therapy for cGVHD is well established consisting of prednisone with or without a calcineurin inhibitor. However, only about 50% of persons have a durable response.[11,32] There are no standard recommendations for second-line treatment of cGVHD and about 75% of patients fail treatment.[33] There are no FDA approved agents in the treatment of cGVHD. Recommendations for therapy are based on a long list of poorly standardized phase 2 trials or retrospective case analyses.[32] Diverse drugs (about 40 are described) are used, including sirolimus, tacrolimus, mycophenolate, methotrexate, extracorporeal photopheresis, monoclonal antibodies, pentostatin, imatinib, low dose IL-2, and others. The decision for which drug to use is based on logistics, cost, failed prior treatments, toxicity profile and subject or clinician preferences.

For many years, cGVHD has been difficult to address because of the lack of standardized criteria for diagnosis, staging and response to therapy. In 2004, as an effort of the NIH-sponsored Consensus Development Project, a series of guidelines were published to address diagnosis and staging, histopathology, biomarkers, assessment of response to therapy, ancillary therapy, supportive care and the design of clinical trials.(2005 NIH consensus papers).[34] These were recently updated based on evidence from prospective validations (2014 NIH consensus papers).[35] Typically, cGVHD usually lasts 2 to 5 years, and approximately 85% of survivors are able to discontinue systemic immune suppression. Five-year survival rates for patients with cGVHD ranged from 72%, 52%, and 25% in patients with low, intermediate, and high risk, respectively, using a Center for Blood and Marrow Transplant Research (CIBMTR) risk score.[36] Treatment goals in management of cGVHD include both alleviation of symptoms and the control and reversion of the destructive immunological process. Therapy for cGVHD is largely unsatisfactory and persons should be treated on investigational clinical protocols whenever possible.[29]

1.2.2 JAK inhibition in cGVHD

JAK inhibitors are agents that block the JAK-signal transducer and activator of transcriptional factor (STAT) pathways, which are involved in the signaling function of many inflammatory cytokines and ultimately impact T-cell differentiation. In particular, JAK1/2 relays signaling of IFN-γ, IL-2, IL-6, IL-12, and IL-23. Given the efficacy of JAK inhibition in relieving symptoms in patients with myelofibrosis related to an excess of proinflammatory cytokines, even in patients who are JAK2 mutation-negative,[37] there has been interest to evaluate JAK inhibition in GVHD.

In addition to the direct impact on T-cell differentiation, there is also evidence that JAK1/2 inhibition impairs the differentiation, maturation, and cytokine production of dendritic cells,[38] thus impacting antigen presentation. JAK1/2 also mediates IFN-γ receptor signaling, which is essential for CXCR3 expression that is involved in T-cell trafficking to target organs. Moreover, murine models of aGVHD have shown that STAT1 and STAT3, which serve as transcription factors after being phosphorylated by activated JAK kinases, are activated in an early stage of aGVHD, and lead to further proinflammatory cytokine production.[39] These data further support the potential role of JAK inhibition in the treatment of GVHD. Ruxolitinib, a selective JAK1/2 inhibitor, has been extensively studied and is approved for patients with myelofibrosis and polycythemia vera, and has recently been evaluated in the setting of GVHD. Of note, STAT phosphorylation has not been studied in animal models or human subjects with cGVHD, and this will be addressed in the current study.

Several studies have demonstrated that treatment with ruxolitinib in murine models of aGVHD has led to significantly improved survival, less weight loss, and less histopathologic evidence of GVHD in target organs.[40-42] In addition, donor T-cells in the ruxolitinib treated mice have maintained alloreactivity and anti-tumor activity. Carniti et al demonstrated that treatment with ruxolitinib led to dose-dependent reduction in IL-6 and IL-12 levels; moreover, CXCR3 expression was decreased on donor T-cells, which led to differential migration of T-cells to target organs compared to control mice. They also showed some evidence of hepatotoxicity from ruxolitinib but no impact on hematologic parameters. Spoerl et al showed that ruxolitinib led to decreased expansion of alloreactive T-cells compared to controls. In addition, T-cell phenotypes differed, where the ruxolitinib treated mice had higher frequencies of Tregs, and lower CD4+ IFN-γ+ cells and T-central memory cells, which are known to maintain GVHD[42]. There was also evidence of direct suppression of STAT3 phosphorylation. Choi et al, showed that ruxolitinib reduced T-cell CXCR3 expression, and reduced GVHD and survival by modulating T-cell trafficking[26,41].

Broad JAK inhibition was evaluated by Park et al [43]using tofacitinib, a JAK1/2/3 inhibitor, in a semi-allogeneic murine model, which led to reduction of GVHD pathology and suppression of donor CD4+ T-cell proliferation and IFN-γ production. It also reduced mucocutaneous GVHD in a skin-specific model. However, the JAK3 pathway is involved in Treg proliferation and survival, as well as hematopoiesis, and response to infectious pathogens. Tofacitinib has not been tested clinically in patients with GVHD, and in general, there is theoretical concern that broad JAK1/2/3 inhibition would lead to toxicities in SCT patients who are at higher risk for cytopenias and infection. Thus, agents with selective JAK1/2 inhibition are preferable in this setting.

Based on the promising preclinical results of ruxolitinib in GVHD, there has been some early clinical experience in patients with GVHD. Spoerl et al reported on their experience treating 6 patients with steroid-refractory aGVHD (n=4) and cGVHD (n=2).[42] The 2 patients with cGVHD had skin involvement and multiple prior therapies, and had a response after 1 week of treatment. These findings were concomitant with decrease in serum IL-6 and IL-2R (soluble IL2 receptor). At a low dose of ruxolitinib, cytopenias were not observed. In a study from Germany, ruxolitinib was used and retrospectively analyzed in 54 patients with steroid-refractory aGVHD and 41 patients with steroid-refractory cGVHD (median 3 prior lines of therapy) across 13 transplant centers.[44] In patients with cGVHD, the overall response rate (defined as 50% decrease of immunosuppression for at least 4 weeks) was 85% with a median time to response of 3 weeks

(range 1-25). Toxicities included cytopenias (17%) and CMV reactivation (15%). There was no increase in malignancy relapse. In addition, responses were not restricted to specific organs. Ruxolitinib off label use for advanced chronic GVHD has also been reported in an abstract of a case series from Emory, with similar results as in the German study (Khoury et al, American Society of Hematology Annual Meeting 2015). These reports support further study of JAK inhibition in patients with steroid-refractory cGVHD.

1.2.3 Baricitinib

Baricitinib (LY3009104, formerly INCB028050, Eli Lilly and Company) is a selective JAK1/2 inhibitor that has been studied in patients with inflammatory conditions such as rheumatoid arthritis, psoriasis, and diabetic nephropathy. It is an oral, potent, and reversible inhibitor of JAK1 (IC_{50}=5.9 nM) and JAK2 (IC_{50}=5.7 nM), with less potency for JAK3, tyrosine kinase 2 (TYK2), or other kinases.[45] In addition, it has demonstrated excellent potency for inhibition of IL-2-, IL-6-, and IL-23- stimulated phosphorylation of JAKs and STATs, and IL-2 induced proliferation of T-cells. In preclinical models of arthritis, it has demonstrated anti-inflammatory effects while preserving humoral immunity and had no hematologic effects.[45] It has been tested in doses of 0.5mg-20mg in over 3000 patients and healthy volunteers, and the safety profile is well understood.[46,47] Phase 1, 2, and 3 studies in RA have been completed, and several studies in patients with psoriasis and diabetic nephropathy are ongoing. Common toxicities seen across studies include decreases in hemoglobin and neutrophils (mean values usually remaining within the normal range), increases in platelets (mean values usually remaining within the normal range), increases in creatinine (mean values usually remaining within the normal range) and increases in exposure in patients with renal impairment, increases in total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides, increases in hepatic enzymes, increases in creatine phosphokinase (CPK), and increased incidence of infections (mostly respiratory). Decreases in neutrophils and hemoglobin and other lab abnormalities have been reversible upon discontinuation of the drug.

The efficacy of baricitinib in the treatment of RA has been demonstrated. A Phase 2a study in patients with RA refractory to disease-modifying anti-rheumatic drugs (DMARDs) showed improvements in signs and symptoms of RA after treatment with baricitinib for 12 weeks, with a flat dose-response curve at 4mg, 7mg, and 10mg daily doses.[48] This study did show an increased incidence of mild to moderate herpes zoster infections. A randomized controlled Phase 2b study using baricitinib for RA with inadequate response to methotrexate at doses of 1, 2, 4, and 8mg showed that patients treated at 4mg and 8mg had significantly better response compared to placebo at 12 weeks.[49] There was no difference between the 4mg and 8mg groups in regards to efficacy. However, there were more hematologic toxicities with the 8mg dose (decreases in neutrophil count and hemoglobin). Other common adverse events included upper respiratory tract infections, and increases in LDL, HDL, creatinine, and CPK. Importantly, there were no cases of opportunistic infections. Based on these results, the 4mg dose was the dose chosen to evaluate in the Phase 3 studies in RA.[50] There is some experience at the NIH using baricitinib in patients with rare autoinflammatory conditions, and per personal communication (data unpublished), there have been cases of BK virus infection. The final results of this study are pending, and infection will be monitored closely on the current protocol.

In regards to pharmacodynamics, baricitinib maximally inhibits cytokine-induced STAT phosphorylation at 2 hours after the dose. A dose of 10mg has shown 70% reduction in IL-6 induced phosphorylation of STAT3, which returns to baseline at 24 to 48 hours without

subsequent dosing[45]. In the Phase 2a study in patients with DMARDs-refractory RA, significant reductions in plasma levels of IL-6, IL-1β, TNF-α were observed after 12 weeks of treatment at both 7mg and 10mg doses.

Baricitinib has not been previously evaluated in the treatment of patients with GVHD. Based on the efficacy of baricitinib in RA through the mechanism of selective JAK1 and JAK2 inhibition, the growing data supporting the use of JAK inhibitors in the treatment of aGVHD and cGVHD, and the dire need for effective second line therapeutic options in cGVHD, we aim to evaluate the safety and efficacy of baricitinib in patients with cGVHD that is refractory to steroids.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Moderate or severe cGVHD (after allogeneic hematopoietic stem cell transplantation) diagnosed and staged per NIH criteria,[4] **Appendix B** and **Appendix C**. Responses to JAK inhibitors have not been restricted to specific organs, so any organ involvement is eligible.

2.1.1.2 Age ≥18 years of age. Because inadequate dosing or adverse event data are currently available on the use of baricitinib in patients <18 years of age, children are excluded from this study.

2.1.1.3 Karnofsky performance score ≥50% (**Appendix A**)

2.1.1.4 Chronic GVHD that did not respond to high-dose corticosteroids (prednisone at 1.0 mg/kg/day for at least 1 week or prednisone at 0.5 mg/kg/day or 1 mg/kg every other day for at least 4 weeks), or second-line therapy (any)

2.1.1.5 If patient is taking systemic therapy for cGVHD at the time of enrollment, they must be on a stable or tapering doses in the preceding 4 weeks.

2.1.1.6 Patients must have normal organ and marrow function as defined below:

– absolute neutrophil count	≥1,000/mcL
– absolute lymphocyte count	≥500/mcL
– platelets	≥50,000/mcL
– hemoglobin	≥9 g/dL
– total bilirubin	≤1.5 X institutional upper limit of normal, unless there is a known history of Gilbert's disease
– AST(SGOT)/ALT(SGPT)	≤3 X institutional upper limit of normal
– Creatinine	< 1.5 times the upper limit of normal, ***or:***
– creatinine clearance	≥50 mL/min/1.73 m^2. Creatinine clearance should be calculated per institutional standard.

2.1.1.7 Primary malignancy for which the patient received transplant has been stable for 3 months prior to enrollment on study

2.1.1.8 The effects of baricitinib on human fetal development are unknown. Women of child-bearing potential and men must agree to use 2 effective forms of contraception (hormonal or barrier method of birth control; abstinence) for the duration of study participation and for at least 7 days after study drug exposure. Should a woman become

pregnant or suspect she is pregnant while she or her partner is participating in this study, or if a man's partner becomes pregnant or suspects she is pregnant while he is participating in this study, she or he should inform their treating physician immediately.

2.1.1.9 Ability of subject to understand and the willingness to sign a written informed consent document.

2.1.2 Exclusion Criteria

2.1.2.1 Systemic immune suppression or systemic therapy for cGVHD started within preceding 4 weeks.

2.1.2.2 Hypersensitivity to JAK inhibitors

2.1.2.3 Any serious medical condition within the previous 4 weeks which places the subject at an unacceptable risk if he or she were to participate in the study or confounds the ability to interpret data from the study, including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmias, acute kidney injury, or psychiatric illness/social situations that would limit compliance with study requirements.

2.1.2.4 Uncontrolled infection, including active HIV-1, Hepatitis B (HBV) and/or Hepatitis C (HCV) infection (positive HBV or HCV viral load in the setting of positive HBV core antibody or surface antibody or HCV antibody). History of HBV or HCV is allowed if there is no uncontrolled viral infection. Because the study agent may impact response to infections, patients with any active viral infection are excluded.

2.1.2.5 Recurrent or progressive malignancy requiring anticancer treatment

2.1.2.6 Other cancer except that for which the transplant was done <2 years before study entry, except non-melanoma skin cancer or carcinoma in situ of the uterine cervix or breast

2.1.2.7 Patients who are receiving any other investigational agents

2.1.2.8 NIH lung score 3 (**Appendix D**)

2.1.2.9 Pregnant women are excluded from this study because the teratogenic effects of baricitinib are unknown. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with baricitinib, breastfeeding should be discontinued if the mother is treated with this agent.

2.1.3 Recruitment Strategies

This protocol may be abstracted into a plain language announcement posted on NIH websites and on NIH social media platforms. In addition, patients will be directly referred to the NIH for this clinical trial through the well-developed NIH chronic GVHD study group referral base. In addition, patients who are referred for the CCR protocol "Natural History Study of Clinical and Biological Factors Determining Outcomes in Chronic Graft-Versus-Host Disease" study (04-C-0281) will be screened for this trial. Also, patients who undergo SCT at the NIH will be eligible for enrollment on this trial, which will provide another mechanism for screening patients. Finally, physicians and patients will be made aware of the study through our patient advocacy groups (National Marrow Donor Program, National Bone Marrow Transplant Link, Blood & Marrow Transplant Information Network, Meredith Cowden Foundation) and other professional forums.

2.2 SCREENING EVALUATION

Screening procedures will be performed on a CCR screening protocol (01C0129), or most commonly on 04C0281 "Natural History of Chronic GVHD." All studies must be completed within 4 weeks prior to enrollment:

- History and physical exam, Karnofsky performance score
- Documentation of cGVHD diagnosis, NIH organ and global severity stage
- Laboratory studies: CBC, platelets, differential, PT/PTT, serum chemistries (including sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorus, blood urea nitrogen [BUN], creatinine/creatinine clearance, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST [SGOT], ALT [SGPT], lactate dehydrogenase [LDH], and uric acid), creatine kinase (CK), urinalysis, pregnancy testing (in women of childbearing potential), thyroid-stimulating hormone (TSH), free T4
- Additional screening studies: Serologies for HIV, HBV, HCV; CMV PCR; blood and urine cultures, respiratory viral panel. Cultures with no growth present at 48 hours will be deemed negative.
- Pulmonary function tests (PFTs): FEV1, FEV1/FVC ratio, RV, RV/TLC, FEF25-75, DLCO; this will include pre- and post-bronchodilator evaluation
- Chest CT scan in inspiration and end-expiration
- Electrocardiogram (ECG) and echocardiogram

For baseline evaluations, please see Section **2.4**.

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

2.3.1 Treatment Assignment and Randomization Procedures

Cohorts

Number	Name	Description
1	*Phase I cohort*	*Patients who have undergone hematopoietic allogeneic transplant and have moderate to severe cGVHD that is refractory to treatment with steroids up to 21 patients, for response assessment at 2-4 mg*
2	*Phase II cohort*	*Patients who have undergone hematopoietic allogeneic transplant and have moderate to severe cGVHD that is refractory to treatment with steroids after response determination in cohort 1.*

Arms

Number	Name	Description
1	*Phase 1 Arm*	*Baricitinib 2 mg per day, increasing to 4 mg per day in patients who have a partial response or unchanged disease at 12 weeks*
2	*Phase II Arm*	*Baricitinib 4 mg per day*

Arm Assignment

Patients in Cohort I will be directly assigned to Arm I. Patients in Cohort II will be directly assigned to Arm II.

2.4 BASELINE EVALUATION

The following studies will be performed at baseline after consent and enrollment on this protocol and within 10 days prior to starting the study drug, unless otherwise indicated below. Tests done at screening that fall within the appropriate timeframe for baseline testing need not be repeated.

- History and physical exam, Karnofsky performance status
- Documentation of cGVHD diagnosis per NIH criteria (ref), NIH organ and global stage (**Appendix D** and **Appendix E**), baseline assessments (clinician assessment form A and patient assessment form B) (**Appendix F** and **Appendix G**) per NIH response criteria,[51] date of cGVHD diagnosis, prior and current treatments, prednisone or other steroid dose, and other patient, donor, and transplant characteristics (**Appendix H**)
- Laboratory studies: CBC with differential, serum chemistries (including sodium, potassium, chloride, CO2, calcium, magnesium, phosphorus, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST (SGOT), ALT (SGPT), lactate dehydrogenase (LDH), uric acid), CK, urinalysis, pregnancy test, TBNK, drug levels if pertinent (tacrolimus, cyclosporine, sirolimus), CRP, C3 and C4, immunoglobulin levels, CMV PCR, BK virus PCR (blood and urine), fasting lipid panel
- Pregnancy test in women that can have children
- MRI of the involved extremity if clinically indicated (acceptable if done within 4 weeks)
- Specialty evaluations of cGVHD (acceptable within 4 weeks): dermatology, ophthalmology, dental, rehabilitation and occupational therapy, gynecology for females
- Occupational therapy evaluation: functional assessment (ACS and HAQ), fatigue assessment (MDFI), and upper extremity use (DASH/MAM) (See **Appendix L**)
- Patient-reported outcome surveys: Lee cGVHD symptom scale, human activity profile, FACT-BMT (See **Appendix I**)
- Optional diagnostic and research biopsies of the skin and mouth, and other organs (only if clinically indicated). Biopsies performed within 3 months prior to enrollment (e.g. on 04-C-0281 “Natural History of Chronic GVHD” protocol) are acceptable. Patients may opt out of research and diagnostic biopsies and these will not be required for initiating study drug.

- Research samples (blood, saliva, oral microbiome swabs) (see Section **5.1**) Saliva and oral microbiome swabs will be collected at the time of the oral biopsy, if performed
- Documentation of concurrent medications

Of note: Patients who have already been enrolled, but who have symptoms suggestive of infection (fever, productive cough, radiologic findings) at the baseline evaluation will have further workup as standard of care to rule out active infection. Patients with active infection will be treated until the infection is under control or antibiotic therapy is completed. Baseline procedures that have exceeded the desired timeframe will be repeated before the patient may begin study therapy.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a phase 1/2 single arm study to evaluate the safety and efficacy of baricitinib at doses of 2mg-4mg in patients with cGVHD after SCT. Doses of 0.5mg-20mg have been studied in patients with autoimmune diseases and have demonstrated a good safety profile (Baricitinib Investigator's Brochure, Eli Lilly and Company). Based on studies in patients with RA, there seems to be a plateau efficacy response at doses above 4mg daily, and it is the 4mg daily dose that was taken to the Phase 3 studies. In addition, in anecdotal experience with JAK inhibitors in patients with GVHD, low doses appear to be sufficient for response.

Patients will be enrolled in up to 2 sequential cohorts of up to 21 patients.

The first cohort of patients will be treated with baricitinib starting at a dose of 2mg daily for 12 weeks. For safety purposes, patients who experience a DLT within the first 4 weeks will be able to restart at 1mg daily, and will continue at this dose as tolerated (see Section **3.1.1**). If they experience a DLT at this dose, they will be taken off treatment. Regarding efficacy, patients who have a complete response (CR) on 2mg daily at 12 weeks will continue the same dose until the 24 week time point for the primary efficacy endpoint. For patients who have a partial response (PR) or unchanged disease at 12 weeks, the dose will be increased to 4mg daily until the primary efficacy endpoint response assessment at 24 weeks. Following any dose increase to 4mg, patients who experience a DLT within the first 4 weeks will have a dose reduction back to 2mg daily. For patients who experience cGVHD progression at any time within the first 12 weeks on 2mg daily, the dose can be increased to 4mg daily up until the primary efficacy endpoint response assessment at 24 weeks, unless they experience a DLT. Prior to the 12 week response assessment, an initial response assessment will occur at 6 weeks, but there will be no dose changes unless there has been progression or toxicities, as outlined. If at least 1 patient in the first cohort has a PR or CR, the remainder of the study will follow the initial schema as above, and 21 evaluable patients will be treated as part of cohort 1. After the primary response assessment, patients who have unchanged or responding disease will have the option to continue baricitinib for an additional 6 months as tolerated.

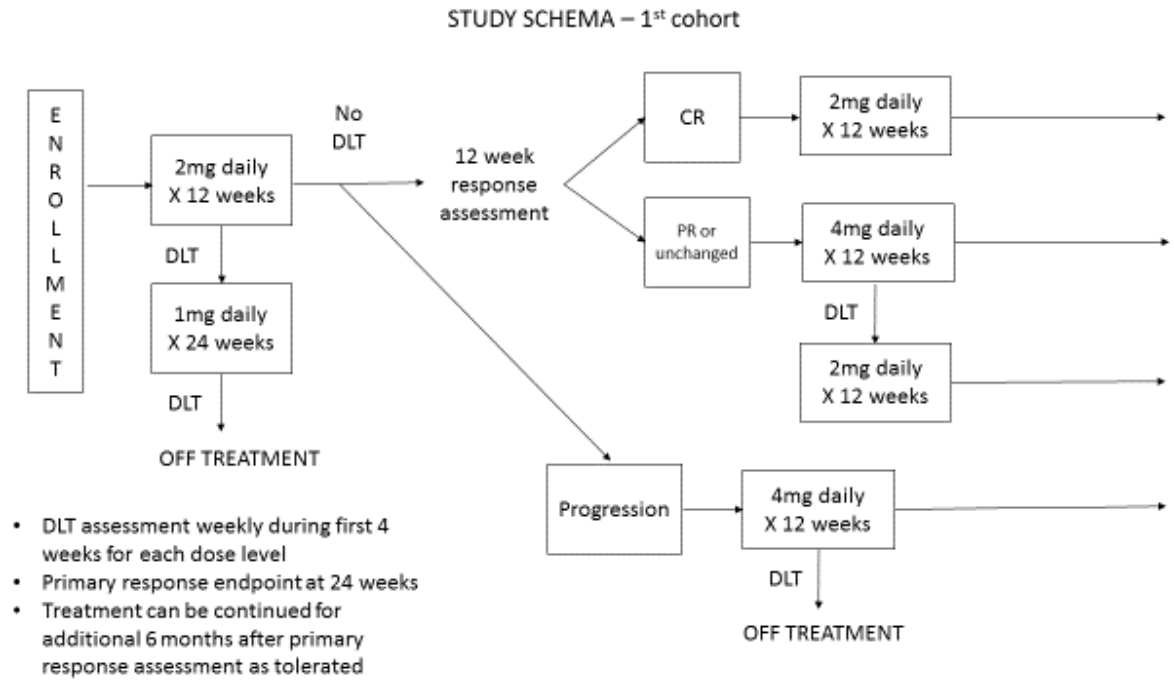
If no patients among the first 7 achieve a CR or PR on 2mg daily at the 12 week response assessment in the first cohort of patients, the second cohort will be enrolled starting at 4mg daily if no safety issues have arisen, with the same parameters for DLT monitoring. Similarly, if 0 of the first 7 treated in cohort 2 have a response, then no further patients will be treated in cohort 2.

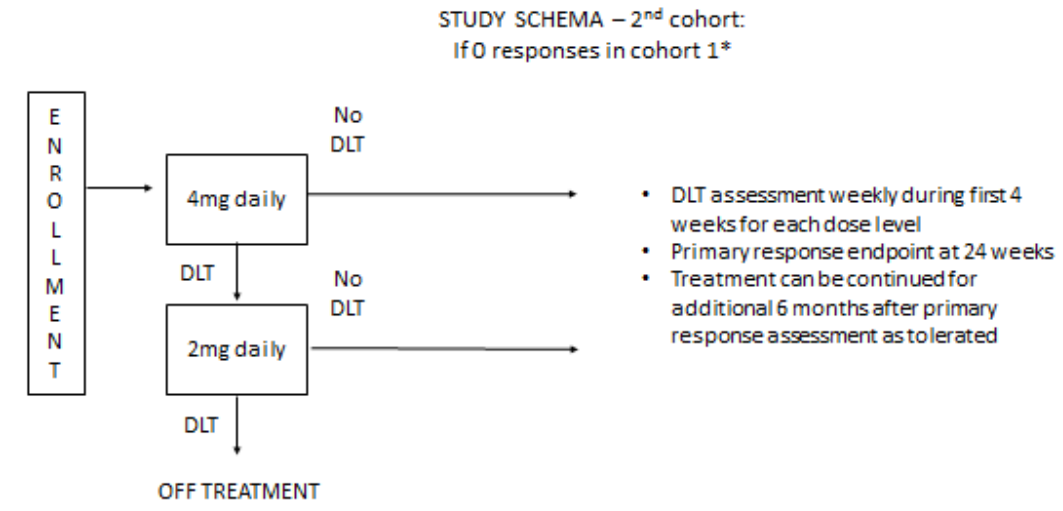
If there is at least one patient with a response in the first 7 patients treated on cohort 2, then 21 evaluable patients will be treated in cohort 2.

Concurrent topical and ancillary treatments for cGVHD are allowed per standards of care and will be recorded (see Section **4**). Other systemic immune suppression must stay stable or be tapered (systemic immunosuppression taper should be attempted no earlier than after 4 weeks on study), throughout the treatment with baricitinib (with up to 2 steroid pulses allowed for disease stabilization per Section **4.1**).

Patients who discontinue therapy for any reason will be followed for up to 24 months after discontinuing baricitinib as indicated in section **3.5**.

Peripheral blood samples will be collected prior to treatment, at 2 weeks, at 12 weeks and every 12 weeks thereafter to evaluate cytokine and cellular profiles, STAT phosphorylation, candidate chronic GVHD biomarkers. Pharmacokinetic studies will also be performed at each dose level on day 1 and after 15 days of treatment (Section **5.1.3**).





*If ≥1 response in cohort 1, 2nd cohort will use identical schema as cohort 1

3.1.1 Dose Limiting Toxicity

DLT will be defined as any grade ≥3 non-hematologic or grade ≥4 hematologic adverse event, or hemoglobin <6.5 g/dL, within 4 weeks of starting any dose level (1mg, 2mg or 4mg) except those that are clearly and incontrovertibly due to extraneous causes. One intrapatient dose de-escalation after a DLT will be permitted in patients who have not experienced cGVHD progression. In patients that have experienced disease progression, further dosing will cease in a patient at the occurrence of the first DLT.

3.1.1.1 Dose Escalation

This study will include an intra-patient dose escalation. The starting dose of baricitinib will be 2mg PO daily, a dose that has been well tolerated in previous studies of patients with autoimmune diseases. The first 7 subjects will be treated for a total of 12 weeks at this dose, unless they demonstrate cGVHD progression prior to this, at which time they will increase the dose to 4mg. If patients have a CR, they will continue at this dose until the primary efficacy endpoint. If patients have a PR or unchanged disease (see Section **6.3**), the dose will increase to 4mg until the primary efficacy endpoint evaluation takes place at 24 weeks, unless they experience a DLT. If at least 1 patient of the first 7 in cohort 1 has a response, subjects will follow the original dose escalation schema. If 0 of these first 7 patients have a response, then patients will begin to be enrolled onto cohort 2, and will be started at the 4mg PO daily dose initially, unless they experience a DLT, at which time they will decrease the dose to 2mg.

As an early stopping rule for safety, if 2/3 or greater patients at any given dose level experiences a dose limiting toxicity requiring dose reduction or discontinuation, that dose will not be subsequently used.

Intra-patient Dose Escalation Schedule	
Dose Level	**Dose of IND Agent**
Level -1	1mg
Level 1	2mg
Level 2	4mg

3.2 DRUG ADMINISTRATION

Baricitinib will be given as 1 mg, 2mg or 4mg tablets to be taken orally once a day on days 1-28 of a 28 day cycle. Each daily dose should be taken at approximately the same time of day. There is no restriction in regards to taking the drug in relation to meals. Patients will be asked to complete a medication diary (see **Appendix J**).

Baricitinib tablets should be swallowed whole and not broken or chewed.

If a dose of baricitinib is missed, it should be taken as soon as possible on the same day, unless it is within 1 hour of the next dose, at which time the dose should not be made up.

Patients who take more than the prescribed dose of baricitinib should be instructed to seek medical care if needed and contact study staff immediately.

3.3 DOSE MODIFICATIONS

Patients who develop grade 2 toxicity (not including comorbidities that are present at baseline prior to treatment) for >7 days should hold baricitinib until the toxicity resolves (≤grade 1) and then restart at the same dose level. Toxicities will be monitored at each study visit. If grade 2 toxicity recurs or worsens, the patient should be reduced to the next lower dose level, unless they are at dose level -1, at which time they should discontinue study drug. Should the toxicity recur

after dose reduction, the patient should be taken off treatment. In the case of multiple simultaneous grade 2 toxicities, these instructions will apply to each individual toxicity separately.

After the 4 week DLT assessment period for any dose level, patients who develop grade 3 non-hematologic or grade 4 hematologic toxicity (not including comorbidities that are present at baseline prior to treatment), or hemoglobin <6.5 g/dL, should hold baricitinib until the toxicity resolves (≤grade 1 or baseline). If the toxicity resolves within 28 days, patients may restart at the next lower dose level, unless they are at dose level -1, at which time they should discontinue the study drug. Should the toxicity recur at grade 3 non-hematologic or grade 4 hematologic toxicity (not including comorbidities that are present at baseline prior to treatment), or hemoglobin <6.5 g/dL, after dose reduction, the patient should be taken off treatment.

Patients who develop grade 4 non-hematologic toxicity should discontinue and be taken off treatment.

Study drug may be held up to 28 days for resolution of grade 2 or grade 3 toxicity. Otherwise, if no resolution within 28 days, patients will be taken off treatment,

For infection related toxicities only: study drug should be held for any infectious toxicity of ≥grade 3. Infection will need to be controlled with appropriate management prior to restarting study drug for grade 3. If the infection occurs at the time of a study evaluation, all of the assessments at that time point will need to be postponed until the infection is controlled. Study drug can be restarted at the same dose level for grade 3 unless other criteria are met for dose reduction as above. Study drug may be held up to 28 days in the setting of uncontrolled infection; otherwise, if no resolution within 28 days, patients will be taken off treatment. Patients who develop grade 4 toxicity related to infection should discontinue and be taken off treatment.

Toxicities are defined as those events that are possible, probably, or definitely related to baricitinib.

3.4 QUESTIONNAIRES

Patient self-report questionnaires administered in this study are part of the standard NIH chronic consensus recommended criteria for the evaluation of cGVHD in clinical trials. Questionnaires will be completed by patients with each cGVHD assessment and response evaluation (see section **3.7**, **Study Calendar**). These standardized assessments are designed to evaluate patient quality of life (FACT-BMT), functional performance (HAP) and symptoms (Lee cGVHD symptom scale). The purpose of these evaluations is to assess the potential benefit of the administered therapy as compared to the baseline. These forms have been extensively used, published and validated. These forms are also standard part of many NCI CCR cGVHD protocols (**Appendix I**). Patient questionnaires are only offered in English and are therefore not required in non-English speaking subjects that may unexpectedly be enrolled on the protocol.

3.5 FOLLOW-UP

All persons will be followed for adverse events for whichever is longer, 30 days after last dose of baricitinib or until return to baseline or stabilization of AE per section **6.1 0** by phone call. Patients who discontinue therapy before completion of the 24 or 48 weeks will be asked to return for a follow up visit to complete their off treatment assessments within 30 days after the last dose

of study drug. Patients who discontinue therapy at the completion of 24 or 48 weeks will complete the off treatment assessments at the last scheduled visit. Following this, patients will be invited for a follow up visit at 3 months after last dose, then followed up by a phone call to the patient and/or the primary physician's office at 12, 18 and 24 months after completing baricitinib. If they choose not to follow up at 3 months, they will be followed up by phone call. The phone call will focus on a) survival status and cause of death if pertinent, b) ongoing systemic treatment for cGVHD and date of discontinuation, c) primary malignancy progression, d) any second primary malignancy, e) return to work part-time or full-time. Primary and contributing causes of death are to be recorded in the CRF and the patient's medical record.

3.6 TELEHEALTH

Telemedicine is the use of interactive audio, video, audio-visual, or other telecommunications or electronic technology by a licensed health care practitioner to deliver clinical services. This protocol will allow the team to practice telemedicine to communicate with patients in real time, to be able to monitor and collect data, as well as the ability to share the patients' health information with other health professionals. Providers may include primary providers, specialists/consultants and nurses. Other members of the healthcare team may also be present to aid with the communication devices, scheduling or records management. These visits may include the following: patient history, verbal exam, symptom reporting, education, and questionnaires.

The patient or patient's legal representative will be informed prior to the use of a telemedicine encounter and consent will be obtained as outlined in the Consent Process and Documentation (section **12.6**).

Telemedicine visits will be arranged through our NIH Clinical Center Health Information Management Department and will be scheduled using NIH-approved remote platforms. Telemedicine visits may be used for follow-up visits if deemed appropriate by the PI. All telemedicine visits must be documented in CRIS like a normal onsite visit and the note should indicate that this visit was performed virtually. Remote visits will be conducted in compliance with NIH guidelines and FDA regulations.

Local Evaluations

A patient may be asked to come to the NIH CC for an in-person assessment or be referred to their local provider or outside lab, at the discretion of the investigator. All physical exams, assessments, and labs used for follow-up visits may also be performed with the patient's local physician or completed at outside labs. For laboratory evaluations conducted with local providers, interlaboratory variability is not a concern. In the case of any visits with participants' local providers or outside labs, records will be obtained.

3.7 STUDY CALENDAR

Assessments[1]	**Screen (D -28 to -1)**	**BL BL / C1 D1**	**C1 D15**	**C2 D1**	**C2 D15**	**C3 D1**	**C3 D15**	**12 weeks C4 D1**	**C4D15**	**C5,6 D1**	**24 weeks C7 D1**	**C8,9 D1**	**36 weeks C10 D1**	**C11, 12 D1**	**48 weeks C12 D28**	**Off Treatment**[13]	**Optional 3 month follow up**[13]
Visit Window			±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	+/-5 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days
Informed Consent	X	--	--	--	--	--	--	--	--	--	--	--	--	--		--	--
NIH Advanced Directives Form[17]		X															
Baricitinib po qd[2]	--	X	X	X	X	X	X	X		X	X[2]	X[2]	X[2]	X[2]	X[2]	--	--
History and Physical Exam	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Confirmation of cGVHD[3]	X	--	--	--	--	--	--	--		--	--	--	--	--		--	--
Body Photography		X	--	--	--	--	--	--		--	X	--	--	--		X	--
Pulmonary Function Testing	X	--	--	--	--	--	--	X		--	X	--	X	--	X	X	--
Imaging[4]	X																--
Pregnancy Test[5]	X	X	X	X	X	X	X	X		X	X	X	X	X	X		--
cGVHD Therapies Recording	X		Throughout the study														
Vital Signs	X	X	X	X	X	X	X	X		X	X	X	X	--	X	X	X
Height	X	--	--	--	--	--	--	--		--	--	--	--	--		--	--
Weight	X	X	X	X	X	X	X	X		X	X	X	X	--	X	X	X
ECHO	X	--	--	--	--	--	--	--		--	--	--	--	--		--	--
ECG[6]	X	--	--	X	--	X	--	X		--	X	--	--	--		--	--
cGVHD New Patient Data Form		X															
Karnofsky Performance Status	X	X	--	--	--	--	--	X		--	X	--	X	--	X	X	X
Additional screening studies[7]	X		--	--	--	--	--	--		--	--	--	--	--		--	--
BK virus PCR (blood & urine)	X	X						X			X		X				

Assessments[1]	**Screen (D -28 to -1)**	**BL BL / C1 D1**	**C1 D15**	**C2 D1**	**C2 D15**	**C3 D1**	**C3 D15**	**12 weeks C4 D1**	**C4D15**	**C5,6 D1**	**24 weeks C7 D1**	**C8,9 D1**	**36 weeks C10 D1**	**C11, 12 D1**	**48 weeks C12 D28**	**Off Treatment**[13]	**Optional 3 month follow up**[13]
Visit Window			±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	+/-5 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days
CBC w/ differential, platelets	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PT, PTT	X																
Serum Chemistry[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CRP, C3, C4[18]	--	X	--	X	--	X	--	X		--	X	--	X	--	X	X	--
Urinalysis, fasting lipid panel	X	--X	--	--	--	--	--	X		--	X	--	X	--	X	X	--
TSH, free T4	X	--	--	--	--	--	--	--		--	--	--	--	--		--	--
cGVHD Assessment and Response Calculation[9]		X	--	--	X	--	--	X		--	X	--	X	--	X	X	--
Lee scale, HAP, FACT-BMT		X			X			X			X		X		X	X	X
AE Monitoring	--		Throughout the study														
Concurrent Drugs	X		Throughout the study														
Dermatology, ophthalmology, dental, gynecology		X									X[14]					X[14]	
Occupational therapy evaluation[15]		X									X[14]					X[14]	
Skin and Oral Biopsies, saliva collection and oral microbiome swabs[10]	--	X	--	--	--	--	--	--		--	X	--	--	--	--	--	--
TBNK	--	X	X		--		--	X			X	--	X	--	X	X[16]	X[16]
Blood for Immunologic Studies (includes PD)[11]	--	X	X	--	--	--	--	X			X	--	X	--	X	X	
Blood for PK Studies[12]	--	X C1D 1	X C1D 15	--	--		--	--X[12] C4D1	X	--	--	--	--	--	--	--	--

Assessments[1]	**Screen (D -28 to -1)**	**BL BL / C1 D1**	**C1 D15**	**C2 D1**	**C2 D15**	**C3 D1**	**C3 D15**	**12 weeks C4 D1**	**C4D15**	**C5,6 D1**	**24 weeks C7 D1**	**C8,9 D1**	**36 weeks C10 D1**	**C11, 12 D1**	**48 weeks C12 D28**	**Off Treatment**[13]	**Optional 3 month follow up**[13]
Visit Window			±5 days	±5 days	±5 days	±5 days	±5 days	±5 days	+/-5 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days
Study drug dispensation/ return/accountability	--	X	--	X		X		X		X	X	X	X	X	X	X	--

1 Clinic visits can occur ± 5 days. All procedures at protocol-driven time points are performed at the NIH Clinical Center, but if circumstances make this impossible, these data points will be collected in collaboration with referring physicians.

2 Baricitinib at assigned doses for 6 months; another 6-month course of treatment will be allowed for patients with response. Only patients who continue therapy beyond 6 months will be required to have clinical monitoring tests during cycles 7 through 12.

3 Use NIH diagnostic criteria for cGVHD (**Appendix B** and **Appendix M**: cGVHD New Patient Data Form. In addition, use **Appendix C** for clinical differentiation of acute versus cGVHD.

4 Chest CT done at screening; a chest CT may be done at response assessments if clinically indicated; a MRI may be done at baseline if clinically indicated

5 Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

6 ECG at indicated intervals screening and as clinically indicated. Prolongation of QTc > 0.5 s or QTc interval increases from baseline > 0.06 s is considered as a safety concern.

7 Serologies for HIV, HBV, HCV, CMV PCR, blood and urine cultures, respiratory viral panel, CMV PCR. Cultures with no growth present at 48 hours will be deemed negative. BK virus PCR (urine) will be performed at baseline.

8 Including at **screening**: sodium, potassium, chloride, CO2, calcium, magnesium, phosphorus, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST (SGOT), ALT (SGPT), lactate dehydrogenase (LDH), and uric acid), creatine kinase (CK); at **baseline and on study assessments** (30-mL) include all screening studies as well as: drug levels if pertinent (tacrolimus, cyclosporine, sirolimus), immunoglobulin levels, CMV PCR at least every other week the first 12 weeks, then every 4 weeks until 24 weeks. CMV PCR will not be performed at remote visits unless clinically indicated. Note: Baseline studies performed within the appropriate timeframe at screening need not be repeated. (See section **2.4**)

9 Includes primary and secondary measurement of response, performance scale, global rating (**Appendix D**, **Appendix E**, **Appendix F**, **Appendix G**, **Appendix I**). Note: The response assessment in **Appendix H** is not performed at baseline.

10 Skin and oral biopsies, saliva and microbiome swab collection will be performed at baseline and after 6 months of treatment, with intent to sample as close to the same area as possible. At baseline, the saliva and oral microbiome swabs will be collected at the time of the oral biopsy, if performed.

[11] Blood (48 mL in 6 CPT tubes) for immunologic studies will be drawn prior to first drug at all timepoints. PD baseline assay will be performed using some of the blood for immunologic studies. PD studies at the peak blood level of baricitinib will be performed on a 6ml (green topped heparin) tube collected at 2 hours post drug at Cycle 1 Day 1. PD studies will be repeated at any increase in drug dose.

[12] For determining serum baricitinib levels (PK), on the first day of each dose level a 3-mL blood (EDTA) sample will be taken pre-dose, then at 1, 2, and 4 hours after the dose. A sample will be collected at 24 hours after the first dose in up to 10 patients as feasible, but is not required on protocol. A trough level blood sample will be collected at the next scheduled visit at 15 (+/-1) days of continuous treatment at the initial dose. The sample will always be collected immediately before the next baricitinib dose to measure a 24 hour PK time point. This collection will also occur following 15 (+/-1) days of continuous treatment after an increase in dose level. The PK sample at week 12 is not collected if no change in dose level occurred. In the event of a serious adverse event or at the end of study, an additional sample may be collected within 24 hours of the last dose at the discretion of the investigator (See Section **5.1**). Every effort will be made to collect samples as prescribed in the timeline. Samples that are collected ± 15 minutes of collection time will not be considered a protocol deviation.

[13] Patients who discontinue study drug before completion will be asked to return to complete off treatment assessments within 30 days after the last dose of study drug. Patients who complete therapy (24 or 48 weeks) will complete the off treatment assessments at the last scheduled visit. All patients, regardless of reason for study drug discontinuation will be followed for adverse events by phone call for at least 30 days for adverse events and invited for an optional follow up visit a 3 months after study drug discontinuation followed by phone calls to the patient or patient's primary physician at 12, 18 and 24 months (if patients choose not to follow up at 3 months, they will be followed up by phone call) (see Section **3.5**)

[14] Subspecialty evaluations are required at baseline. Subsequent evaluations at 6 months and off treatment will be arranged based on organ involvement and medical need of individual patients. All response assessments will be performed by the transplant clinical team.

[15] Functional assessment (ACS and HAQ), fatigue assessment (MDFI), and upper extremity use (DASH/MAM) (See **Appendix L**)

[16] If PI deems TBNK is necessary at this visit.

[17] As indicated in section **12.3**, all subjects will be offered the opportunity to complete an NIH advanced directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required.

[18] CRP, C3, C4 will not be performed at remote visits unless clinically indicated.

3.8 COST AND COMPENSATION

3.8.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures are performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by an insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.8.2 Compensation

Participants will not be compensated on this study.

3.8.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.9 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

3.9.1 Criteria for removal from protocol therapy

- Completion of 12-month course of protocol therapy
- Progressive cGVHD or malignancy requiring new line of systemic therapy
- Participant requests to be withdrawn from active therapy
- Positive pregnancy test
- Unacceptable toxicity as defined in Sections **3.1.1** and **3.3**
- Dose interruption longer than 28 days
- Investigator discretion

The PI is to be notified of all discontinuations from study drug. The reason for dose modification/discontinuation should be recorded in the CRF and in the patient's medical records.

3.9.2 Off-Study Criteria

- Completed 2 year follow up period
- Subject withdrawal from follow-up period
- Patient lost to follow-up
- Investigator discretion
- Death

3.9.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within one month and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, an IRB approved certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4 CONCOMITANT MEDICATIONS/MEASURES

All medications (prescription and non-prescription), treatments and therapies taken throughout the study must be recorded on the appropriate page of the CRF. Patients will be advised to contact the study team before starting any new medications.

4.1 CONCOMITANT CORTICOSTEROID THERAPY AND TAPERING GUIDELINE

During the study, patients may remain on corticosteroids with intent to taper. A steroid taper will be allowed to begin earliest at 4 weeks after starting on the Phase 1b continuation phase or Phase 2 study, with a 10% (of starting dose) decrease per week. The study allows maximum two total pulses of steroids with subsequent rapid taper for cGVHD flares associated with the study drug initiation and/or one time later for any flares or worsening of cGVHD symptoms during steroid or other immunosuppression taper or treatment interruptions. Typical corticosteroid pulse is defined as up to 2 mg/kg/day prednisone or equivalent tapered to the pre-pulse baseline within 3 weeks. Steroid pulses require the PI's approval. Administration steroid pulses will be carefully recorded in the protocol case report forms.

4.2 OTHER TREATMENTS FOR CGVHD

Patients who are taking concomitant systemic agents for control of cGVHD, such as calcineurin inhibitors (e.g., tacrolimus or cyclosporine) or other immunosuppressants (e.g., mycophenolate or sirolimus) must be on a stable or tapering dose in the preceding 4 weeks with an intent to stop if possible after corticosteroids are at stable or supplementation doses (maximum 7.5 mg prednisone/day) or discontinued. Patient should not receive any investigational drugs or initiate any systemic therapy for cGVHD once started on baricitinib. Patients should not be undergoing extracorporeal photopheresis (ECP) concomitantly with study drug.

4.3 OTHER ALLOWED CONCOMITANT THERAPY

Ancillary therapy and supportive care considered necessary for the patient's wellbeing may be administered at the discretion of the PI and will follow the NIH Blood and Marrow Transplant Consortium guidelines for supportive care: http://intranet.cc.nih.gov/bmt/clinicalcare/guidelines.shtml. Any ancillary or supportive care which may have some effect on efficacy analysis including topical cGVHD treatments will be carefully recorded in the CRF.

4.4 PROHIBITED CONCOMITANT THERAPY

Given risk of concurrent NSAID use to decrease potential of the kidney to respond to hemodynamic changes and subsequent renal dysfunction, NSAID use will not be allowed during the course of baricitinib treatment.

Baricitinib does not have significant impact on CYP enzymes, and thus the potential to cause clinically significant interaction via CYP are low. There is no specific contraindication on this study for CYP-metabolized agents.

In addition, radiation therapy, cancer chemotherapy, biologic or immunotherapy is prohibited during participation in this study. Concomitant use of other investigational agents is not permitted while persons are receiving study drug.

5 CORRELATIVE STUDIES FOR RESEARCH

5.1 BIOSPECIMEN COLLECTION

Please note that tubes and media may be substituted based on availability with the permission of the PI or laboratory investigator.

5.1.1 Skin and oral biopsy, saliva collection, oral microbiome swabs

Skin and oral research biopsies will be performed before treatment and after 6 months of baricitinib treatment (with intent to sample as close to the same area as possible). Immunohistochemistry methods will be applied to look for T-cell infiltrates, and IFN-induced factors in the oral mucosa and erythematous skin. The advantage of histology is the greater amount of information on cell populations and functional changes in situ of the disease. These biopsies will be obtained by one of the study investigators and processed, stored and analyzed at the Blood Processing Core (Dr. Figg's Lab). A biopsy sample will be also sent to the NCI pathology laboratory. Patients will have an option to decline any of these research biopsies. Biopsy samples collected on the 04-C-0281 cGVHD natural history study can be also used for these studies if obtained in the timeframe as part of the screening evaluations for this study.

Whole saliva and oral swabs of the buccal mucosa, tongue and gingiva will be collected at the same time that the buccal mucosal biopsies are performed to evaluate the salivary proteome, microbiome and cytokine profile at baseline and after 6 months of baricitinib treatment. The samples may be analyzed using a variety of methods including immunohistochemistry, microscopy, gene expression profiling, microbial sequencing, and protein-based assays in order to assess oral tissues for immune changes and for local specific markers of response or lack thereof to baricitinib therapy.

5.1.2 Immunologic Analyses Using Plasma and PBMCs

1. Blood: Blood will be collected, and PBMC and plasma will be cryopreserved for later batch analyses of markers relevant to cGVHD activity. Cellular markers of active cGVHD have been proposed, although not verified at multiple institutions or validated in prospective trials[27]. Heparinized plasma will be assayed for potential markers of cGVHD activity (including but not limited to BAFF, IFN-induced chemokines). Pharmacodynamic of baricitinib (inhibition of cytokine-induced STAT phosphorylation) will be assayed prior to drug administration and 2 hours post administration on the first day of cycle 1 and at any later increase in drug dosage. Monocyte transcriptome assessments of IFN-inducible genes should be noted to be an experimental endpoint with potential relevance to cGVHD pathogenesis. PBMC will be cryopreserved for subsequent flow cytometry of cell populations and sorting of monocytes for transcriptional analysis of genes upregulated in active cGVHD. The primary collection of blood for these analyses of baricitinib effect on cGVHD will be collected prior to dose and 2 hours after dose at the following timepoints: baseline, at the time of any increase in dose level. Each aliquot contains 10 x 10^6 cells—with no more than cells in a single vial. All samples collected will be cryopreserved and frozen for future analyses as detailed in Section **5.2.1**.
2. Plasma will be assayed for BAFF, CXCL9/CXCL10, IL-6, TNFα, and other IFN-induced chemokines. Take one 1 mL aliquot of plasma from each of the CPTs, without disturbing the cell interface, and place into standard cryovials. Barcode as buffy plasma and store at -80°C. All samples collected will be cryopreserved and frozen for future analyses as detailed in Section **5.2.1**.
    1. Additionally, ELISA assays may include but not be limited to the following proposed biomarkers of cGVHD: CXCL9, MMP3, DKK3, ST2, CD163
    2. Additional or alternative plasma factors will be considered based upon relevant cGVHD biomarkers identified by the end of biospecimen accrual.
3. Monocyte transcriptome: Monocytes will be sorted from PBMC for Nanostring evaluation of the monocyte transcriptome. This would be done on cryopreserved cells at the end of the study. Monocytes circulate throughout the body, are responsive to a variety of cytokines in tissues affected by cGVHD and may therefore serve as a reporter for changes in cGVHD-affected tissues.
4. Lymphocyte populations. Assays characterizing lymphocyte populations will be performed to include, but not be limited to, assessments of %CXCR3+ T-cells, %T-reg cells and %CD21 B-cells. Furthermore, multilineage lymphocyte immune reconstitution after transplant will be investigated to examine the impact of JAK1/2 inhibition on lymphopoiesis (CD3, CD4, CD8, B and NK populations). At baseline prior to dose, 2 weeks, 12 weeks, 24 weeks, 36 weeks, and 48 weeks and if PI deems necessary at end of treatment and followup visits, one 3mL lavender (EDTA) tube will be drawn and lymphophenotyping will be performed using Clinical Center's CLIA certified Immunophenotyping panel and reported in the CRIS. Further research assessments of the percentages of regulatory T cells, of naïve, memory and effector T cells and of B cell transitional, naïve and memory populations will be done in the Blood Processing Core (Dr. Figg's Lab). Active cGVHD has been associated with decreases in Treg populations,

reduced thymopoiesis (fewer naïve T cells) and increases in CD21- transitional B cell populations.

The assays indicated are designed to assess the alterations in skin, oral mucosa and in circulating lymphocytes and plasma that may result from baricitinib. If there is an increase in Th1 cells or a shift in Treg populations, this may be reflected in circulating T cell populations, plasma cytokines and tissue infiltrates.

5.1.3 Measurement of Baricitinib Serum Levels

For each dose level of baricitinib administered, one plasma sample will be collected per patient for measurement of baricitinib concentration after at least 7 days of continuous treatment (on day 15 of that cycle). This testing is performed to ensure that drug concentrations do not exceed baricitinib exposures previously studied. Each time the baricitinib dose is increased or decreased an additional single sample will be collected after at least 7 days of continuous treatment on the new dose (on day 15 of that cycle). The sample will always be collected immediately before taking the next baricitinib dose. In addition, on the first day of each dose level, blood will be taken pre-dose, then at 1, 2, and 4 hours after the dose. A sample will be collected at 24 hours after the dose in up to 10 patients as feasible, but is not required on protocol. The sample at week 12 is not collected if no change in dose level occurred. In the event of a serious adverse event or at the end of study, an additional sample may be collected within 2 hours of the last dose at the discretion of the investigator. A 3-mL blood sample will be collected immediately before taking the daily baricitinib dose. Actual dosing dates and times will be recorded. These sample collections will occur at the protocol scheduled evaluation visits at the NIH Clinical Center. Every effort will be made to collect samples as prescribed in the timeline. Samples that are collected ± 15 minutes of collection time will not be considered a protocol deviation.

In the event of a serious adverse event (SAE) or at the end of the study, an additional sample may be collected within 24 hours of the last dose, at the discretion of the investigator. If this sample is collected, it will be as soon as possible after identification of the event and the time of the last dose and the time of sample collection will be recorded.

All samples for measurement of baricitinib will be collected, processed, stored, documented and the Blood Processing Core (Dr. Figg's Lab). Plasma samples will be batch tested for baricitinib concentration not more than two years after collection using a validated liquid chromatography with tandem mass spectrometry method, with a limit of quantification of 0.5 ng/mL, by the Clinical Pharmacology Program of the NCI, directed by William Figg.

5.1.4 Sample processing

Please email Clinical Pharmacology Blood Processing Core (BPC) at NCIBloodcore@mail.nih.gov at least 24 hours before the scheduled research blood draw time and before patient treatment start times (the Friday before is preferred).

For sample pickup, page **102-11964**.

For immediate help, call the main line for the BPC at (240) 760-6180. If no answer, call the main clinical pharmacology lab phone number at (240) 760-6190.

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov.

The samples will be processed, barcoded, and stored in Dr. Figg's lab until requested by the investigator.

5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.

5.2.1 Sample Procedures

Blood and tissue samples, collected for the purpose of research under IRB-approved protocols of the Experimental Transplantation and Immunology Branch and the Immune Deficiency Cellular Therapy Program will be stored and may be archived by the Blood Processing Core (BPC) will be barcoded, with data entered and stored in the Labmatrix utilized by the BPC. This is a secure program, with access to Labmatrix limited to defined Figg lab personnel, who are issued individual user accounts. Installation of Labmatrix is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen.

Labmatrix creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without Labmatrix access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

Samples are stored in locked freezers at -85°C (sera and plasma) or under liquid nitrogen (cells), according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times. Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in Labmatrix. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

5.2.1.1 Protocol Completion/Sample Destruction

Once primary research objectives for the protocol are achieved, researchers can request access to remaining samples for human subjects research, providing they have both approval of the Principal Investigator of the original protocol under which the samples or data were collected and either an IRB-approved protocol and patient consent or an OHSRP determination that the activity is exempt from IRB review. Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. The PI will record any loss or

unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **7.2 Error! Reference source not found.**.

Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the Labmatrix. It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

Data will be prospectively collected and entered into an NCI 21 CFR Part 11-compliant data capture system using pre-designed CRFs. All persons must have signed an Informed Consent and have an on-study confirmation of eligibility form completed before entering on the study. Complete records will be maintained on each patient including the hospital chart with any supplementary information obtained from outside laboratories, radiology reports, or physician's records. These records will be the primary source documents that form the basis for the research record. The primary source documentation will assure the availability of the following: on-study information, including patient eligibility data and patient history; flow sheets, specialty forms for pathology, radiation, or surgery; and off-study summary sheet, including a final assessment by the treating physician.

The PI will be responsible for overseeing entry of data into a 21 CFR Part 11-compliant data capture system provided by the NCI CCR and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the first study intervention, Study Day 1, through 30. Beyond 30 days after the last intervention, only adverse events which are serious and related to the study intervention need to be recorded.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

End of study procedures: Data will be stored according to HHS, FDA regulations and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **7.2.1**.

6.1.1 Eligibility Checklist

The eligibility checklist is to be completed at study entry by the protocol research nurse who will forward the checklist to the Central Registration Office.

6.1.2 Adverse Events

Grade 1 adverse events will not be collected on this protocol.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows (check all that apply):

_X_ De-identified data in an NIH-funded or approved public repository.

_X_ De-identified data in BTRIS (automatic for activities in the Clinical Center)

_X_ De-identified or identified data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through (check all that apply):

_X_ An NIH-funded or approved public repository. Insert name or names: clinicaltrials.gov.

_X_ BTRIS (automatic for activities in the Clinical Center)

_X_ Approved outside collaborators under appropriate individual agreements.

_X_ Publication and/or public presentations.

When will the data be shared? (check all that apply)

_X__ Before publication.

_X_ At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

Not applicable. No genomic data, large scale or otherwise, is generated on this study.

6.3 RESPONSE CRITERIA

6.3.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with baricitinib.

Evaluable for efficacy: Patients who complete 6 months of therapy will be evaluable for the primary endpoint of efficacy assessment. Patients who progress earlier will be also included in

the analysis of efficacy. Patients should have received at minimum of 75% of planned baricitinib doses to be evaluable for the primary efficacy 6 month endpoint.

6.3.2 Efficacy Analysis

The primary evaluation point is overall response at 24 weeks using the NIH cGVHD response criteria measures[51]. The overall response score will be assessed as CR, PR, or lack of response as per NIH guidelines. The organ-specific and other subcomponents of the overall response score will be analyzed individually and absolute values recorded.

Up to 2 corticosteroid pulses will be allowed, one for initial flares and one for late flares as described in Section **4.1**.

Response will be assessed every 12 weeks from the start of baricitinib. To ensure comparability, baseline and on-study methods for response assessment will be performed using identical grading, scale or techniques. The Chronic GVHD Assessment (Clinician) Form will be completed at each 12 week evaluation visit (**Appendix F**). Included in that form are both organ-specific primary measurements and clinician-assessed secondary measurements. The response of each affected organ will be evaluated and an overall response will be determined.

6.3.2.1 Response Criteria

Efficacy will be assessed using NIH consensus criteria measuring for therapeutic response in clinical trials for cGVHD.

- **CR** is defined as resolution of all manifestations in each organ or site
- **PR** is defined as improvement at least 1 organ or site without progression in any other organ or site. The criteria for PR and progression are provided in **Appendix K**
- **Lack of Response:** including unchanged, mixed response, and disease progression:
- **Mixed response**: CR or PR in at least 1 organ accompanied by progression in another organ
- **Disease progression**: see **Appendix K** for organ criteria
- **Unchanged**: Outcomes that do not meet the criteria for CR, PR, disease progression, or mixed response

As outlined in Section **3.7**, type of involved organ, location and its measurements will be recorded at scheduled evaluations and reported on the appropriate CRF, equal to "Chronic GVHD Assessment (Clinician) Form," (**Appendix F**). All other measurements not being included in primary assessment but clinically related to cGVHD (e.g., change of pigmentation) will be reported in the source documents.

Skin and skin appendages: Skin assessment will be based on the NIH 0-3 Skin Score, which correlates with cGVHD severity, symptoms, and survival (**Appendix D**). Clinician-perceived severity of sclerosis will also be captured on a 0-10 scale. Patient-reported symptoms will be captured on a 0-10 scale and on the Lee symptom scale.

Musculoskeletal connective tissue: Assessment of joint range of motion will be performed by the photographic range of motion (P-ROM) scale and the NIH 0-3 Joint Score, which correlate with changes in joint involvement. In a prior study, both scales performed well but the Joint/Fascia scale better reflected clinical perception of improvement, and the P-ROM better reflected the clinical perception of worsening[33]. If these measurements are discrepant, priority

will be given to the NIH 0-3 scale when improvement is detected, and to P-ROM when worsening is detected. If the resolution cannot be achieved then the priority will be given to the NIH 0-3 Joint/Fascia scale, as the P-ROM is of more recent origin and still deemed exploratory in the 2014 NIH cGVHD organ staging recommendations[4].

Eyes: The NIH Eye Score uses a scale of 0-3 based on symptoms, need for eye drops, and use of therapeutic procedures or devices. This has been shown to detect improvement of worsening in ocular cGVHD. Patient-reported symptoms will be captured on a 0-10 scale and on the Lee symptom scale.

Mouth: Mouth assessments on the NIH-modified Oral Mucosa Rating Scale (OMRS) include:

> (1) mucosal erythema by 0-3 grading based on the color intensity, (2) lichen-type hyperkeratosis by 0-3 grading based on the percentage of oral surface area,(3) ulceration by 0-6 based on percentage of oral surface area

Gastrointestinal tract: Gastrointestinal (GI) symptoms will be graded through interview by the investigator according to 0-3 severity scales, and weight will be measured at each visit.

Liver: Involvement of liver is graded according to the levels of total serum bilirubin, alkaline phosphatase, and alanine aminotransferase (ALT).

Lung: Absolute percent predicted of the forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), single breath diffusion lung capacity for carbon monoxide (DLCO), total lung capacity (TLC), and residual volume (RV) will be measured on pulmonary function testing (post-bronchodilator response values, as cGVHD of the lungs is not a bronchodilator-responsive process). The %FEV1 will be used for response assessment. Symptoms will be graded through interview by the investigator according to the NIH Symptom Scale 0-3. Slope of %FEV1 will also be measured.

Genitals: Patient-reported symptoms will be captured on a 0-10 scale.**Global chronic GVHD Rating:** The overall clinical impression of patient's cGVHD will be recorded on a 4-point (0-3) scale on the Chronic GVHD Assessment (Clinician) Form.

Chronic GVHD Improvement Scale: The overall changes of patient's cGVHD symptoms during previous 3 months will be recorded on a 7-point (-3 to +3) scale on the Chronic GVHD Assessment (Clinician) Form.

Chronic GVHD Symptom Severity Scale: The overall severity of patient's cGVHD symptoms will be recorded on an 11-point (0-10) numeric scale on the Chronic GVHD Assessment (Clinician) Form.

Lee symptom scale was developed as a 30-item symptom scale with 7 subscales to capture the cGVHD-specific symptom burden (**Appendix I**). This symptom scale showed to correlate with persons' self-assessed mild, moderate, and severe cGVHD manifestations in cross-sectional validation analysis. Evidence supports the validity, reliability, and sensitivity to chronic GVHD severity.

NIH organ 0-3 scoring (**Appendix D**) will be collected at the evaluation endpoints.

6.3.2.2 Summary of Response Measures

i. Primary response measures

1. Skin: NIH 0-3 Skin Score

2. Joints: P-ROM (1-7 and 1-4) and NIH Joints Fascia Score
3. Eye: NIH 0-3 Eye Score
4. Mouth: NIH-modified 0-12 OMRS
5. GI: GI 0-3 clinician symptom severity scale
6. Liver: bilirubin, alkaline phosphatase, ALT
7. Lung: %FEV1
8. Clinician global assessment scale (3-point, 7-point change, 11-point)

ii. Secondary assessments

1. Overall response rate at 12 weeks of therapy
2. NIH organ scoring
3. Rate of >50% reduction of immunosuppressive therapy at 24 weeks and 48 weeks (steroid pulses on study per section 4.1 will not count towards this assessment)
4. Overall survival
5. Platelet count, CRP, C3, C4, albumin
6. Lee symptom scale, HAP, FACT-BMT
7. Skin and oral biopsies (if positive at baseline)
8. MRI (if positive baseline)
9. Pharmacokinetics
10. Pharmacodynamic/correlative studies

6.3.2.3 Other endpoints to be recorded at the evaluation time points: Need for secondary systemic therapy for GVHD, malignancy progression, discontinuation of immune suppression, steroid doses, other immunosuppressive drug doses, new topical treatments introduced, intensity of immunosuppression scale, NIH global severity (**Appendix E**), survival, progression-free/malignancy-free survival, disability-free survival.

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements. Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention **s**hould be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a weekly basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 SPONSOR PROTOCOL/SAFETY REPORTING

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2))

8.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see section **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
    - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient or subject convenience) is not considered a serious adverse event.
    - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject 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. (21CFR312.32)

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 4.0.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.2 Assessment of Safety Events

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to section **6.1**. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor with the exception of any listed in section **8.4**.

8.3 Reporting of Serious Adverse Events

Any AE that meets protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form. Any exceptions to the expedited reporting requirements are found in section **8.4**.

All SAE reporting must include the elements described in section **8.2**.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form

and instructions can be found at:
https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 WAIVER OF EXPEDITED REPORTING TO CCR

As death/hospitalization due to disease progression are part of the study objectives (efficacy-response rate), and captured as an endpoint in this study, they will not be reported in expedited manner to the sponsor. However, if there is evidence suggesting a causal relationship between the study drug and the event, report the event in an expedited manner according to section **8.3**.

8.5 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATORS

The CCR Office of Regulatory Affairs will send all reports to the manufacturer as described below.

The PI or designee will report all Serious Adverse Events to the IND Manufacturer within 3 days of the Investigator(s) becoming aware of them.

Fax all SAE forms to: Lilly Global Patient Safety at 866-644-1697

Additionally, the IND manufacturer will be provided with copies of all investigational product-related reports submitted to regulatory authorities.

8.6 REPORTING PREGNANCY

All required pregnancy reports/follow-up to OSRO will be submitted to: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. Forms and instructions can be found here:
https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

8.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy become known,

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (section **8.1.2**) should be reported as SAEs.

The outcome of all pregnancies should be followed up and documented.

8.6.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for at least 7 days after the last dose of baricitinib.

Pregnancy of the patient's partner is not considered to be an AE. The outcome of all pregnancies occurring from the date of the first dose until 28 days after the last dose should, if possible, be followed up and documented. Pregnant partners may be offered the opportunity to participate in an institutional pregnancy registry protocol (e.g., the NIH IRP pregnancy registry study) to provide data about the outcome of the pregnancy for safety reporting purposes.

8.7 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

8.8 SPONSOR PROTOCOL DEVIATION REPORTING

A Protocol Deviation is defined as any non-compliance with the clinical trial Protocol, Manual of Operational Procedures (MOP) and other Sponsor approved study related documents, GCP, or protocol-specific procedural requirements on the part of the participant, the Investigator, or the study site staff inclusive of site personnel performing procedures or providing services in support of the clinical trial.

It is the responsibility of the study Staff to document any protocol deviation identified by the Staff or the site Monitor in the CCR Protocol Deviation Tracking System (PDTS) online application. The entries into the PDTS online application should be timely, complete, and maintained per CCR PDTS user requirements.

In addition, any deviation to the protocol should be documented in the participant's source records and reported to the reviewing IRB per their guidelines. OSRO required protocol deviation reporting is consistent with E6(R2) GCP: Integrated Addendum to ICH E6(R1): 4.5 Compliance with Protocol; 5.18.3 (a), and 5.20 Noncompliance; and ICH E3 16.2.2 Protocol deviations.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure:

- that the rights of the participants are protected;
- that the study is implemented per the approved protocol, Good Clinical Practice and standard operating procedures; and,
- the quality and integrity of study data and data collection methods are maintained.

Monitoring for this study will be performed by NCI CCR Office of Sponsor and Regulatory Oversight (OSRO) Sponsor and Regulatory Oversight Support (SROS) Services contractor. Clinical site monitoring activities will be based on OSRO standards, FDA Guidance E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) March 2018, and applicable regulatory requirements.

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by OSRO. CMPs will be protocol-specific, risk-based and tailored to address human subject protections and integrity of the study data. OSRO will determine the intensity and frequency of monitoring based on several factors, including study type, phase, risk, complexity, expected enrollment rate, and any unique attributes of the study and the site. The Sponsor will conduct a periodic review of the CMP to confirm the plan's continued appropriateness. A change

to the protocol, significant or pervasive non-compliance with GCP, or the protocol may trigger CMP updates.

OSRO SROS Monitoring visits and related activities will be conducted throughout the life cycle of each protocol. The first activity is before the study starts to conduct a Site Assessment Visit (SAV) (as warranted), followed by a Site Initiation Visit (SIV), Interim Monitoring Visit(s) (IMVs), and a study Close-Out Visit (COV).

Some monitoring activities may be performed remotely, while others will occur at the study site(s). Monitoring visit reports will describe visit activities, observations, and associated action items or follow-up required for resolution of any issues, discrepancies, or deviations. Monitoring reports will be distributed to the study PI, NCI CCR QA, CCR Protocol Support Office, coordinating center (if applicable), and the Sponsor regulatory file.

The site Monitor will inform the study team of any deviations observed during monitoring visits. If unresolved, the Monitor will request that the site Staff enter the deviations in the CCR Protocol Deviation Tracking System (PDTS) for deviation reporting to the Sponsor and as applicable per institutional and IRB guidance.

10 STATISTICAL CONSIDERATIONS

The primary objectives of the study are to determine the tolerability and efficacy of baricitinib in patients with steroid-refractory cGVHD. The primary efficacy objective is to treat a total of 21 patients in either cohort 1 or cohort 2 in order to have 80% power to detect a response rate consistent with 30% and ruling out 10%, with a one-sided significance level of 0.10.

Patients will first be enrolled onto cohort 1, and in an initial futility analysis, if 0 of the first 7 patients enrolled in cohort 1 have responded, then subsequent patients will be accrued to cohort 2, starting treatment at the higher dose (4mg daily). If 1 or more of the initial 7 patients treated in cohort 1 has a response, then a total of 21 evaluable patients will be treated in cohort 1.

If patients are enrolled onto cohort 2, and if 0 of the first 7 patients enrolled in cohort 2 have responded, then no further patients will be accrued onto the trial. On the other hand, if 1 or more of the initial 7 evaluable patients enrolled in cohort 2 have responded then a total of 21 evaluable patients will be treated in cohort 2.

As an early stopping rule for safety, if 2/3 or greater patients at any given dose level experiences a dose limiting toxicity requiring dose reduction or discontinuation, that dose will not be subsequently used. Accrual will continue at a lower dose level with no further dose escalation, unless this occurs at the lowest dose level, at which time accrual to the study will be stopped.

If patients are enrolled in both cohort 1 and cohort 2, then up to 28 evaluable patients may be required (either 21 in cohort 1 or 7 in cohort 1 and 21 in cohort 2). In order to allow for a small number of inevaluable patients, the accrual ceiling will be set at 31. It is anticipated that 8-12 patients may be enrolled onto this protocol per year; thus, 2 to 4 years may be required to accrue up to 31 patients.

11 COLLABORATIVE AGREEMENTS

11.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)

Baricitinib is provided by Eli Lilly and Company under a CRADA (# 34604).

12 HUMAN SUBJECTS PROTECTIONS

12.1 RATIONALE FOR SUBJECT SELECTION

No subjects will be excluded from participation based on gender, race or ethnicity. The study will be open to all subjects who satisfy the inclusion criteria and provide an informed consent to the protocol.

12.2 PARTICIPATION OF CHILDREN

As there is inadequate published data on baricitinib in children, this study will be limited to subjects age 18 years or older.

12.3 PARTICIPATION OF NIH SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **12.5**), all subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) to assess ongoing capacity of the subjects and to identify an LAR, as needed.

Please see section **12.6.1** for consent procedure.

12.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

12.4.1 Related to baricitinib

Potential risks of baricitinib include the range of toxicities described in Section **14.1.2** and the consent form. There may also be unexpected side effects. All subjects will be carefully monitored for side effects.

12.4.2 Related to Blood Collection

Minor complications including bleeding, pain, and hematoma formation at the site of blood draws, or infections may rarely occur.

12.4.3 Related to Tissue Biopsy

Skin and oral punch biopsy is a minor surgical procedure that may be associated with temporary bleeding, hematoma at the site, local infection and postoperative discomfort. These risks are small (generally <5%) and transient.

12.4.4 Related to Pulmonary Function Tests

PFTs are safe for most participants; however, some may experience dizziness, shortness of breath and fainting. In rare PFTs may lead to a collapsed lung. In participants with asthma, PFTs may precipitate an asthma attack.

12.4.5 Related to ECG and echocardiogram

Other than possibly experiencing some minor skin irritation from the electrodes there are no anticipated risks related to complete the electrocardiogram and/or the echocardiogram.

12.4.6 Related to Questionnaires

The potential risk of questionnaires include questions that may be sensitive in nature.

12.4.7 Related to Radiation Exposure

A CT scan is done at screening; however, all screening is performed on a separate study. Therefore, radiation risks are assessed to the screening protocols.

12.5 RISKS/BENEFITS ANALYSIS

The benefits of the study include the potential to improve knowledge of the biology of cGVHD and impact of JAK inhibition in the treatment of this disease. In addition, if shown to be effective, the study drug may improve overall outcomes after SCT, a curative therapy for many hematologic malignancies, as well as have implications for prevention. Individual patients may benefit from participation in this protocol if treatment stabilizes or improves their cGVHD. Patients may also benefit by knowing they are participating in a study aimed at improving treatment of cGVHD, which we ultimately hope will benefit future patients. The risks of the study to participants are minimal compared to the potential benefits to them or to the overall knowledge and future study of JAK inhibition in cGVHD.

12.6 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant or consent designee(s) as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant/consent designee. Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual

(non-electronic) signature on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location, but is not required.

Both the investigator and the participant will sign the document using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

For the optional biopsy, the patient will consent at the time of the procedure. If the patient refuses the optional biopsy at that time, the refusal will be documented in the medical record and in the research record.

12.6.1 Consent Process for Adults Who Lack Capacity to Consent to Research Participation

For participants addressed in section **12.3**, an LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR, as described in Section **12.6**.

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

13.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met

- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable, Food and Drug Administration (FDA).

13.2 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Cancer Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the/each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site(s) and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NCI CCR.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14 PHARMACEUTICAL INFORMATION

14.1 BARICITINIB (IND # 129360)

14.1.1 Source

Baricitinib will be provided by the manufacturer Eli Lilly and Company under a clinical trials agreement.

14.1.2 Toxicity

As of August 2021, approximately 13,800 subjects have received baricitinib since the start of clinical development program.

A large, randomized trial of tofacitinib (a JAK 1/2/3 inhibitor) in patients with rheumatoid arthritis detected higher risk of heart attack, stroke, cancer and blood clots and death when compared to standard therapy with anti-TNF drugs. Based on these studies in September 2021, FDA extended this warning to baricitinib (JAK 1/2) and another JAK inhibitor drug used in arthritis. This warning has not been extended to similar drugs used for cancer (or GVHD).

The following potential treatment related side effects have been identified:

Increased Adverse Events Due to Increased Exposures in Patients with Renal Impairment: Data from completed studies indicate that subjects with renal impairment have increased exposures to baricitinib. Increased exposure could place a person at increased risk for any other risk that is related to exposure. Therefore, adjustment in dose has been implemented in clinical studies to compensate for these observed differences. Investigators should follow dosing guidelines specified in the protocol, and monitor creatinine in study subjects and follow protocol drug interruption and discontinuation criteria.

Blood Clots in the Blood Vessels

Increased incidence of pulmonary embolism, venous and arterial thrombosis with another JAK inhibitor vs. TNF blockers. Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving baricitinib.

Data from the placebo-controlled time period from the integrated safety analysis of Phase 2/3 RA studies showed a numerical imbalance in the reports of DVT/PE, with more events reported in the baricitinib 4-mg group compared to the placebo group. The exposure-adjusted incidence rate (EAIR) of DVT/PE for baricitinib-treated RA patients over long-term exposures [0.45] was similar to the background rates published in the literature. There was no pattern of increased or decreased risk in any given 48-week time period including long-term exposures. Risk factors found more commonly in patients with these events included prior history of DVT/PE, obesity, and older age. In a retrospective observational study of baricitinib in RA patients, a higher incidence rate of venous thromboembolic events was observed compared to patients treated with TNF blockers.

Baricitinib should be used with caution in patients with risk factors for deep vein thrombosis or pulmonary embolism (DVT/PE) and enrollment of patients with multiple risk factors should be carefully considered in clinical trials. If clinical features of DVT/PE occur, interrupt baricitinib, evaluate promptly, and institute appropriate treatment.

Myelosuppression: Baricitinib is anticipated to down-regulate the JAK pathway and result in changes to WBC counts. Although dose-related decreases in neutrophils and other phagocytic cell lines have been observed, neutropenia and lymphocytopenia have been observed infrequently. Investigators should monitor leukocyte parameters in study subjects and follow protocol drug interruption and discontinuation criteria.

Increased Infections (including opportunistic infections and herpes zoster): In addition to the observed decreases in phagocytic cells, JAK inhibition down-regulates cytokines related to the immune system. Although infections and infestations were the most frequently reported SOC of TEAEs, an excess occurrence of infections typically considered to be opportunistic has not been observed in clinical studies with baricitinib. The incidence rate of herpes zoster observed in baricitinib studies is within the range reported in observational studies and clinical trials of patients with RA, including the rate observed in placebo recipients. Investigators should monitor subjects for clinical signs and symptoms of infectious events, including herpes zoster. If a subject is clinically diagnosed with herpes zoster, the investigator should interrupt investigational product, initiate standard of care (including antiviral therapy and relevant supportive care as appropriate), monitor for multi-dermatomal involvement or other evidence of dissemination, and follow subjects until clinical recovery of skin lesions (vesicles). For study subjects at risk for herpes zoster, investigators should encourage, and offer to provide, vaccination against varicella/zoster prior to starting investigational product in clinical trials (at least 4 weeks before randomization).

Increased Cardiovascular Events: Higher rate of MACE (defined as cardiovascular death, myocardial infarction, and stroke) with another JAK inhibitor vs. TNF blockers in RA patients. Higher rate of all-cause mortality, including sudden cardiovascular death with another Janus kinase inhibitor (JAK) vs. TNF blockers in rheumatoid arthritis (RA) patients. Increases in mean total cholesterol, LDL, HDL, and triglycerides have been noted in studies with baricitinib. Nuclear magnetic resonance data indicate that the changes in cholesterol are due primarily to

increases in the number of HDL particles without a change in HDL particle size; an increase in the number of large LDL particles with no significant increases in small, medium-small or very small LDL particles; and an increase in the number of total, as well as medium and small, very low density lipoprotein (VLDL) particles. The mean values for the HDL/LDL ratio did not change. These changes in lipid particles, particularly in view of the observed increase in large LDL particles, suggest that the overall effect on the vasculature may not be atherogenic[52-54]. Data from *A Randomized, Double-Blind, Placebo- Controlled, Dose-Ranging, Parallel-Group, Phase 2b Study of LY3009104 in Patients with Active Rheumatoid Arthritis on Background Methotrexate Therapy (Study JADA)* [46] suggest that concomitant use of statins can ameliorate the effect on lipids. Any increase in cholesterol carries a potential risk of cardiovascular events. Data from patients with RA given 4 to 15 mg baricitinib QD or 5 mg baricitinib BID have shown no clinically meaningful changes in vital signs or ECG parameters for baricitinib versus placebo. Investigators should monitor vital signs and carefully review ECGs for findings that may be associated with cardiovascular events. Investigational product should be interrupted or discontinued if major adverse cardiovascular events occur.

Fetal Malformations: Reproductive toxicity was observed in rat and rabbit toxicology studies, including maternal toxicity and skeletal malformations in the rat fetus. A decrease in mating performance (fertility and copulation indices) was observed in the male rat fertility study. This change occurred without effects on spermatogenesis as assessed by histopathology and semen/sperm endpoints. Pregnant women should not participate in clinical studies of baricitinib.

To manage any potential risks, women and men of reproductive potential should avoid becoming pregnant or fathering a child by using 2 forms of highly effective contraceptives while participating in clinical studies and for at least 7 days following exposure to baricitinib. If the patient becomes pregnant, study drug should be discontinued for the duration of the pregnancy and any subsequent period of breastfeeding.

Malignancies: Baricitinib has immunomodulatory effects on the immune system. Effects on the immune system may permit emergence of malignancies previously contained by the immune system. No signals concerning effects of baricitinib on malignancy have emerged from clinical studies. Long-term safety evaluations for baricitinib are ongoing. Patients should be monitored closely for evidence of neoplasia or malignancy, and study drug should be discontinued if such events occur.

Higher rate of lymphomas and lung cancers with another JAK inhibitor vs. TNF blockers in RA patients.

Pharmacologic Interaction between NSAIDs and Baricitinib to Decrease the Capacity of the Kidney to Respond to Hemodynamic Changes: Among patients in Study JADA[46], with at least 1 creatinine value ≥ 1.3 mg/dL, two-thirds of them had other data to suggest that an intercurrent illness with transient hemodynamic effects had occurred preceding or coincident with the increased creatinine value and that concomitant use of a NSAID may be associated with an increased risk of increased creatinine and decreased GFR in this circumstance.

14.1.3 Formulation and preparation

The drug product is supplied for clinical study use as tablets and is composed of baricitinib and the inactive ingredients microcrystalline cellulose, mannitol, croscarmellose sodium, and

magnesium stearate. Each tablet contains baricitinib equivalent to 1 mg, 2 mg, or 4 mg of the free base compound.

14.1.4 Stability and Storage

Please refer to label for storage information.

The drug substance is stable at room temperature.

14.1.5 Administration procedures

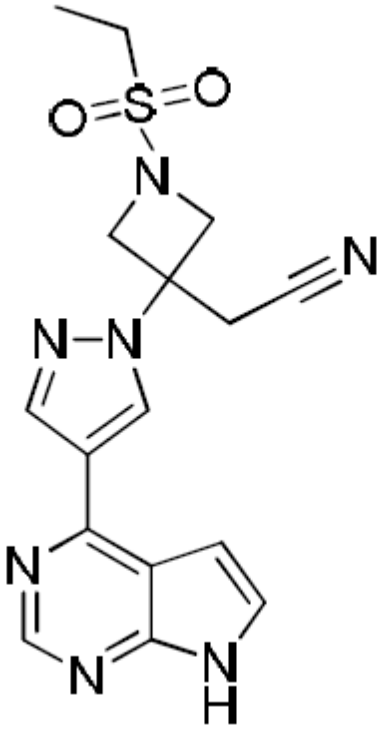
Please see section **3.2**.

14.1.6 Incompatibilities

Molecular Formula: $C_{16}H_{17}N_7O_2S$

Molecular Weight: 371.42

Molecular Structure:



Interactions:

The potential for an effect of baricitinib on the PK of oral contraceptives (OC) was evaluated in Study JAGD[46], conducted in healthy female subjects. Oral doses of 10 mg baricitinib QD had no clinically significant effect on AUC or C_{max} of the ethinyl estradiol or levonorgestrel components of Microgynon 30®, a commonly used estrogen progestogen combination OC.

Because in vitro data suggested that baricitinib was a P-gp substrate, the potential for baricitinib to interact with digoxin, a commonly used P-gp probe substrate, was evaluated in healthy male subjects (Study JAGL)[46]. Coadministered of 10 mg baricitinib with digoxin did

not have a clinically significant effect on the systemic exposure to, or renal excretion of, digoxin. Baricitinib is, therefore, unlikely to act as a P-gp inhibitor.

An open-label drug-drug interaction study (Study JADB)[46] was conducted in patients with RA to evaluate the effects of coadministration of baricitinib (5 mg BID or 10-15 mg QD) and methotrexate (7.5-25 mg weekly) on the PK profiles of each drug, as well as methotrexate's metabolite, 7-OH-methotrexate. Baricitinib coadministration did not significantly affect dose normalized C_{max} or AUC of methotrexate or 7-OH-methotrexate. Methotrexate co-administration had no significant effect on the geometric mean C_{max} or AUC of baricitinib. Thus, dosing regimens of baricitinib and methotrexate need not be altered when these 2 drugs are co-administered.

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16 PPENDICES

APPENDIX A: 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 B: DIAGNOSTIC CRITERIA OF CHRONIC GVHD

Screening/Baseline

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 sclerosus-like features	□ Depigmentation	□ Sweat impairment □ Ichthyosis □ Keratosis pilaris □Hypopigmentation □Hyperpigmentation	□ Erythema □ Maculopapular rash □ Pruritus
Nails		□ Dystrophy □ Longitudinal ridging, splitting, or brittle features □ Onycholysis □ Pterygium unguis □ Nail loss [5,6]		
Scalp and body hair		□ New onset of scarring or nonscarring scalp alopecia[7] □ Scaling, papulosquamous lesion	□ Thinning scalp hair, typically patchy, coarse, or dull [8] □ Premature grey hair	

Organ or Site	Diagnostic Features[1]	Distinctive Features[2]	Others[3]	Common Features[4]
Organ or Site	**Diagnostic Features[1]**	**Distinctive Features[2]**	**Others[3]**	**Common Features[4]**
Mouth	□ Lichen-type features □ Hyperkeratotic plaques □ Restriction of mouth opening from sclerosis	□ Xerostomia □ Mucocele □ Mucosal atrophy □ Pseudomembranes [6] □ Ulcers[6]		□ Gingivitis □ Mucositis □ Erythema □ Pain
Eyes		□ New onset dry, gritty, or painful eyes [9] □ Cicatricial conjunctivitis □ Keratoconjunctivitis sicca [9] □ Confluent areas of punctuate keratopathy	□ Photophobia □ Periorbital hyperpigmentation □ Blepharitis [10]	
Genitalia	□ Lichen planus-like features □ Vaginal scarring or stenosis	□ Erosions [6] □ Fissures [6] □ Ulcers [6]		
Lung	□ Bronchiolitis obliterans diagnosed with lung biopsy	□ Bronchiolitis obliterans diagnosed with PFTs [12] and radiology [9]		□ BOOP [13]

Organ or Site	Diagnostic Features[1]	Distinctive Features[2]	Others[3]	Common Features[4]
Hematopoietic and immune				□Thrombocytopenia □ Eosinophilia □ Lymphopenia □ Hypo- or hypergamma-globulinemia □ Autoantibodies (AIHA and ITP)[14]
Muscle, Fascia, joints	□ Fasciitis □ Joint stiffness or contractures secondary to sclerosis	□ Myositis or polymyositis	□ Edema □ Muscle cramps □ Arthralgia or arthritis	
Other				□ Pericardial or pleural effusions □ Ascites □ Peripheral neuropathy □ Nephrotic syndrome □ Myasthenia gravis □ Cardiac conduction abnormality or cardiomyopathy

1. Sufficient to establish the diagnosis of cGVHD
2. Seen in cGvHD, but insufficient alone to establish a diagnosis of cGvHD
3. Can be acknowledged as part of the cGVHD symptomatology if the diagnosis is confirmed
4. Seen with both acute and cGVHD
5. Usually symmetric—affects most nails
6. In all cases, infection, drug effects, malignancy, or other causes must be excluded
7. After recovery from chemoradiation therapy
8. Not explained by endocrine or other causes

APPENDIX C: CLINICAL DIFFERENTIATION OF ACUTE AND CHRONIC GVHD

Category	Time of Symptoms After HCT or DLI	Presence of Acute GVHD Features	Presence of Chronic GVHD Features[2]
Acute GVHD			
Classic acute GVHD	≤ 100 days	Yes	No
Persistent, recurrent, or late-onset acute GVHD	> 100 days	Yes	No
Chronic GVHD			
Classic cGVHD	No time limit	No	Yes
Overlap cGVHD	No time limit	Yes	Yes

1. Abbreviations: HCT: hematopoietic cell transplantation; DLI: donor lymphocyte infusion
2. See **Appendix B** for features

APPENDIX D: ORGAN SPECIFIC AND GLOBAL SCORING 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		☐ Superficial 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___

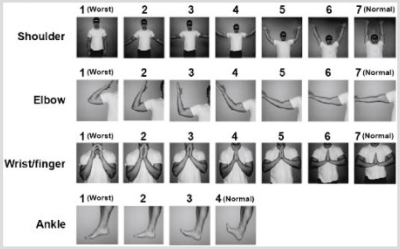
☐ Pericardial Effusion___ ☐ Peripheral Neuropathy___ ☐ Eosinophilia > 500/µl___

☐ 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 CGVHD

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: CHRONIC GVHD ASSESSMENT (CLINICIAN) FORM

FORM A

Current Patient Weight: _____ Today's Date: _____ MR#/Name: _____

CHRONIC GVHD ACTIVITY ASSESSMENT - CLINICIAN

Health Care Provider Global Ratings: 0=none 1= mild 2=moderate 3=severe	**Where would you rate the severity of this patient's chronic GvHD symptoms on the following scale, where 0 is cGVHD symptoms that are not at all severe and 10 is the most severe cGVHD symptoms possible:** 0 1 2 3 4 5 6 7 8 9 10 **cGvHD symptoms not at all severe** — **Most severe cGvHD symptoms possible**	**Over the <<time>> would you say that this patient's cGvHD is** +3= Very much better +2= Moderately better +1= A little better 0= About the same -1=A little worse -2=Moderately worse -3=Very much worse

Mouth	**Erythema**	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3
	Lichenoid	None	0	Lichen-like changes (<25%)	1	Lichen-like changes (25-50%)	2	Lichen-like changes (>50%)	3
	Ulcers	None	0			Ulcers involving (≤20%)	3	Severe ulcerations (>20%)	6
						Total score for all mucosal changes			

Gastrointestinal-Esophageal • Dysphagia OR Odynophagia	*0= no esophageal symptoms* *1=Occasional dysphagia or odynophagia with solid food or pills during the past week* *2=Intermittent dysphagia or odynophagia with solid foods or pills, but not for liquids or soft foods, during the past week* *3=Dysphagia or odynophagia for almost all oral intake, on almost every day of the past week*
Gastrointestinal-Upper GI • Early satiety OR • Anorexia OR • Nausea & Vomiting	*0= no symptoms* *1=mild, occasional symptoms, with little reduction in oral intake during the past week* *2=moderate, intermittent symptoms, with some reduction in oral intake during the past week* *3=more severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the past week*
Gastrointestinal-Lower GI • Diarrhea	*0= no loose or liquid stools during the past week* *1= occasional loose or liquid stools, on some days during the past week* *2=intermittent loose or liquid stools throughout the day, on almost every day of the past week,* ***without requiring*** *intervention to prevent or correct volume depletion* *3=voluminous diarrhea on almost every day of the past week,* ***requiring*** *intervention to prevent or correct volume depletion*

Lungs (Liters and % predicted) • Bronchiolitis Obliterans	FEV1		FVC		Single Breath DLCO (adjusted for hemoglobin)			TLC		RV
Liver Values	Total serum bilirubin	mg/dL	ULN	mg/dL	ALT	U/L	ULN U/L	Alkaline Phosphatase	U/L	ULN U/L
Baseline Values	Total Distance Walked in 2 or 6 Mins: ☐ 2 min ☐ 6 min				Karnofsky or Lansky		Platelet Count K/uL	Total WBC	K/uL	Eosinophils %
	☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause): _____ ☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause): _____ ☐ Abnormality present but explained entirely by non-GVHD documented cause (specify site/alternate cause): _____									

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN (FORM A)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
SKIN *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	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
If skin features score = 3, BSA% of non-moveable sclerosis/fasciitis _____ How would you rate the severity of this patient's skin and/or joint tightening on the following scale, where 0 is not at all severe and 10 is the most severe symptoms possible: 0 1 2 3 4 5 6 7 8 9 10 Symptoms not at all severe … Most severe symptoms possible				
EYES	☐ No symptoms 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):_____				
LUNGS	☐ 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)
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA	☐ 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):_____				

Shoulder

❑ Not done

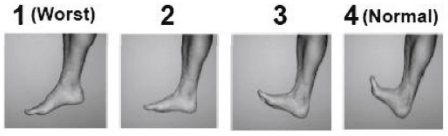
Elbow

❑ Not done

Wrist/finger

❑ Not done

Ankle



❑ Not done

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____

APPENDIX G: CHRONIC GVHD ASSESSMENT (PATIENT) FORM

FORM B

Today's Date: _____ MR#/Name: _____

CHRONIC GVHD ACTIVITY ASSESSMENT-PATIENT SELF REPORT

Symptoms **Please rate how severe the following symptoms have been in the last seven days. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.**	**Not Present** 0	1	2	3	4	5	6	7	8	9	**As Bad As You Can Imagine** 10
Your **skin itching** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **skin and/or joint tightening** at their WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **mouth sensitivity** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **genital discomfort** at its WORST? (Women – vagina, vulva, or labia) (Men – penis)	O	O	O	O	O	O	O	O	O	O	O

Eyes	What is your main complaint with regard to your eyes?	
	Please rate how severe this symptom is, from 0 (not at all severe) to 10 (most severe):	0 1 2 3 4 5 6 7 8 9 10

Patient Global Ratings:

1. Overall, do you think that your chronic graft versus host disease is mild, moderate or severe?
1= mild
2=moderate
3=severe

2. Please circle the number indicating how severe your chronic graft versus host disease symptoms are, where 0 is cGvHD symptoms that are not at all severe and 10 is the most severe chronic GvHD symptoms possible.

0 1 2 3 4 5 6 7 8 9 10

cGvHD symptoms not at all severe — Most severe cGvHD symptoms possible

3. Compared to a month ago, overall would you say that your cGvHD symptoms are:

+3= Very much better
+2= Moderately better
+1=A little better
0= About the same
-1=A little worse
-2=Moderately worse
-3=Very much worse

APPENDIX H: DATA COLLECTION ELEMENTS

A. PATIENT ENROLLMENT

Recipient

- Date of birth, age, gender, race, ethnicity
- Height
- Weight
- Karnofsky Performance Status
- Date of original diagnosis of the underlying disease (month/year)
- Diagnosis for which transplant was performed
- Date and type of transplant
- Myeloablative or non-myeloablative conditioning regimen
- Stem cell source (marrow, blood, cord)
- Acute GVHD yes/no (classic, late)
- Chronic GVHD date of diagnosis
- Chronic GVHD classification (classic, overlap)
- Prior systemic therapy for cGVHD
- Baseline cGVHD manifestations **(Appendix B**, NIH scores (**Appendix D**), Forms A and B (**Appendix F** & **Appendix G**) and cGVHD New Patient Data form (**Appendix M**: cGVHD New Patient Data Form)
- Intensity of current immunosuppression: None, Mild (single agent prednisone ≤0.5 mg/kg/day), Moderate (prednisone ≥0.5 mg/kg/day and or any single agent/modality), High (2 or more agents/modalities ±prednisone ≥0.5 mg/kg/day)
- Clinician's impression of activity: Inactive, off systemic therapy or topical immunosuppression; Inactive, on systemic therapy or topical immunosuppression; Active, irrespective of the level of current therapy; Highly Active, irrespective of the level of current therapy
- Findings of consultations done at screening

Donor

- Related or Unrelated
- HLA matched or mismatched
- Haploidentcal (yes-no)

B. STUDY DRUG ADMINISTRATION AND RESPONSE FOR EACH COURSE OF THERAPY GIVEN

- Dates and times study drug given
- Actual dose given
- Response assessment at timepoints (CR, PR, unchanged- SD, progression - PD, mixed - MR)

C. LABORATORY AND DIAGNOSTIC TEST DATA

- All Clinical laboratory and diagnostic test results done at screening and timepoints, except diagnostic tests which are not specified in the protocol, and if the results are not needed to document the start or end of an adverse event that requires reporting.
- All tests done to document resolution of adverse events

D. ADVERSE EVENTS

- Baseline AEs
- All grade ≥ 2 events per cycle
- All deaths, to include cause of death

E. CONCOMITANT TREATMENTS

- Systemic therapy for chronic GVHD
- Prednisone dose (or prednisone equivalent)
- New topical therapy and organ site
- Steroid pulses (date and starting dose)
- Therapy for AEs

F. OFF STUDY

- Date and reason for off treatment
- Date and reason for off study

APPENDIX I: PATIENT REPORTED OUTCOMES QUESTIONNAIRES

Lee Chronic GVHD Symptom Scale

	Not at all	Slightly	Moderately	Quite a bit	Extremely
SKIN:					
a. Abnormal skin color	0	1	2	3	4
b. Rashes	0	1	2	3	4
c. Thickened skin	0	1	2	3	4
d. Sores on skin	0	1	2	3	4
e. Itchy skin	0	1	2	3	4
EYES AND MOUTH:					
f. Dry eyes	0	1	2	3	4
g. Need to use eye drops frequently	0	1	2	3	4
h. Difficulty seeing clearly	0	1	2	3	4
i. Need to avoid certain foods due to mouth pain	0	1	2	3	4
j. Ulcers in mouth	0	1	2	3	4
k. Receiving nutrition from an intravenous line or feeding tube	0	1	2	3	4
BREATHING:					
l. Frequent cough	0	1	2	3	4
m. Colored sputum	0	1	2	3	4
n. Shortness of breath with exercise	0	1	2	3	4
o. Shortness of breath at rest	0	1	2	3	4
p. Need to use oxygen	0	1	2	3	4
EATING AND DIGESTION:					

q. Difficulty swallowing solid foods	0	1	2	3	4
r. Difficulty swallowing liquids	0	1	2	3	4
s. Vomiting	0	1	2	3	4
t. Weight loss	0	1	2	3	4
MUSCLES AND JOINTS:					
u. Joint and muscle aches	0	1	2	3	4
v. Limited joint movement	0	1	2	3	4
w. Muscle cramps	0	1	2	3	4
x. Weak muscles	0	1	2	3	4
ENERGY:					
y. Loss of energy	0	1	2	3	4
z. Need to sleep more/take naps	0	1	2	3	4
aa. Fevers	0	1	2	3	4
MENTAL AND EMOTIONAL:					
bb. Depression	0	1	2	3	4
cc. Anxiety	0	1	2	3	4
dd. Difficulty sleeping	0	1	2	3	4

FACT-BMT (Version 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-BMT (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-BMT (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
BMT1	I am concerned about keeping my job (include work at home)	0	1	2	3	4
BMT2	I feel distant from other people	0	1	2	3	4
BMT3	I worry that the transplant will not work	0	1	2	3	4
BMT4	The effects of treatment are worse than I had imagined	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
BMT5	I am able to get around by myself	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
BMT7	I have concerns about my ability to have children	0	1	2	3	4
BMT8	I have confidence in my nurse(s)	0	1	2	3	4
BMT9	I regret having the bone marrow transplant	0	1	2	3	4
BMT 10	I can remember things	0	1	2	3	4
Br1	I am able to concentrate (e.g., reading)	0	1	2	3	4
BMT 11	I have frequent colds/infections	0	1	2	3	4
BMT 12	My eyesight is blurry	0	1	2	3	4
BMT 13	I am bothered by a change in the way food tastes	0	1	2	3	4
BMT 14	I have tremors	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
BMT 15	I am bothered by skin problems (e.g., rash, itching)	0	1	2	3	4
BMT 16	I have trouble with my bowels	0	1	2	3	4
BMT 17	My illness is a personal hardship for my close family members	0	1	2	3	4
BMT 18	The cost of my treatment is a burden on me or my family	0	1	2	3	4

	Still Doing This Activity	*Have Stopped Doing This Activity*	*Never Did This Activity*
1. Getting in and out of chairs or bed (without assistance)			
2. Listening to the radio			
3. Reading books, magazines, or newspapers			
4. Writing (letters, notes)			
5. Working at a desk or table			
6. Standing (for more than 1 minute)			
7. Standing (more than 5 minutes)			
8. Dressing or undressing (without assistance)			
9. Getting clothes from drawers or closets			
10. Getting in or out of a car (without assistance)			
11. Dining at a restaurant			
12. Playing cards/table games			
13. Taking a bath (no assistance needed)			
14. Putting on shoes, stockings, or socks (no rest or break needed			
15. Attending a movie, play, church event, or sports activity			
16. Walking 30 yards (27 meters)			
17. Walking 30 yards (nonstop)			
18. Dressing/undressing (no rest break needed)			
19. Using public transportation or driving a car (99 miles or less)			
20. Using public transportation or driving a car (100 miles or more)			
21. Cooking your own meals			
22. Washing or drying dishes			
23. Putting groceries on shelves			
24. Ironing or folding clothes			

	Still Doing This Activity	*Have Stopped Doing This Activity*	*Never Did This Activity*
75. Walking 3 miles or golfing 18 holes without a riding cart			
76. Walking 3 miles (nonstop)			
77. Swimming 25 yards			
78. Swimming 25 yards (nonstop)			
79. Bicycling 1 mile			
80. Bicycling 2 miles			
81. Bicycling 1 mile (nonstop)			
82. Bicycling 2 miles (nonstop)			
83. Running or jogging 1/4 mile			
84. Running or jogging 1/2 mile			
85. Playing tennis or racquetball			
86. Playing basketball/soccer (game play)			
87. Running or jogging 1/4 mile (nonstop)			
88. Running or jogging 1/2 mile (nonstop)			
89. Running or jogging 1 mile			
90. Running or jogging 2 miles			
91. Running or jogging 3 miles			
92. Running or jogging 1 mile in 12 minutes or less			
93. Running or jogging 2 miles in 20 minutes or less			
94. Running or jogging 3 miles in 30 minutes or less			

	Still Doing This Activity	*Have Stopped Doing This Activity*	*Never Did This Activity*
51. Carrying a large suitcase or bowling (one game)			
52. Vacuuming carpets			
53. Vacuuming carpets (5 minutes nonstop)			
54. Painting (interior/exterior)			
55. Walking 6 blocks on level ground			
56. Walking 6 blocks on level ground (nonstop)			
57. Carrying out the garbage			
58. Carrying a heavy load of groceries			
59. Climbing 24 steps			
60. Climbing 36 steps			
61. Climbing 24 steps (nonstop)			
62. Climbing 36 steps (nonstop)			
63. Walking 1 mile			
64. Walking 1 mile (nonstop)			
65. Running 110 yards (100 meters) or playing softball/baseball			
66. Dancing (social)			
67. Doing calisthenics or aerobic dancing (5 minutes nonstop)			
68. Mowing the lawn (power mower, but not a riding mower			
69. Walking 2 miles			
70. Walking 2 miles (nonstop)			
71. Climbing 50 steps (2 1/2 floors)			
72. Shoveling, digging, or spading			
73. Shoveling, digging, or spading (5 minutes nonstop)			
74. Climbing 50 steps (nonstop)			

	Still Doing This Activity	*Have Stopped Doing This Activity*	*Never Did This Activity*
25. Dusting/polishing furniture or polishing a car			
26. Showering			
27. Climbing 6 steps			
28. Climbing 6 steps (nonstop)			
29. Climbing 9 steps			
30. Climbing 12 steps			
31. Walking 1/2 block on level ground			
32. Walking 1/2 block on level ground (nonstop)			
33. Making a bed (not changing sheets)			
34. Cleaning windows			
35. Kneeling/squatting to do light work			
36. Carrying a light load of groceries			
37. Climbing 9 steps (nonstop)			
38. Climbing 12 steps (nonstop)			
39. Walking 1/2 block uphill			
40. Walking 1/2 block uphill (nonstop)			
41. Shopping (by yourself)			
42. Washing clothes (by yourself)			
43. Walking 1 block on level ground			
44. Walking 2 blocks on level ground			
45. Walking 1 block on level ground (nonstop)			
46. Walking 2 blocks on level ground (nonstop)			
47. Scrubbing (floors, walls, or cars)			
48. Making a bed (changing sheets)			
49. Sweeping			
50. Sweeping (5 minutes nonstop)			

APPENDIX J: MEDICATION DIARY

Today's date _____Page 1

Patient Name_____ Patient Study ID_____

(*initials acceptable)*

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle.
2. You will take your dose baricitinib each day at approximately the same time. Baricitinib tablets should be swallowed whole, and should not be broken, chewed or opened. You will take ____ ____mg tablets each day.
3. Record the date, the number of capsules of each size you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring your pill bottle and this form to your physician when you go for your next appointment.

Date	**Day**	**Time of daily dose**	**# of tablets taken**			**Comments**
			1 mg	**2 mg**	**4 mg**	
	1					
	2					
	3					
	4					
	5					
	6					
	7					
	8					
	9					
	10					
	11					
	12					
	13					
	14					

Patient Name_____ Patient Study ID_____

(*initials acceptable)*

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle.
2. You will take your dose baricitinib each day at approximately the same time. Baricitinib tablets should be swallowed whole, and should not be broken, chewed or opened. You will take ___ ___mg tablets each day.
3. Record the date, the number of capsules of each size you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring your pill bottle and this form to your physician when you go for your next appointment.

Date	**Day**	**Time of daily dose**	**# of tablets taken**			**Comments**
			1 mg	**2 mg**	**4 mg**	
	15					
	16					
	17					
	18					
	19					
	20					
	21					
	22					
	23					
	24					
	25					
	26					
	27					
	28					

Patient's Signature: _____ Date: _____

Physician's Office will complete this section:

1. Date patient started protocol treatment_____ Date patient was removed from study _____
2. Patient's planned daily dose_____ Total number of pills taken this month _____

Physician/Nurse/Data Manager's Signature _____

APPENDIX K: RESPONSE DETERMINATION FOR CHRONIC GVHD TRIALS BASED ON CLINICIAN ASSESSMENTS

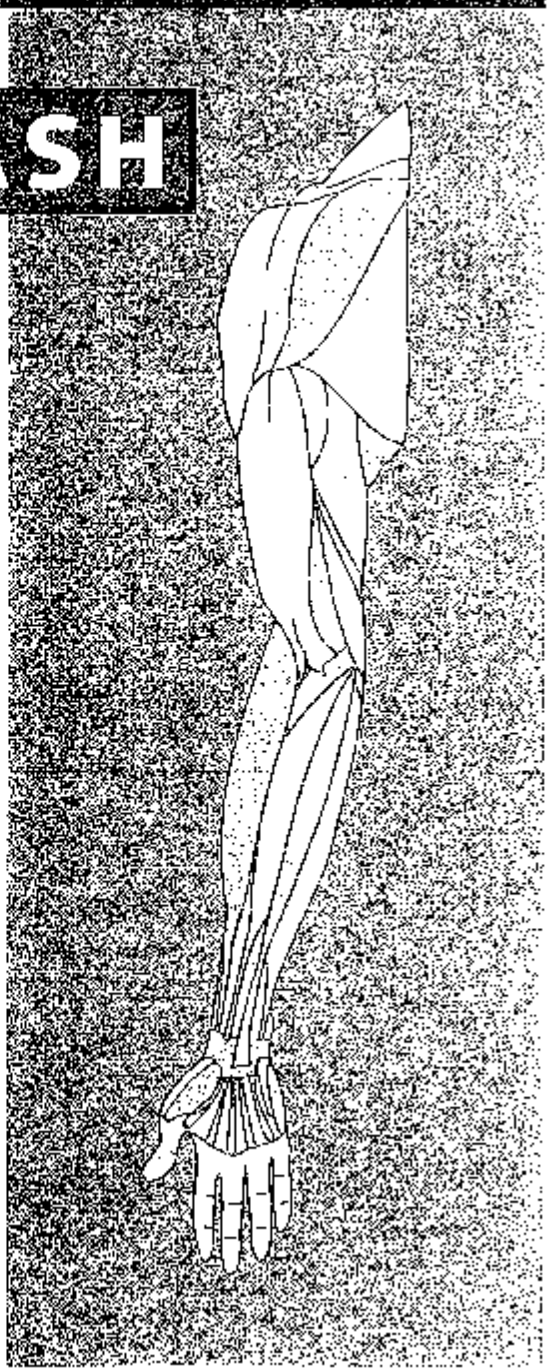
Organ	Complete Response	Partial Response	Progression
Skin	NIH Skin Score 0 after previous involvement	Decrease NIH Skin Score by 1 or more points	Increase in NIH Skin Score by 1 or more points, except 0 to 1
Eyes	NIH Eye Score 0 after previous involvement	Decrease in NIH Eye Score by 1 or more points	Increase in NIH Eye Score by 1 or more points, except 0 to 1
Mouth	NIH Modified OMRS 0 after previous involvement	Decrease in NIH Modified OMRS of 2 or more points	Increase in NIH Modified OMRS of 2 or more points
Esophagus	NIH Esophagus Score 0 after previous involvement	Decrease in NIH Esophagus Score by 1 or more points	Increase in NIH Esophagus Score by 1 or more points, except 0 to 1
Upper GI	NIH Upper GI Score 0 after previous involvement	Decrease in NIH Upper GI Score or more points	Increase in NIH Upper GI Score by 1 or more points, except 0 to 1
Lower GI	NIH Lower GI Score 0 after previous involvement	Decrease in NIH Lower GI Score by 1 or more points	Increase in NIH Lower GI Score by 1 or more points, except from 0 to 1
Liver	Normal ALT, alkaline phosphatase, and Total bilirubin after previous elevation of 1 or more	Decrease by 50%	Increase by 2 x ULN
Lungs	-Normal %FEV1, alkaline phosphatase, and Total bilirubin after previous elevation of 1 or more -If PFTs not available, NIH Lung	-Increase by 10% predicted absolute value of %FEV1 -If PFTs not available, decrease in NIH Lung Symptom	-Decrease by 10% predicted absolute value of %FEV1 -If PFTs not available, increase in NIH Lung Symptom

Organ	Complete Response	Partial Response	Progression
	Symptom Score 0 after previous involvement	Score by 1 or more points	Score by 1 or more points, except 0 to 1
Joints and fascia	Both NIH Joint and Fascia Score 0 and P-ROM score 25 after previous involvement by at least 1 measure	Decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 point for any site	Increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 point for any site
Global	Clinician overall severity score 0	Clinician overall severity score decreases by 2 or more points on a 0-10 scale	Clinician overall severity score increases by 2 or more points on a 0-10 scale

APPENDIX L: OCCUPATIONAL THERAPY EVALUATION FOR FUNCTIONAL ASSESSMENT, FATIGUE ASSESSMENT, AND UPPER EXTREMITY USE

DISABILITIES OF THE ARM, SHOULDER AND HAND

THE DASH



INSTRUCTIONS

This questionnaire asks about your symptoms as well as your ability to perform certain activities.

Please answer *every question*, based on your condition in the last week, by circling the appropriate number.

If you did not have the opportunity to perform an activity in the past week, please make your *best estimate* on which response would be the most accurate.

It doesn't matter which hand or arm you use to perform the activity; please answer based on your ability regardless of how you perform the task.

Activity Card Sort, 2nd Edition
Recovering Version Form B

Name _____ Date of Onset _____
Date Of Birth _____ Date _____
Tester _____

Number	Activity	Not Done Before Current Illness or Injury	Continued to Do During Illness or Injury	Doing Less Since Illness or Injury	Given Up Due to Illness or Injury	Done Previously	New Activity Since Illness or Injury	Score
	Instrumental							
1	Shopping in a Store		1	0.5	0	1	1	
2	Shopping for Groceries		1	0.5	0	1	1	
3	Dishes		1	0.5	0	1	1	
4	Laundry		1	0.5	0	1	1	
5	Yard Maintenance		1	0.5	0	1	1	
6	Taking Out the Trash		1	0.5	0	1	1	
7	Cooking Dinner		1	0.5	0	1	1	
8	Household Maintenance		1	0.5	0	1	1	
9	Fixing Things Around the House		1	0.5	0	1	1	
10	Driving		1	0.5	0	1	1	
11	Getting Gas		1	0.5	0	1	1	
12	Car Maintenance		1	0.5	0	1	1	
13	Going to Doctor or Therapy		1	0.5	0	1	1	
14	Taking Care of a Pet		1	0.5	0	1	1	
15	Paying Bills		1	0.5	0	1	1	
16	Managing Investments		1	0.5	0	1	1	
17	Resting		1	0.5	0	1	1	
18	Beauty/Barbershop		1	0.5	0	1	1	
19	Child Care		1	0.5	0	1	1	
20	Work (paid)		1	0.5	0	1	1	
	Total Instrumental							Current _____ Previous _____ % Retained ____
	Low-Demand Leisure							
21	Spectator Sports		1	0.5	0	1	1	
22	Recreational Shopping		1	0.5	0	1	1	
23	Cooking as a Hobby		1	0.5	0	1	1	
24	Sewing (clothing or household, including mending)		1	0.5	0	1	1	
25	Needle Crafts (knitting, needlepoint, quilting)		1	0.5	0	1	1	
26	Hand Crafts		1	0.5	0	1	1	
27	Table Games (checkers)		1	0.5	0	1	1	
28	Computer (e-mail, paying bils, shopping)		1	0.5	0	1	1	
29	Computer Games		1	0.5	0	1	1	
30	Collecting		1	0.5	0	1	1	
31	Playing Cards (solitaire, poker, bridge)		1	0.5	0	1	1	
32	Putting Together Puzzles		1	0.5	0	1	1	
33	Crossword or Sudoku Puzzles		1	0.5	0	1	1	
34	Photography		1	0.5	0	1	1	
35	Drawing/Painting		1	0.5	0	1	1	
36	Interior Decorating		1	0.5	0	1	1	
37	Playing a Musical Instrument		1	0.5	0	1	1	
38	Reading Magazines/Books		1	0.5	0	1	1	
39	Reading Newspaper		1	0.5	0	1	1	
40	Reading the Bible/Religious Materials		1	0.5	0	1	1	
41	Singing in Choir or Group		1	0.5	0	1	1	
42	Creative Writing/Journal		1	0.5	0	1	1	
43	Letter Writing		1	0.5	0	1	1	
44	Bird Watching		1	0.5	0	1	1	
45	Going to the Museum		1	0.5	0	1	1	
46	Going to Garden or Park		1	0.5	0	1	1	
47	Attending Concerts		1	0.5	0	1	1	
48	Going to Casino		1	0.5	0	1	1	
49	Bingo/Lottery		1	0.5	0	1	1	
50	Going to the Theater		1	0.5	0	1	1	
51	Watching Movies		1	0.5	0	1	1	
52	Watching Television		1	0.5	0	1	1	
53	Listening to Music		1	0.5	0	1	1	
54	Listening to Radio		1	0.5	0	1	1	
55	Sitting and Thinking		1	0.5	0	1	1	
	Total Low-Demand-Leisure Activities							Current _____ Previous _____ % Retained ____
	High-Demand Leisure							
56	Swimming		1	0.5	0	1	1	
57	Playing Team Sports		1	0.5	0	1	1	

Number	Activity	Not Done Before Current Illness or Injury	Continued to Do During Illness or Injury	Doing Less Since Illness or Injury	Given Up Due to Illness or Injury	Done Previously	New Activity Since Illness or Injury	Score
58	Woodworking		1	0.5	0	1	1	
59	Bowling		1	0.5	0	1	1	
60	Golfing		1	0.5	0	1	1	
61	Walking		1	0.5	0	1	1	
62	Running		1	0.5	0	1	1	
63	Exercising		1	0.5	0	1	1	
64	Yoga/Pilates/Tai Chi		1	0.5	0	1	1	
65	Playing Tennis or Other Racquet Sports		1	0.5	0	1	1	
66	Hiking		1	0.5	0	1	1	
67	Bicycling		1	0.5	0	1	1	
68	Yard Games		1	0.5	0	1	1	
69	Camping		1	0.5	0	1	1	
70	Canoeing/Boating/Sailing		1	0.5	0	1	1	
71	Fishing		1	0.5	0	1	1	
72	Gardening/Growing Flowers		1	0.5	0	1	1	
	Total High-Demand-Leisure Activities							Current _____ Previous _____ % Retained ____
	Social							
73	Studying for Personal Advancement		1	0.5	0	1	1	
74	Traveling Local/Regional		1	0.5	0	1	1	
75	Traveling National/International		1	0.5	0	1	1	
76	Parties/Picnics		1	0.5	0	1	1	
77	Family Gatherings		1	0.5	0	1	1	
78	Talking on the Telephone		1	0.5	0	1	1	
79	Visiting with Family/Friends Who Are Ill		1	0.5	0	1	1	
80	Visiting with Friends		1	0.5	0	1	1	
81	Eating at a Restaurant		1	0.5	0	1	1	
82	Dancing		1	0.5	0	1	1	
83	Going to Place of Worship		1	0.5	0	1	1	
84	Volunteer Work		1	0.5	0	1	1	
85	Going to Children's or Grandchildren's Activities		1	0.5	0	1	1	
86	Storytelling With Children		1	0.5	0	1	1	
87	Being With Spouse or Partner		1	0.5	0	1	1	
88	Dating/Spending Time With Friends		1	0.5	0	1	1	
89	Entertaining at Home or Club		1	0.5	0	1	1	
	Total Social Activities							Current _____ Previous _____ % Retained ____

Global ACS Scores:

Current Activity (sum total of Current Activity sectional scores) _____

Previous Activity (sum total of Previous Activity sectional scores) _____

Percent Retained (divide global Current Activity score by global Previous Activity score) _____

Identify the five most important activities to you (they may be those you no longer do):

1

2

3

4

5

HEALTH ASSESSMENT QUESTIONNAIRE (HAQ-DI)©

Name: _____ Date: _____

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
DRESSING & GROOMING				
Are you able to:				
Dress yourself, including shoelaces and buttons?	☐	☐	☐	☐
Shampoo your hair?	☐	☐	☐	☐
ARISING				
Are you able to:				
Stand up from a straight chair?	☐	☐	☐	☐
Get in and out of bed?	☐	☐	☐	☐
EATING				
Are you able to:				
Cut your own meat?	☐	☐	☐	☐
Lift a full cup or glass to your mouth?	☐	☐	☐	☐
Open a new milk carton?	☐	☐	☐	☐
WALKING				
Are you able to:				
Walk outdoors on flat ground?	☐	☐	☐	☐
Climb up five steps?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Devices used for Dressing (button hook, zipper pull, etc.)
☐ Built up or special utensils
☐ Crutches
☐ Cane
☐ Wheelchair
☐ Special or built up chair
☐ Walker

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Dressing and grooming ☐ Arising ☐ Eating ☐ Walking

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
HYGIENE				
Are you able to:				
Wash and dry your body?	☐	☐	☐	☐
Take a tub bath?	☐	☐	☐	☐
Get on and off the toilet?	☐	☐	☐	☐
REACH				
Are you able to:				
Reach and get down a 5 pound object (such as a bag of sugar) from above your head?	☐	☐	☐	☐
Bend down to pick up clothing from the floor?	☐	☐	☐	☐
GRIP				
Are you able to:				
Open car doors?	☐	☐	☐	☐
Open previously opened jars?	☐	☐	☐	☐
Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Are you able to:				
Run errands and shop?	☐	☐	☐	☐
Get in and out of a car?	☐	☐	☐	☐
Do chores such as vacuuming or yard work?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Raised toilet seat ☐ Bathtub bar ☐ Long-handled appliances for reach

☐ Bathtub seat ☐ Long-handled appliances in bathroom ☐ Jar opener (for jars previously opened)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Hygiene ☐ Reach ☐ Gripping and opening things ☐ Errands and chores

Your ACTIVITIES: To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?

COMPLETELY	MOSTLY	MODERATELY	A LITTLE	NOT AT ALL
☐	☐	☐	☐	☐

Your PAIN: How much pain have you had IN THE PAST WEEK?
On a scale of 0 to 100 (where zero represents "no pain" and 100 represents "severe pain"), please record the number below.

☐☐☐

Your HEALTH: Please rate how well you are doing on a scale of 0 to 100 (0 represents "very well" and 100 represents "very poor" health), please record the number below.

☐☐☐

MANUAL ABILITY MEASURE (MAM-36)

Patient ID: _____ Today's Date: _____/_____/_____

Age: _____ Gender: _____ Highest Level of Education: _____

Race (White, African American, American Indian, Asian-Pacific, Mixed Races, Don't know)

Are you Hispanic? ____ Yes, ____ No

Are you currently employed? If so, what is your occupation (job title)?

_____

If not, what was your occupation before you were diagnosed with your current condition?

_____

What is your diagnosis for coming to the clinic? _____

How long ago were you diagnosed with this condition? _____

Do you have any other medical problems that affect the use of your hands?

If you have had hand surgery, or if you have surgery scheduled, please indicate the date(s) and what was/will be done:

_____

Which is your dominant hand?
Right ____, Left ____, Ambidextrous ____, Don't know ____

Which hand(s) has limited function or hand use? Both ____, Right ____, Left ____

Do you live alone now?
Yes ____

No ____, with _____

Instructions:

Please circle one response regarding how easy or how hard it is for you to perform the following tasks.

Easy (4) = I can do the activity without any problem.
A little hard (3) = I usually do the task myself, although it takes longer or more effort now than before (i.e., before having current diagnosis/condition/disability). Sometimes, there is pain or discomfort when I do the task.
Very hard (2) = It is very hard for me to do the task and I usually ask others to do it for me unless no one is around.
Cannot do (1) I am unable to do the task all by myself.
Almost Never do (0) = I have not done and almost will never do the task, even though I think I can do it.

Task	Easy	A little hard	Very hard	Cannot do	Never do
Eat a sandwich	4	3	2	1	0
Drink a glass of water	4	3	2	1	0
Pick up a half-full water pitcher	4	3	2	1	0
Use a spoon or fork	4	3	2	1	0
Butter bread (Put butter or jam on the bread)	4	3	2	1	0
Cut meat on a plate with a knife	4	3	2	1	0
Squeeze toothpaste	4	3	2	1	0
Brush teeth	4	3	2	1	0
Brush or comb hair	4	3	2	1	0
Wash hands	4	3	2	1	0
Wring a towel	4	3	2	1	0
Zip pants	4	3	2	1	0
Zip a jacket	4	3	2	1	0
Button clothes	4	3	2	1	0
Fasten a clothes snap or hook	4	3	2	1	0
Cut nails with a nail clipper	4	3	2	1	0
Tie shoes with laces	4	3	2	1	0
Use a remote control	4	3	2	1	0
Key in telephone numbers	4	3	2	1	0

Turn door knob to open a door	4	3	2	1	0
Turn key to open a lock	4	3	2	1	0
Carry a shopping bag with a hand loop	4	3	2	1	0
Open a previously-opened wide-mouth jar (jam, pickle)	4	3	2	1	0
Open a previously-unopened carton box (milk, cereal)	4	3	2	1	0
Pour liquid from a bottle into a glass	4	3	2	1	0
Open a medicine bottle with child-proof top	4	3	2	1	0
Open an envelope without a letter opener	4	3	2	1	0
Peel vegetables or fruits	4	3	2	1	0
Count money (bills and coins)	4	3	2	1	0
Take things out of a wallet (bills, papers, credit cards)	4	3	2	1	0
Write 3 to 4 sentences legibly	4	3	2	1	0
Turn pages of a book	4	3	2	1	0
Shuffle and deal cards	4	3	2	1	0
Use a hammer or screwdriver	4	3	2	1	0
Fold clothes after laundering	4	3	2	1	0
Take a CD/DVD out of its case and put it onto a player/drive	4	3	2	1	0

Multi-Dimensional Fatigue Inventory

The next questions are about how you have been feeling lately. Please place one "X" for each statement.

The more you agree with the statement, the more you should place an "X" in the direction of "yes, that is true." The more you disagree with the statement, the more you should place an X in the direction of "no, that is not true."

Take for example the statement: "I FEEL RELAXED."

If you think that this statement is entirely true, that you have been feeling relaxed lately, you would place an "X" in the box labeled "1."

yes, that is true ☒ ☐ ☐ ☐ ☐ no, that is not true
1 2 3 4 5

1. I feel fit.	yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true	1 2 3 4 5
2. Physically I feel only able to do a little.	yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true	1 2 3 4 5
3. I feel very active.	yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true	1 2 3 4 5
4. I feel like doing all sorts of nice things.	yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true	1 2 3 4 5
5. I feel tired.	yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true	1 2 3 4 5
6. I think I do a lot in a day.	yes, that is true ☐ ☐ ☐ ☐ ☐ no, that is not true	1 2 3 4 5

7. When I am doing something, I can keep my thoughts on it.	yes, that is true	1	2	3	4	5	no, that is not true
8. Physically I can take on a lot.	yes, that is true	1	2	3	4	5	no, that is not true
9. I dread having to do things.	yes, that is true	1	2	3	4	5	no, that is not true
10. I think I do very little in a day.	yes, that is true	1	2	3	4	5	no, that is not true
11. I can concentrate well.	yes, that is true	1	2	3	4	5	no, that is not true
12. I am rested.	yes, that is true	1	2	3	4	5	no, that is not true
13. It takes a lot of effort to concentrate on things.	yes, that is true	1	2	3	4	5	no, that is not true
14. Physically I feel I am in a bad condition.	yes, that is true	1	2	3	4	5	no, that is not true
15. I have a lot of plans.	yes, that is true	1	2	3	4	5	no, that is not true
16. I tire easily.	yes, that is true	1	2	3	4	5	no, that is not true

17. I get little done.	yes, that is true	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	no, that is not true
18. I don't feel like doing anything.	yes, that is true	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	no, that is not true
19. My thoughts easily wander.	yes, that is true	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	no, that is not true
20. Physically I feel I am in an excellent condition.	yes, that is true	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	no, that is not true

APPENDIX M: CGVHD NEW PATIENT DATA FORM

Baricitinib for cGVHD (16-C-0094)

New Patient Data Form (Baseline)

Karnofsky Score: Date on Study:_____

Disease Characteristic	
Diagnosis	

Transplant information:		
Date of transplant		
Type of transplant	□ Bone marrow □Bone marrow & PBSC □Cord Blood □Other □ Peripheral blood stem cell (PBSC) □ Donor Mobilized	
Haploidentical Transplant	□ yes □ no	
Donor relationship	_____	
Degree of HLA match:	□ 8/8, 10/10 or 12/12 □ HLA Mismatch	
2nd transplant (allo or auto) □Y □N		
Early post transplant events		
Acute GVHD	□Y □N	
DLI	□Y □N	
cGVHD history	Date of cGVHD Diagnosis: _____ GVHD Classification □ Classic □ Overlap	

Prior Systemic therapy for cGVHD (list all medications/therapies)	
□ Tacrolimus □ Sirolimus □ Cyclosporine □ Cellcept □ Imatinib □ Rituximab □ Prednisone □ ECP □ Anti-thymocyte globulin □ Methotrexate □ Dacluzimab □ Ruxolitinib □ Pomalidomide Please list all other therapy previously taken for cGVHD:	
Current Systemic therapy for cGVHD (list all medications/therapies, and add dose just for steroids)	□Y □N
□ Tacrolimus □ Sirolimus □ Cyclosporine □ Cellcept □ Imatinib □ Rituximab □ ECP □ Ruxolitinib □ Methotrexate □ Ibrutinib □ Pomalidomide □ Prednisone (dose) _____ Please list all others:	
Current topical therapy for cGVHD	□Y □N
If yes, list all topical therapy:	
Intensity of current immunosuppression: ***see note on bottom of page 3**	
□ None □ Mild (single agent prednisone<0.5 mg/kg/day) □ Moderate (prednisone≥0.5 mg/kg/day and/or any single agent/modality) □ High (2 or more agents/modalities ± prednisone≥0.5 mg/kg/day)	

Clinician's impression of activity □ Inactive, off systemic therapy or topical immunosuppression □ Inactive, on systemic therapy or topical immunosuppression □ Active, irrespective of the level of current therapy □ Highly active, irrespective of the level of current therapy	
BOS	□ Y (1. FEV1<75% and FEV1/FVC ratio <0.7or 2. FEV1<75% and ratio >_0.7 must have RV or RV/TLC >120% PLUS CT c/w air trapping) □ N

LIP Print Name:_____ LIP Signature:_____

Date of Evaluation:_____

Timepoint: Baseline_____

* - for "Intensity of current immunosuppression" scale on page 2 just systemic immunosuppression should be considered (PUVA and ursodiol are not systemic immunosuppressive agents, and ECP can be considered as systemic immunosuppressive agent/modality for that scale)