Abbreviated Title: Ibrutinib for Chronic GvHD

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Title: A Study of Front Line Ibrutinib without Corticosteroids for Newly Diagnosed Chronic Graft-versus-Host Disease

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Drug Name:	Ibrutinib
IND Number:	146697
Sponsor:	Center for Cancer Research
Manufacturer:	Pharmacyclics LLC
Supplier	Pharmacyclics LLC

Commercial Agents: None

COORDINATING CENTER: NCI

SAFETY MONITORING COMMITTEE (SMC): NCI INTRAMURAL SMC

PRÉCIS

Background:

- Chronic graft-versus-host disease (GvHD) is the leading cause of late morbidity and non-relapse mortality following allogeneic hematopoietic stem cell transplantation (alloHSCT), occurring in 40-60% long-term survivors.
- Chronic GvHD occurs due to the dysfunctional peripheral tolerance during post-transplant hematopoietic reconstitution that allows the development and persistence of alloreactive donor-derived T and B cells.
- Prednisone is the front-line therapy; however, about 50% of participants have steroid-refractory disease and there is no standard second-line therapy.
- The most attractive approach for controlling chronic GvHD would be early therapy intervention which could prevent the most severe and irreversible clinical manifestations.
- Anti-B-cell therapy delivered early in chronic GvHD could be effective and steroid-sparing.
- Ibrutinib, reversible small molecule inhibitor of Bruton's tyrosine kinase, has been shown to be well-tolerated and effective in phase 1b/2 trial for steroid refractory chronic GvHD.

Objective:

- To evaluate efficacy of ibrutinib as a first-line treatment for persons with newly diagnosed chronic GvHD by measuring the overall response rate (complete response [CR] + partial response [PR]) at 6 months, according to the 2014 NIH Consensus Criteria

Eligibility:

- Newly diagnosed, moderate or severe chronic GvHD according to the 2014 NIH Consensus Criteria, requiring systemic immunosuppression
- Age ≥ 18 years old
- Karnofsky performance status ≥ 60%
- History of prior alloHSCT; any donors, conditioning regimens and graft sources are allowed
- Adequate cardiac, hepatic and other organ function
- Adequate laboratory parameters

Design:

- Multi-center, non-randomized, phase II study
- Two-stage design will be used to determine the overall response rate (CR + PR) at 6 months
- Continuous daily dose of ibrutinib 420 mg by mouth, with the potential for dose reductions to 280 mg and 140 mg
- The accrual ceiling will be set at 40 participants, allowing for a total of up to 28 evaluable subjects.

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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 Objective

- To evaluate the efficacy of ibrutinib as a first-line treatment for persons with newly diagnosed chronic graft-versus-host disease (GvHD) by measuring the overall response rate (complete response [CR] + partial response [PR]) at 6 months, according to the 2014 NIH Consensus Criteria

1.1.1 Secondary Objective(s)

- To evaluate safety of ibrutinib for newly diagnosed chronic GvHD
- To evaluate failure-free survival (FFS)
- To evaluate 24 months post-treatment follow-up for survival

1.1.2 Exploratory Objective(s)

- To evaluate chronic GvHD response rate at 6 weeks, 3 months, 9 months and 1 year
- To evaluate the duration of chronic GvHD response
- To evaluate ability to taper steroids and other systemic immunosuppression
- To evaluate need for steroid pulses
- To evaluate the need for therapy change
- To evaluate subject-reported outcomes by the NIH Chronic GvHD Activity Assessment-Patient Self Report-Form B, the Lee Symptom Scale and the SF36
- To monitor for recurrence of the original malignancy or development of new cancers

- To evaluate changes in T and B regulatory and effector subsets, in patterns of gene expression in tissue biopsies and blood samples and in proposed plasma biomarkers in order to correlate these changes with clinical assessments of chronic GVHD

1.2 BACKGROUND AND RATIONALE

1.2.1 Graft-versus-Host-Disease

Allogeneic hematopoietic stem cell transplantation (alloHSCT) is a potentially curative therapy for people with aggressive or relapsed/refractory hematologic malignancies. In 2015 the Center for International Blood and Marrow Transplant Research estimated approximately 8,000 alloHSCT were performed in the US.(1) Chronic GvHD is the most common cause of late morbidity and non-relapse mortality following alloHSCT, occurring in about 40-60% of long-term survivors.(2-4) Importantly, the incidence and prevalence of chronic GvHD are on the rise due to multiple factors including: more transplantation of older adults, increased use of mobilized peripheral blood as a stem cell source and improved early post-transplant survival.(5) Chronic GvHD is characterized by immunosuppression and immune-dysregulation resulting in decreased organ function, increased risk of infection, and reduced quality of life (QOL) in patients otherwise cured of their cancer.(6, 7) One of the major obstacles to clinical research in chronic GvHD has been the lack of standardized criteria for the diagnosis, staging and measurements of response to therapy.(8, 9) In 2005 the National Institutes of Health (NIH) Consensus Conference consolidated expert opinions and standardized recommendations for diagnosis and staging, histopathology, biomarkers, response criteria, ancillary therapy and supportive care, and design of clinical trials. The Chronic GvHD Consortium was subsequently established to conduct multicenter studies on chronic GvHD and many retrospective and prospective longitudinal studies have been published over the last nine years further validating the NIH Consensus Criteria.(5, 10-16) In 2014, now with 9-year experience, the experts met again to update and improve on the original recommendations and clarify controversies.(17-22) The 2014 NIH Consensus Criteria provide greater specificity and more accurate measures of the disease burden.

1.2.1.1 Clinical Manifestations

Symptoms of chronic GvHD occur gradually, starting in average 6 months after transplantation. Chronic GvHD targets skin, mouth, eyes, gut, liver, lungs, joints and genitourinary system; it may be restricted to single site, but more frequently several organ-sites are included. Early diagnosis is important because the goal of treatment is control of symptoms and the prevention of irreversible organ damage. In the past, any manifestations of GvHD present beyond 100 days following alloHSCT were arbitrarily defined as chronic GvHD. The NIH Consensus Criteria recognizes two major categories of GvHD, each one with 2 subcategories. (17) Chronic GvHD is separated from acute GvHD not by time frame from alloHSCT, but by the presence of diagnostic and distinctive clinical manifestations. Diagnosis of chronic GvHD requires at least one diagnostic sign (manifestation that establish the diagnosis of chronic GvHD without the need for further testing) or at least one distinctive sign (manifestation highly suggestive of chronic GvHD but insufficient alone to establish the diagnosis) confirmed by biopsy, laboratory test, or by radiology in the same or another organ (**Appendix A**). In the absence of histological or clinical signs characteristic of chronic GvHD, persistence, recurrence or new onset of maculopapular erythematous rash, gastrointestinal symptoms or cholestatic hepatitis should be classified as acute GvHD, regardless of the time after transplantation. The 2014 NIH Consensus Criteria have

defined the overlap category as the presence of acute GvHD manifestations in a patient diagnosed with chronic GvHD.

1.2.1.2 Pathophysiology

Chronic GvHD occurs due to the dysfunctional peripheral tolerance during post-transplant hematopoietic reconstitution that allows the development and persistence of alloreactive donor-derived T and B cells.(23-29) The exact role of, and interactions among, different T- and B-cell subsets and influence of cytokines has not been fully elucidated. Chronic GvHD is considered to be a disease of immune dysregulation where donor-derived immune cells react against host cell populations and tissues. It is likely that unique donor-recipient immune factors play a role in development of chronic GvHD. Degeneration of the thymus, due to age, prior acute GvHD, or transplant conditioning, results in decrease in negative selection of alloreactive CD4+ T cells. In addition, peripheral tissue damage from previous acute GvHD or inflammation may lead to release of normally sequestrated, cryptic auto-antigens to the periphery. T-cell dysregulation then leads to cytokine response with increased production of interleukin (IL)-4, -5, and -11, and release of fibrogenic cytokines such as IL-2, transforming growth factor-β1 and TNF-α, resulting in immunodeficiency, target organ injury and fibrosis. CD4+CD25+ regulatory T cells (Tregs) are generated in the thymus and are thought to play a key role in the maintenance of immunologic self-tolerance. In preclinical studies, these Tregs have been shown to prevent GvHD by suppressing alloreactive donor T cells, while preserving graft-versus-leukemia (GvL) effect.(30) In human studies, patients noted to have a higher relative frequency of Tregs after alloHSCT had lower rate and severity of GvHD, lower rate of non-relapse mortality, and equivalent relapse mortality.(31)

Finally, there is increasing evidence of the role of B-cell dysregulation in the development of chronic GvHD.(27, 32-35) Augmented B-cell responses in chronic GvHD result in marked abnormalities in B-cell homeostasis and signaling pathways, but the mechanisms responsible for aberrant B-cell homeostasis and the inability to establish B-cell tolerance in patients with chronic GvHD is not fully understood. In addition to the production of auto- and allo-reactive antibodies, it has been suggested that B-cell activation may result from antibody-independent process such as antigen presentation, cytokine and chemokine release and immunoregulatory dysfunction with high production of B-cell activating factor (BAFF) in the lymphoid microenvironment.(26) (36)

1.2.1.3 Prevention

The most attractive approach for controlling chronic GvHD would be the prevention of the most severe and irreversible clinical manifestations while maintaining GvL effect. The major barrier in developing effective preventive measures for chronic GvHD is still our limited understanding of chronic GvHD pathophysiology and availability of effective therapy interventions. Advances in pharmacologic prevention and treatment of acute GvHD, the major risk factor for chronic GvHD, have not resulted in corresponding decrease in incidence of chronic GvHD. Although some recipient, donor and transplant characteristics are modifiable to minimize the risk of chronic GvHD, majority of these approaches have very limited impact.

1.2.1.4 Treatment

Current therapies for chronic GvHD are profoundly unsatisfactory and are based on administration of toxic drugs which are also globally immunosuppressive and ultimately fail in two thirds of patients.(9, 37-40) Prednisone, alone or in conjunction with calcineurin inhibitors,

have been the front line therapy since 1980s, but more than 50% of the patients eventually relapse or become refractory. Because of frequent morbidity with the prolonged use of high-dose steroids, a number of drugs have been investigated as a first- or second-line therapy.(38, 41) Unfortunately, most of these studies were conducted before the NIH criteria and were of poor design and reproducibility.(42)

The 2005 and 2014 NIH Consensus Conference for chronic GvHD established the platform and regulatory pathway guidelines to study chronic GvHD and help the field move forward. New insights regarding the pathogenesis of chronic GvHD have started to emerge and novel therapeutic strategies, such as drugs targeting B cells, expanding T regulatory cells and targeting the processes implicated in fibrosis, are under active investigations. However, currently there is still no FDA-approved therapy for chronic GvHD and development of well-designed prospective and innovative therapeutic studies is an urgent unmet clinical need. The goal of therapy is to stop destructive immunological processes, improve symptoms, and establish immunological tolerance with ultimate withdrawal of immunosuppressive therapy. The most attractive approach for controlling chronic GvHD would be the prevention of the most severe and irreversible clinical manifestations. Selective modulation of alloreactive response and inflammation, rather than general immunosuppression, might be a promising mechanism for reducing GvHD while preserving a beneficial GvL effect.

The potential treatment benefits of B-cell-targeted therapies are via (1) total B-cell depletion, (2) BAFF receptor inhibition and (3) BCR signal inhibition. Inhibitors of specific B-cell signaling pathways, both small molecules and monoclonal antibodies, are now available for clinical use and are being applied in the treatment of B-cell malignancies.(27, 43-46) These new agents can also be used to identify and potentially modify specific abnormalities of B-cell homeostasis. These observations may explain occasional responses of chronic GvHD to the therapy with rituximab. Rituximab has shown efficacy in a prevention of chronic GvHD with concurrent prevention of alloreactive B cell development.(43, 47-49) However, in combination with steroids, rituximab had only partial efficacy for treatment of steroid-refractory and new-onset chronic GvHD.

1.2.2 Ibrutinib

Ibrutinib (Imbruvica®) is a first-in-class selective, orally bioavailable, reversible small molecule inhibitor of Bruton's tyrosine kinase (BTK) co-developed by Pharmacyclics LLC and Janssen Research & Development LLC for the treatment of B-cell malignancies. As of May 2016, ibrutinib has been approved in the US and EU for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy, patients with chronic lymphocytic leukemia (CLL)/small lymphocytic leukemia (SLL) and patients with Waldenström's macroglobulinemia (WM). In January 2017 ibrutinib was approved by FDA for patients with marginal zone lymphoma who have received at least one prior anti-CD20-based therapy. In August of 2017 ibrutinib was approved by the FDA for treatment of patients with steroid-refractory chronic GvHD after failure of one or more lines of systemic therapy. It is currently under investigation as an anti-cancer agent in various B-cell malignancies, acute myeloid leukemia (AML) and solid tumors, both as a single agent and in treatment combinations.

1.2.2.1 Summary of Nonclinical Data

Pharmacology

In vitro and preclinical studies have shown that ibrutinib forms a covalent bond with a cysteine residue (Cys-481) in the BTK ATP binding site, leading to sustained inhibition of BTK enzymatic activity.(50) BTK, a member of the Tec kinase family, is an important signaling molecule of the B-cell antigen receptor (BCR) and chemokine receptor pathways. The pivotal role of BTK in signaling through the BCR and chemokine receptor results in activation of pathways necessary for B-cell development trafficking, chemotaxis, and adhesion. BTK appears to regulate B cell survival by directly regulating the classical pathway in response to B-cell-activating factor of the tumor necrosis family (BAFF) under both BCR and BAFF-R signaling, as well as by inducing the components of the alternative pathway for sustained NF-κB activation in response to BAFF. BTK may also reverse interleukin-2 inducible kinase (ITK) polarization allowing for activation and proliferation of Th1 and CD8 T cells and skewing away from a Th2 cytokine profile.(51) Ibrutinib was evaluated in vitro for its ability to inhibit purified BTK and selected members of the closely related Tec and Src/Ab1 family kinases. With only a few exceptions, a 10-fold or greater selectivity was demonstrated for BTK relative to the off-target kinases.

Based on preclinical data, blockade of the BCR signaling pathway by ibrutinib in CLL has 2 major effects: (1) direct induction of apoptosis and (2) inhibition of cell homing and migration to chemokines and subsequent adhesion to cellular substrates. In preclinical models, ibrutinib caused a transient early lymphocytosis and profoundly inhibited CLL progression, as assessed by weight, development of hepatosplenomegaly, and survival. Furthermore, ibrutinib inhibited the proliferation of cell lines derived from DLBCL patients with a median effective concentration (EC50) of 1 or 2 nM. Studies with AML patient-derived blasts and established AML cell lines suggested BTK as a potential therapeutic target in AML.

Recent studies show that in addition to specific CD4+ T cell subsets, B cells are key mediators of chronic GvHD. Dysfunctional B cells have been identified in chronic GvHD, where patients have a relatively higher number of activated memory B cells, higher levels of BAFF, and donor-derived alloantibodies(28). It has been demonstrated that pathogenic antibody deposition occurs in human chronic GvHD, and a network of alloreactive T helper cells, including Th1, Th2, Th17 and Tfh (T follicular helper) cells infiltrate tissues and produce effector cytokines thereby causing antibody deposition, tissue fibrosis, similar to autoimmunity. In addition, genetic studies confirmed that ITK and BTK are independently critical for chronic GvHD and ibrutinib, which hits both targets showed its effectiveness in both a T-cell driven and alloantibody-driven chronic GVHD models clearly demonstrating therapeutic benefits from ibrutinib treatments. Ibrutinib treatment delayed progression, improved survival and ameliorated clinical and pathological manifestations in sclerodermatous and alloantibody-driven chronic GvHD mice models.

Toxicity

General toxicity studies in rat and dog have identified lymphoid tissues (lymphoid depletion) and the gastrointestinal (GI) tract (soft feces/diarrhea, with or without inflammation) as the target organs with potential relevance to human safety. No treatment-related effects were observed in central nervous system or respiratory system in rats at any dose tested. In vitro and in vivo genetic toxicity studies with ibrutinib found no evidence of genotoxicity. In rat and rabbit embryo-fetal toxicity studies, ibrutinib administration was associated with fetal loss, decreased fetal weights, and malformations (teratogenicity). There were no effects observed on male or female fertility or reproductive capacities in a rat fertility study. Results from an immunotoxicity

assessment of ibrutinib in rats were consistent with the expected pharmacology of the drug and included dose-associated decreases in B-lymphocyte numbers, lymphoid depletion in the white pulp of the spleen and decreased immunoglobulin responses to keyhole limpet hemocyanin (KLH) immunization. Cardiovascular assessments in dog safety pharmacology and toxicity studies identified decreased heart rate and prolonged PR intervals related to ibrutinib administration as a relevant finding.

No MTD was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day (1400 mg/day). Healthy subjects were exposed up to single dose of 1680 mg. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg.

1.2.2.2 Summary of Clinical Data

In the current clinical development program (as of November 12th, 2022), ibrutinib is being evaluated in over 72 ongoing and completed company-sponsored clinical studies in healthy subjects and in subjects with recurrent B-cell lymphomas, including CLL/SLL, MCL, follicular lymphoma (FL), DLBCL, multiple myeloma (MM), WM, marginal zone lymphoma (MZL), AML, chronic GvHD and solid tumors. Safety data from completed studies are available for 2326 subjects treated with single-agent ibrutinib and for 3447 subjects treated with ibrutinib in combination with immunotherapy or chemoimmunotherapy (5,261 subjects with hematologic malignancies, cGVHD, or solid tumors, 460 healthy volunteers, 22 subjects with COVID-19 related pulmonary distress, and 30 subjects from a hepatic impairment study). In addition, 9 early access programs are ongoing or completed and 201 initiated-studies including 43 collaborations are ongoing or completed.

The exposure-response analysis of Study MCL3002 on safety showed that there was no association between systemic exposure and the incidence of major hemorrhage, liver function abnormalities (Grade ≥ 3), neutropenia, diarrhea (Grade ≥ 2), TEAEs leading to death, or TEAEs leading to ibrutinib dose reduction. An effect of ibrutinib versus placebo treatment was observed on TEAEs leading to ibrutinib discontinuation, all Grade ≥ 3 TEAEs, all serious TEAEs, Afib (any), any hemorrhage, and infection (Grade ≥ 3). Of these, only Afib (any) and any hemorrhage showed a significant exposure response relationship with $AUC_{\tau,ss}$ within the exposure range obtained in the ibrutinib treatment arm.

Description of Investigational Drug Product and Pharmacokinetics

Ibrutinib is available as 140 mg capsules. Following oral administration of ibrutinib at doses ranging from 420 to 840 mg/day, exposure to ibrutinib increased proportionally to doses increased with substantial intersubject variability. Administration of ibrutinib in a fasted condition resulted in approximately 60% of exposure (area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration [AUClast]) as compared to administration either in fed condition (30 minutes after a high-fat breakfast), or when drug was taken 30 minutes before or 2 hours after a meal. Based on data for the effects of food, ibrutinib could be taken with or without food at approximately the same time each day. Ibrutinib absorption from the GI tract is practically complete, as minimal fecal excretion of unchanged ibrutinib in combination with high levels of oxidative metabolites (liver and gut metabolism) and a lack of reduction products (gut microflora metabolism) was observed in the human mass balance study. Ibrutinib is extensively metabolized, as evidenced by a human mass balance study in 6 male subjects dosed with a single 140-mg ibrutinib solution admixed with [14C]-ibrutinib.

Ibrutinib is predominantly cleared by 3 primary cytochrome P450 (CYP) 3A-mediated metabolic pathways, one of them being epoxidation of the acryloyl moiety, followed by hydrolysis to form the dihydrodiol PCI-45227. The two other main pathways are hydroxylation of the distal phenyl moiety and oxidative piperidine ring opening. The mean half-life (t1/2) of ibrutinib ranged from 4 to 13 hours, with a median time to maximum plasma concentration (Tmax) of 2 hours. Excretion is predominantly via the feces with approximately 80% recovered mostly within 2 days, whereas ~8% was excreted in urine. Approximately 1% of ibrutinib was recovered as unchanged drug, all in feces. Intravenous clearance as determined in an absolute bioavailability study was 62 and 76 L/h in fasted and fed condition, respectively. In line with the high first-pass effect, the apparent oral clearance is much higher, in the order of 2000 and 1000 L/h in fasted and fed condition, respectively. Overall, these PK characteristics resulted in minimal accumulation of both parent compound and metabolite PCI-45227 on repeated daily dosing of ibrutinib. Steady state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure.

A hepatic impairment study was performed in non-cancer subjects administered a single dose of 140 mg ibrutinib under fasting conditions. Ibrutinib AUC last increased 2.7-, 8.2- and 9.8-fold in subjects with mild (n=6; Child-Pugh Class A), moderate (n=10; Child-Pugh Class B) and severe (n=8; Child-Pugh Class C) hepatic impairment, respectively (**Appendix J**). The free fraction of ibrutinib also increased with degree of impairment, with 3.0%, 3.8%, and 4.8% in subjects with mild, moderate, and severe liver impairment, respectively, compared to 3.3% in plasma from matched healthy controls within this study. The corresponding increase in unbound ibrutinib exposure is estimated to be 4.1-, 9.8-, and 13-fold in subjects with mild, moderate and severe impairment, respectively.

Hematologic Malignancies

Pooled safety data from a total of 1,600 subjects treated with ibrutinib monotherapy in 21 studies that have completed primary analysis or final analysis included in the CSR as of the 12 November 2022 cutoff date for the current IB update are summarized below.

The most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N = 1,600):

Any grade TEAE >10%[a]	Any grade TEAEs related to ibrutinib > 5%[a]	Grade 3 or 4 TEAEs > 2%[a]
Diarrhea Fatigue Nausea Cough Pyrexia Anemia Upper Respiratory Tract Infection Neutropenia Edema peripheral Thrombocytopenia	Diarrhea Fatigue Nausea Cough Pyrexia Anemia Upper Respiratory Tract Infection Neutropenia Thrombocytopenia Muscle spasms	Diarrhea Fatigue Anemia Neutropenia Thrombocytopenia Pneumonia Hypertension Urinary tract infection Atrial fibrillation Febrile neutropenia

Any grade TEAE >10%[a]	Any grade TEAEs related to ibrutinib > 5%[a]	Grade 3 or 4 TEAEs > 2%[a]
Muscle spasms Constipation Arthralgia Vomiting Decrease in appetite Dyspnea Headache Pneumonia Rash Hypertension Abdominal pain Back pain Contusion Dizziness Urinary tract infection Sinusitis	Constipation Arthralgia Vomiting Decrease in appetite Pneumonia Rash Stomatitis Increased tendency to bruise Platelet count decreased	Hypokalemia Hyponatremia Abdominal pain Cellulitis Neutrophil count decreased

[a] *Source is Table 5 of IB (v16).*

Among the 1600 subjects in the integrated analysis of monotherapy studies, 16.7% discontinued ibrutinib therapy due to a TEAE. The most frequently reported TEAEs leading to treatment discontinuation were pneumonia (1.48%), sepsis (0.8%), thrombocytopenia (0.7%), and subdural hematoma (0.6%), and respiratory failure (0.5%). Fatal TEAEs were reported in 9.9% of subjects during study treatment or within 30 days of discontinuation of treatment. The most frequently reported causes of fatal AEs included pneumonia (1.4%), sepsis (0.8%), respiratory failure (0.4%), and disease progression (including mantle cell lymphoma [0.5%], disease progression [0.5%], chronic lymphocytic leukemia [0.4%], and diffuse large B-cell lymphoma [0.4%]).

Integrated data from 2849 subjects from 22 combination therapy studies that have completed their primary analysis or final analysis included in the CSR as of 12 November 2022 are briefly summarized below. Therapies used in combination with ibrutinib in these studies, included BR (bendamustine and rituximab), FCR (fludarabine, cyclophosphamide, and rituximab), ofatumumab, and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), etc.

The most frequently reported TEAEs in subjects receiving ibrutinib in combination therapy (N = 2849):

Most Commonly reported TEAEs >10%[a]	Most Commonly reported TEAEs >5%[a]	Most Commonly reported Serious TEAEs > 2%[a]
Neutropenia Diarrhea Nausea	Neutropenia Diarrhea Nausea	Neutropenia Diarrhea Thrombocytopenia

Most Commonly reported TEAEs >10%[a]	Most Commonly reported TEAEs >5%[a]	Most Commonly reported Serious TEAEs > 2%[a]
Thrombocytopenia Fatigue Anemia Pyrexia Upper respiratory tract infection Constipation Vomiting Rash Headache Cough Muscle spasms Pneumonia Edema peripheral Arthralgia Decrease in appetite Contusion Insomnia Peripheral sensory neuropathy Stomatitis Abdominal pain Back pain Hypertension Myalgia Platelet count decreased Neutrophil count decreased Rash maculo-papular Hypokalemia Dyspnea Dizziness Pain in extremity Urinary tract infection Dyspepsia White blood cell count decreased	Thrombocytopenia Fatigue Anemia Pyrexia Upper respiratory tract infection Constipation Vomiting Rash Headache Pneumonia Decrease in appetite Contusion Febrile neutropenia Cough Arthralgia Edema peripheral Hypertension Platelet count decreased Neutrophil count decreased Muscle spasms Myalgia Rash maculo-papular Stomatitis Dizziness Dyspepsia White blood cell count decreased Epistaxis Lymphocyte count increased Atrial fibrillation	Fatigue Anemia Pneumonia Febrile neutropenia Atrial fibrillation Hypertension Leukopenia Neutrophil count decreased Urinary tract infection White blood cell count decreased Platelet count decreased Rash maculo-papular Hypokalemia Lymphocyte count increased Lymphocyte count decreased Hyponatremia Leukocytosis Syncope Lymphopenia

[a] *Source is Table 9 of IB (v16).*

Among the 2849 subjects in the integrated analysis of combination therapy studies, 528 subjects (18.5%) discontinued ibrutinib treatment due to a TEAE. The most frequently reported TEAEs leading to treatment discontinuation were pneumonia (1.6%), atrial fibrillation (1.1%), diarrhea (0.7%), neutropenia (0.6%), and thrombocytopenia (0.5%). Fatal TEAEs were reported in 7.4% of subjects. The most frequently reported fatal TEAEs (other than disease progression) were

diffuse large B-cell lymphoma (0.6%), pneumonia (0.6%). All other TEAEs leading to death were reported for 3 or fewer subjects each.

1.2.2.3 Summary of Clinical Data in Chronic GvHD

The Th2/Th17-cells which contribute to the pathogenesis of chronic GvHD rely upon ITK to drive intracellular activation and immune reactivity towards healthy tissues. By blocking the threshold activation of ITK, ibrutinib can impede the activation of these pathogenic T-cells while still permitting immune activity against pathogenic affronts. BTK, on the other hand, is important for B-cell activation and differentiation. Inhibition of BTK has been shown to be important in ameliorating autoimmune diseases with B-cell dysfunction such as rheumatoid arthritis and lupus. Genetic studies have confirmed that ITK and BTK are independently critical for chronic GvHD and ibrutinib has demonstrated its effectiveness in both T-cell driven and alloantibody driven chronic GvHD models. In animal models of chronic GvHD, mice that were ITK or BTK deficient did not develop chronic GvHD, indicating that both BTK and ITK are important to chronic GvHD development. Since ibrutinib inhibits both BTK and ITK, ibrutinib has the potential to have an impact on both B and T cells that are critical in the pathogenesis of GvHD and may have the potential to provide a clinically meaningful benefit for patients with chronic GvHD. Preclinical results demonstrate a substantial therapeutic benefit of ibrutinib treatment to reduce the prolonged effects of chronic GvHD.

Chronic GvHD is a leading cause of non-relapse related mortality in the transplant setting and there are no approved therapies for chronic GvHD. Ibrutinib offers a novel mechanism of action as a potent inhibitor of BTK that also inhibits ITK. Ibrutinib has the potential to have an impact on both B and T cells that are critical in the pathogenesis of chronic GvHD.

In humans, phase 1/2-study of ibrutinib in 42 patients with steroid-refractory chronic GvHD showed that 420 mg/day of ibrutinib was well tolerated with a robust clinical response. Analysis of soluble plasma factors associated with inflammation, fibrosis, and chronic GvHD from treated patients showed a significant decrease over time. Overall response rate was 67%, with 71% and 48% responders showing a sustained response of ≥20 and ≥32 weeks, respectively. During the study 75% responders reduced steroids to <0.15 mg/kg/d and 5 responders were able to discontinue steroids. Most common adverse events (AEs) were fatigue (57%), diarrhea (36%), muscle spasms (29%), nausea (26%), and bruising (24%). Grade ≥3 AEs were pneumonia (n=6), fatigue (n=5), and diarrhea (n=4). Serious AEs (SAEs) occurred in 52% subjects and grade ≥3 SAEs in 40%, included pneumonia (n=5), septic shock (n=2), and pyrexia (n=2). Two fatal events (multilobular pneumonia and pulmonary aspergillosis) were reported. Results from this trial led the FDA granting ibrutinib a breakthrough designation and in August 2017 regulatory approval for chronic GvHD after failure if one or more lines of systemic therapy. This first ever indication for the systemic treatment of chronic GvHD was given based on the results using the NIH criteria response measures. Taken together, these proof-of-principle findings support exploring ibrutinib as a treatment for newly diagnosed chronic GvHD. The phase III, randomized, multicenter, placebo control study of ibrutinib in conjunction with high-dose steroids as a front-line therapy for newly diagnosed chronic GvHD is currently in progress (NCT02959944).

TEAEs in >20%, >10% and >2% of Subjects who Received Ibrutinib for chronic GvHD:

Most Commonly reported TEAEs >20%	Most Commonly reported TEAEs >10%	Most Commonly reported Serious TEAEs > 2%
Fatigue Diarrhea	Fatigue Diarrhea	Fatigue Diarrhea Pyrexia Pneumonia Hypokalemia Cellulitis Stomatitis Hypertension Thrombocytopenia Dyspnea Anemia Hyperglycemia

1.2.2.4 Potential Risks and Guidance for Investigators

Based on currently available data, ibrutinib has an acceptable safety profile as monotherapy among the B-cell malignancies studied and when combined with chemo-immunotherapy. This is supported extensively by data from the randomized, comparator-controlled studies.

1.2.2.4.1 Bleeding-related events

There have been reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria. In an in-vitro platelet function study, inhibitory effects of ibrutinib on collagen induced platelet aggregation were observed. Initially, subjects were excluded from participation in specific ibrutinib Phase 2 and 3 studies if they required warfarin or other vitamin K antagonists. Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib unless specified in the protocol. Supplements such as fish oil and vitamin E preparations should be avoided. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery, depending upon the type of surgery and the risk of bleeding.

1.2.2.4.2 Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib therapy. Some of these infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) and hepatitis B reactivation have occurred in subjects treated with ibrutinib. Cases of hepatitis E. which may be chronic, have occurred in patients treated with ibrutinib. Subjects should be monitored for symptoms (fever, chills,

weakness, confusion, vomiting, jaundice, and abnormal liver function tests) and appropriate therapy should be instituted as indicated.

1.2.2.4.3 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib. Subjects should be monitored for fever, weakness, or easy bruising and/or bleeding. Monitor complete blood counts monthly.

1.2.2.4.4 Interstitial Lung Disease

Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib. Monitor subjects for pulmonary symptoms indicative of ILD. If symptoms develop, interrupt ibrutinib and manage ILD appropriately. If symptoms persist, consider the risks and benefits of ibrutinib treatment and follow the dose modification guidelines as needed.

1.2.2.4.5 Cardiac Arrythmias and cardiac failure

Atrial fibrillation, and atrial flutter, and cases of ventricular tachyarrhythmia and cardiac failure including some fatal events, have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmia. At baseline and then periodically, monitor subjects clinically for cardiac arrhythmia and cardiac failure. Subjects who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest discomfort or new onset of dyspnea) should be evaluated clinically, and if indicated, have an ECG performed. For cardiac arrhythmias or cardiac failure consider the risks and benefits of ibrutinib treatment, and follow the dose modification guidelines.

1.2.2.4.6 Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with ibrutinib therapy. Subjects at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. Monitor subjects closely and take appropriate precautions.

1.2.2.4.7 Non-melanoma skin cancer and Other Cancers

Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma of the skin) have been reported with more frequency and maybe related to the use of ibrutinib. Other cancers have been observed in patients who have been treated with ibrutinib. These include solid tumors, skin cancer, and cancers of the blood. Monitor subjects for the appearance of other cancers.

1.2.2.4.8 Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe and are generally managed with supportive therapies including antidiarrheals and antiemetics. Subjects should be monitored carefully for gastrointestinal AEs and cautioned to maintain fluid intake to avoid dehydration. Medical evaluation should be made to rule out other etiologies such as *Clostridium difficile* or other infectious agents. Should symptoms be severe or prolonged, ibrutinib treatment should be modified according to protocol guidelines.

1.2.2.4.9 Rash

Rash has been commonly reported in subjects treated with either single-agent ibrutinib or in combination with chemotherapy. Most rashes were mild to moderate in severity. Isolated cases of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) have been reported in subjects treated with ibrutinib. Subjects should be closely monitored for signs and symptoms suggestive of SCAR including SJS. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events including erythema, urticaria, and angioedema have been reported.

1.2.2.4.10 Hypertension

Hypertension has been commonly reported in subjects treated with ibrutinib. Monitor subjects for new onset of hypertension or hypertension that is not adequately controlled after starting ibrutinib. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

1.2.2.4.11 Aspergillosis

Preliminary information from a Phase 1b, single US-center CTEP study (ClinicalTrials.gov Identifier NCT02203526) of primary central nervous system lymphoma (PCNSL) using a novel immune-chemotherapy regimen of dose-adjusted temozolomide, etoposide, DOXIL®, dexamethasone, ibrutinib, and rituximab (DA-TEDDI-R) confirmed 4 cases of invasive aspergillosis in the first 18 patients that initiated treated. Three of the 4 confirmed cases had a fatal outcome. Additionally, 3 clinically suspected cases were reported in the same study, in which all 3 patients experienced Grade 3 lung infections; however, aspergillosis could not be diagnostically confirmed (bronchoalveolar lavage and blood cultures in 2 patients were negative for fungi). Two additional ISTs in subjects with relapsed/refractory CNS lymphoma are currently ongoing with single agent ibrutinib, and both allow the concomitant use of systemic steroids to control symptomatic disease. One case of invasive aspergillosis was reported for each of these studies, with incidences of 5.0% and 2.6%, respectively, for an overall incidence of 7.8% across all three IST/CTEP studies.

There are currently no company sponsored clinical trials ongoing in PCNSL or CNS lymphoma. In a recent analysis of completed and ongoing sponsored ibrutinib clinical trials (N=3038), the reported incidence of aspergillosis was 0.49%, which was similar to the reported pooled incidence in 4 active comparator studies (0.5%) across the ibrutinib clinical development. Based on the existing clinical experience with ibrutinib in subjects with B-cell malignancies under approved indications, an exact association between ibrutinib and invasive aspergillosis could not be established at this time. Currently invasive aspergillosis risk with ibrutinib is estimated if given with concurrent steroids being at least 5-10% and with ibrutinib as a single agent risk is estimated at 2-5% in this current protocol setting. (Michail Lionakis, NIAID, personal communication).

1.2.2.4.12 Stroke

Cases of stroke, with and without changes in heartbeat rhythm and/or hypertension have been reported with the use of ibrutinib. Some of these cases have led to death. Seek immediate medical attention if you notice or someone notices in you: sudden numbness or weakness in the limbs (especially on one side of the body), sudden confusion, trouble speaking or understanding

speech, sight loss, difficulty walking, loss of balance or lack of coordination, sudden severe headache with no known cause. These may be signs and symptoms of stroke.

1.2.3 Study Rationale

For more than three decades the most widely used first-line systemic therapy of chronic GvHD has been prednisone alone or in conjunction with calcineurin inhibitors (cyclosporine(52) or tacrolimus [TAC]); however, this approach has a durable response rate of less than 50%. Currently there is no FDA-approved therapy for newly diagnosed chronic GvHD and development of well-designed prospective and innovative therapeutic studies is an urgent unmet clinical need.

In this study we propose the use of ibrutinib as the front-line therapy for newly diagnosed chronic GvHD, instead of high-dose steroids. Our central hypothesis is that ibrutinib will be effective and well tolerated as a single agent, front-line systemic therapy for newly diagnosed chronic GvHD.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Newly diagnosed moderate or severe chronic Graft versus Host Disease (GvHD) (according to the 2014 NIH Consensus Criteria, requiring systemic immunosuppression

2.1.1.2 History of prior allogeneic Hematopoietic Stem Cell Transplant (HSCT) (any donors, conditioning regimens and graft sources are allowed).

2.1.1.3 Subjects may have ongoing acute GvHD features (e.g., erythematous rash, elevated liver enzymes, diarrhea) which are in the opinion of the investigator responding to therapy.

2.1.1.4 Stable doses of other immunosuppressive medications (e.g., calcineurin inhibitors, mycophenolate mofetil, rapamune, etc.) with no dose increase in the 2 weeks prior to study treatment initiation. Doses may be adjusted for trough levels.

2.1.1.5 Age ≥ 18 years old

2.1.1.6 Karnofsky performance status ≥ 60% (**Appendix B**)

2.1.1.7 Laboratory parameters as defined below:

- Serum creatinine ≤ 2.0 x ULN
- AST and ALT ≤ 3 x ULN (≤ 5 x ULN if unequivocal liver GvHD)
- Total bilirubin ≤ 3 x ULN
- Absolute neutrophil count ≥ 1.0 x 10^9/L (no growth factor support allowed)
- Platelets > 50 x 10^9/L (no transfusions allowed ≤ 7 days prior to enrollment)

2.1.1.8 Ability to understand and willingness to sign a written informed consent form

2.1.1.9 The effects of ibrutinib on the developing fetus are unknown. For this reason and because tyrosine kinase inhibitors may be teratogenic, female subjects of childbearing

potential and men must agree to use highly effective methods of birth control (hormonal or barrier method of birth control; abstinence) prior to study entry, during the period of therapy, and for 30 days after the last dose of study drug.

2.1.2 Exclusion Criteria

2.1.2.1 Relapsed or progressive malignant disease (other than minimal residual disease

2.1.2.2 History of other malignant diseases, including post-transplant lymphoproliferative disease, with the following exceptions:

- Malignancy treated with curative intent and with no evidence of active disease present for more than 3 years prior to prior to study treatment initiation and felt to be at low risk for recurrence
- Adequately treated non-melanomatous skin cancer or lentigo malignant melanoma without current evidence of disease
- Adequately treated cervical carcinoma in situ without current evidence of disease

2.1.2.3 Received previous systemic treatment for chronic GvHD other than ≤ 0.5 mg/kg/day of prednisone equivalent for more than 7 days. Subject may be on steroids that were used to treat acute GvHD and then developed chronic GvHD before completing a taper. At the time of enrollment, the dose should be ≤ 0.5 mg/kg/day of prednisone equivalent with no dose increase in the preceding 2 weeks before study treatment initiation

2.1.2.4 Prior or current treatment with:

- Ibrutinib since the time of transplant (participants may have received ibrutinib prior to transplant for indications other than chronic GvHD)
- Extracorporeal photopheresis (ECP) for acute GvHD ≤ 2 weeks prior to study treatment initiation; including any treatment with ECP for chronic GvHD.
- Rituximab or other anti-B cell specific antibodies ≤ 4 weeks prior to study treatment initiation.
- Any systemic investigational agents ≤ 4 weeks prior to study treatment initiation

2.1.2.5 Impaired cardiac function including any one of the following:

- Myocardial infarction, unstable angina or acute coronary syndrome ≤ 6 months prior to study treatment initiation
- Class 3 or 4 congestive heart failure, uncontrolled arrhythmia or uncontrolled hypertension at any time

2.1.2.6 Uncontrolled infections (including prior aspergillosis) not responsive to antibiotics, antiviral medicines, or antifungal medicines

2.1.2.7 Known bleeding disorder or subjects who received a strong cytochrome P450 (CYP) 3A inhibitor ≤ 7 days prior to the first dose of ibrutinib or requirement for continuous treatment with a strong CYP3A inhibitor (**Appendix C**)

2.1.2.8 Active hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody or hepatitis B surface antigen or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result to be enrolled.

2.1.2.9 Known hypersensitivity to ibrutinib

2.1.2.10 Pregnant women are excluded from this study because ibrutinib has potential for teratogenic and abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ibrutinib, breastfeeding should be discontinued if the mother is treated with ibrutinib. Women who are planning to become pregnant and men who plan to father a child while enrolled in this study or ≤ 30 days after the last dose of study drug are excluded.

2.1.2.11 Any other reason at the discretion of the investigators and documented in the medical record that may raise concerns about the subject safety or ability to participate on this study

2.1.2.12 Currently active, severe hepatic impairment Child-Pugh class C according to the Child Pugh classification (**Appendix J**)

2.1.3 Recruitment Strategies

This protocol may be abstracted into a plain language announcement posted on NIH websites (i.e., clinicaltrials.gov) and on NIH social media platforms.

2.2 SCREENING EVALUATION

2.2.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images
- Review of existing photographs or videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes

2.2.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the subject has signed the consent for this study for screening. Screening studies must be completed within 14 days prior to enrollment unless otherwise specified below. Assessments performed at outside facilities within the timeframes below may also be used to determine eligibility once a participant has signed the consent.

2.2.2.1 Clinical Assessments

- Karnofsky performance score (**Appendix B**).
- Physical examination to include: general appearance of the subject, height and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system. Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature.
- Medical history and Demographics
- prior and concomitant medications
- Moderate or severe chronic GvHD via Chronic GvHD Assessment:
    - Diagnostic Criteria for Chronic GvHD (**Appendix A**)
    - NIH Organ Specific Staging and Global Scoring of Chronic GvHD (**Appendix D** and **Appendix E**)

2.2.2.2 Laboratory Evaluations

- CBC with differential
- Chemistry panels (as noted) or specific analyte including: Creatinine and potassium (i.e., or Acute Care Panel); calcium and phosphate (i.e., or Mineral Panel); ALT, AST, total bilirubin (i.e., or Hepatic Panel)
- Lactic dehydrogenase (LDH), uric acid
- Coagulation panel, including: PT/INR and aPTT
- CMV/EBV
- Hepatitis Serologies will include hepatitis C antibody, hepatitis B surface antigen, and hepatitis B core antibody. If hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody is positive, then PCR to quantitate hepatitis B DNA or hepatitis C RNA must be performed (within 28 days of enrollment).
- Pregnancy test: Urine or serum pregnancy test for women of childbearing potential. If positive, pregnancy must be ruled out by ultrasound to be eligible.

2.2.2.3 Other Assessments and Procedures

- ECG: 12-lead ECG will be done in triplicate (≥ 1 minute apart). Subjects should be in supine position and resting for at least 10 minutes before study-related ECGs.

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

2.3.1 NCI Registration 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.

2.3.2 For Participating Site Registration

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 MI-3, CCR Participating Site Participant Registration & Status Updates found https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825. When a participant has a status change (e.g., subject screened on the study, does not meet eligibility criteria and is removed from the study, participant is taken off protocol therapy or off study, etc.), the Participant Status Update Form will be supplied by the CCR study coordinator. Send the completed form to the CCR study coordinator.

2.3.3 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a laboratory parameters may be rescreened.

2.3.4 Treatment Assignment (for registration purposes only)

Cohort

Number	Name	Description
1	*Cohort 1*	*Participants with newly diagnosed moderate or severe chronic GvHD requiring systemic immunosuppression*

Arm

Number	Name	Description
1	*Arm 1*	*Ibrutinib as a continuous daily dose by mouth*

Randomization and Arm Assignment

Participants in Cohort 1 will be directly assigned to Arm 1.

2.4 BASELINE EVALUATION

Tests or evaluations performed during screening and that are within the window for prior to treatment do not need to be repeated. All of the following to be performed within 7 days before treatment.

2.4.1 Clinical Evaluations

- History and Physical Exam
- Concomitant medication review

- Karnofsky performance score (**Appendix B**).
- Physical examination to include: general appearance of the subject, weight, examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system. Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature.
- Chronic GvHD Activity Assessment (Clinician) Form A (**Appendix F**).

2.4.2 Laboratory Evaluations

- CBC with differential
- Chemistry panels (as noted) or specific analyte including: Creatinine and potassium (i.e., or Acute Care Panel); calcium and phosphate (i.e., or Mineral Panel); ALT, AST, total bilirubin (i.e., or Hepatic Panel)
- Others: Lactic dehydrogenase (LDH), uric acid
- Serum Immunoglobulins: IgA, IgG and IgM levels.

2.4.3 Other Assessments and Procedures

- Participant Self-Assessments: All subjects in the study will complete the Chronic GvHD Activity Assessment-Patient Self Report-Form B, Lee Chronic GvHD Symptom Scale and SF36 Form (**Appendix G**).
- Pulmonary Function Tests (PFTs): Subjects should be evaluated for oxygen saturation or have PFTs, if not performed ≤ 3 months prior to study treatment initiation. It is not a part of inclusion/exclusion criteria.
- Non-contrast chest CT (if clinically indicated)

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a multi-center, two-stage, phase 2 study.

Subjects with newly diagnosed moderate or severe chronic GvHD according to the NIH criteria, who need systemic therapy, will be started on ibrutinib as a continuous daily dose of 420 mg by mouth. Treatment will continue in cycles consistent of 28 days on outpatient basis.

Participants with response at 6 months (CR+PR) will continue therapy until 12 months.

Participants who have a perception of benefit from ibrutinib therapy may continue on ibrutinib past the 12-month timepoint, based also on investigator discretion and discussion for up to 24 months.

Subjects may continue on stable doses of their immunosuppressive medications with the intent to taper it. See Section **4.1**.

Addition of any systemic immunosuppressive therapy aimed at controlling chronic GvHD symptoms is prohibited and will be considered treatment failure. Participants in need of additional systemic immunosuppressive therapy will be taken off ibrutinib treatment.

Subjects may remain on topical therapy for chronic GvHD (See Section **4.2**).

One steroid pulse (i.e., prednisone equivalent of 0.5-2 mg/kg/day) is allowed (See Section **4.1.2**).

Up to 28 evaluable subjects will be enrolled and treated for up to 24 months. Enrollment will occur in 2 stages: in the first stage 14 subjects will be enrolled, and if ≥ 4 subjects have a response (CR+PR at 6 months) the accrual will continue until a total of at least 25 evaluable subjects have been enrolled. As it may take 3 to 6 months to determine if a subject has experienced a response, a temporary pause in the accrual may be necessary to ensure that enrollment to the second stage is warranted.

Evaluation of chronic GvHD diagnosis per NIH criteria (**Appendix A**) and Chronic GvHD Organ Specific Staging and Global Scoring (**Appendix D** and **Appendix E**) will be performed at screening. Chronic GvHD Organ Specific Staging and Global Scoring (**Appendix D** and **Appendix E**) evaluations will be repeated at 9 months and 12 months, and every 3 months until off treatment.

Chronic GvHD Activity Assessment (Clinician) Form A (**Appendix F**) will occur at baseline, at 6 weeks and then 3, 6, 9 and 12 months from the start of ibrutinib by the bone marrow transplant physician and/or nurse practitioner trained in chronic GvHD assessments.

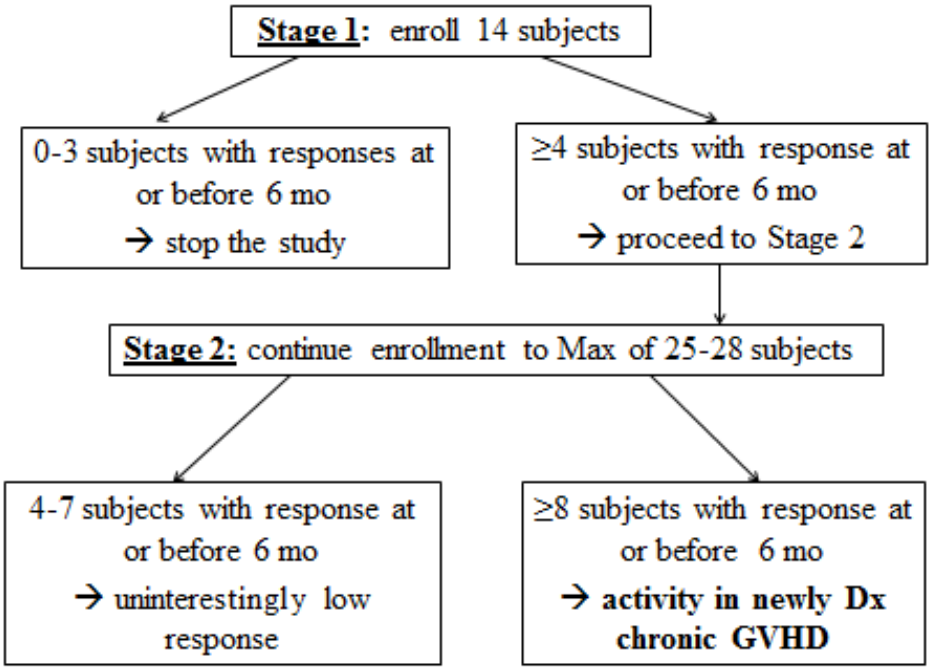
Response will be assessed according to the 2014 NIH Consensus Criteria (**Appendix H**) and as defined under Section **6.3.1** Response Criteria.

Participant self-assessments will occur at cycle 1 day 1, at 6 weeks and then 3, 6, 9 and 12 months from the start of ibrutinib (**Appendix G**).

Research blood samples will be collected for correlative science at the start of treatment with ibrutinib, and at 6 weeks, 3, 6, and 12 months from the start of ibrutinib therapy.

The post-treatment follow-up phase will begin once a subject discontinues ibrutinib treatment.

Study Schema:



3.2 DRUG ADMINISTRATION

For this study we will use an ibrutinib dose of 420 mg (3 x 140 mg capsules) taken once a day on every day of every cycle.

Ibrutinib capsules should be swallowed whole and should not be broken, chewed or opened. Each dose of ibrutinib should be taken at approximately same time each day with 8 ounces (approximately 240 mL) of water. If a dose of ibrutinib is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.

Missing < 20% doses in the first six months is allowed. Treatment with ibrutinib will be discontinued if the subject has missed ≥ 20% doses in the first six months of the study.

Participants will be asked to keep a medication diary (**Appendix I**). The first dose will be delivered in the clinic on Day 1, after which subsequent dosing is typically on an outpatient basis. Ibrutinib will be dispensed to subjects in bottles at each visit. Unused ibrutinib dispensed during previous visits must be returned to the site and drug accountability records updated at each visit. Returned capsules must not be redispensed to anyone.

3.2.1 Dose Adjustments for participants on CYP3A4 inhibitors

Participants who are treated with certain medications that are mild and moderate CYP3A4 inhibitors will start ibrutinib at a lower dose.

A list of common CYP3A inhibitors and inducers is provided in **Appendix C**. For further information, please refer to the current version of the ibrutinib IB and examples of inhibitors, inducers, and substrates can be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/.

Drug	Ibrutinib dose modification
• Mild CYP3A inhibitors	420 mg once daily. No dose adjustment required
• Moderate CYP3A inhibitors	420 mg once daily. No dose adjustment required
• Voriconazole at any dose or • Posaconazole at doses less than or equal to suspension 200 mg BID	280 mg once daily
• Posaconazole suspension 200 mg TID or 400 mg BID • Posaconazole IV injection 300 mg once daily • Posaconazole delayed-release capsules 300 mg once daily	140 mg once daily
• Other strong CYP3A inhibitors	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt IMBRUVICA

If these medications are later discontinued, ibrutinib dose may be increased to 420 mg.

3.3 DOSE MODIFICATIONS

3.3.1 Overdose

There is no specific experience in the management of ibrutinib overdose in participants. Subjects who ingest more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

3.3.2 Dose Modification for Adverse Reaction

Dose reductions will be required for any of the following toxicities:

- Grade 3 ANC (< 1,000/μL) with an associated temperature ≥ 38.5°C
- Grade 4 ANC (< 500/μL) for more than 7 days
- Grade 3 thrombocytopenia (< 50,000/μL) in the presence of clinically significant bleeding events
- Grade 4 thrombocytopenia (< 25,000/μL)
- Grade 3 or 4 nausea, vomiting, or diarrhea despite optimal anti-emetic and/or anti-diarrheal therapy

- Any other Grade 4 or unmanageable Grade 3 toxicity attributed to ibrutinib
- Optional dose reduction can be done also at investigator discretion for any bothersome toxicity

Recommended Dosage Modifications for Adverse Reactions		
Adverse Reaction	**Occurrence**	**Dose Modification after Recovery**
Grade 2 cardiac failure	First	Restart at 280 mg daily[a]
	Second	Restart at 140 mg daily[a]
	Third	Discontinue Ibrutinib
Grade 3 cardiac arrhythmias	First	Restart at 280 mg daily[a]
	Second	Discontinue Ibrutinib
Grade 3 or 4 cardiac failure Grade 4 cardiac arrhythmias	First	Discontinue Ibrutinib
Other Grade 3 or 4 non-hematological toxicities[b] Grade 3 or 4 neutropenia with infection or fever Grade 4 hematological toxicities	First	Restart at 280 mg daily
	Second	Restart at 140 mg daily
	Third	Discontinue Ibrutinib

[a] Evaluate the benefit-risk before resuming treatment
[b] For Grade 4 non-hematologic toxicities, evaluate the benefit-risk before resuming treatment

If the dose of ibrutinib is reduced, at the investigator's discretion, the dose of ibrutinib may be re-escalated after 4 weeks of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction.

3.3.2.1 Ibrutinib Dose Modifications – General:

Occurrence	**Action to be taken**
Hematologic Adverse Events	
First	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at the original dose level
Second	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at 1 dose level below that for which the toxicity occurs (i.e., 280 mg/day for 420 mg/day dose)

Occurrence	Action to be taken
Third	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at 1 dose level below that for which the toxicity occurs (i.e., 140 mg/day for 280 mg/day dose)
Fourth	Discontinue ibrutinib
Non-Hematological Adverse Events	
First	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose level
Second	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at 1 dose level below that for which the toxicity occurs
Third	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at 1 dose level below that for which the toxicity occurs
Fourth	Discontinue ibrutinib

3.3.2.2 Dose modification for atrial fibrillation:

For Grade 3 or 4 atrial fibrillation or persistent atrial fibrillation of any grade, consider the risks and benefits of ibrutinib treatment. If clinically indicated, the use of anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation.

3.3.2.3 Dose modifications for hepatic impaired subjects:

- Ibrutinib is metabolized in the liver and therefore subjects with clinically significant chronic hepatic impairment at the time of Screening (Child- Pugh class C) are excluded from study participation. Refer to **Appendix J** for Child-Pugh classification. For subjects with a direct bilirubin > 3 x ULN (Grade 3 CTCAE), ibrutinib will be held until the bilirubin returns to ≤ 1.5 x ULN (Grade 1 CTCAE) or baseline. Upon reduction to ≤1.5 x ULN ibrutinib will be re-started at one dose level below that for which the toxicity occurs (see **Table 1** for dose modification schedule).
- For subjects whose baseline AST/ALT is ≤ 3 x ULN, if ALT or AST increases to >5 x ULN (Grade 3 CTCAE) ibrutinib will be held until the ALT/AST value returns to ≤3 x ULN (Grade 1 CTCAE) or baseline. Ibrutinib will be re-started at one dose level below that for which the toxicity occurs.
- For subjects whose baseline AST/ALT is between 3 to 5 x ULN (because of chronic GvHD), if ALT/AST increases to 1.5 x baseline level then ibrutinib will be held until the ALT/AST value returns to ≤ 3 x ULN or baseline. Ibrutinib will be re-started at one dose level below that for which the toxicity occurs.

Table 1: Ibrutinib Dose Modifications for Hepatic Impairment

Occurrence	Action to be Taken

First	Withhold study drug until recovery to Grade ≤ 1 CTCAE or baseline; restart at 1 dose level below that for which the toxicity occurs (280 mg/day for 420 mg/day dose)
Second	Withhold study drug until recovery to Grade ≤ 1 CTCAE or baseline; restart at 1 dose level below that for which the toxicity occurs 140 mg/day for 280 mg/day dose)
Third	Discontinue study drug

Treatment with ibrutinib will be discontinued if because of unacceptable toxicity the subject has missed drug for more than a total of 28 days in the first six months of the study.

3.4 PARTICIPANT SELF-ASSESSMENTS (ENGLISH SPEAKING SUBJECTS ONLY)

Participant self-report questionnaires administered in this study are part of the standard NIH chronic consensus recommended criteria for the evaluation of chronic GvHD in clinical trials. These standardized assessments are designed to evaluate participant quality of life and symptoms. Questionnaires will include Lee Symptom Scale, SF36 form and the NIH Form B-Chronic GvHD Activity Assessment-Patient Self Report (**Appendix G**). 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 chronic GvHD protocols. In a recent study median time for persons to complete these forms was 15 minutes (range 8-22 minutes). See the Study Calendar in **Appendix K** for timepoints of participant self-assessments.

3.5 POST-TREATMENT EVALUATIONS

All participants after last dose will be then followed by a phone call to the participant and/or the primary physician's office at 12 and 24 months after starting the first dose of ibrutinib. The phone call will focus on collecting data: a) survival status and primary and contributing cause of death if pertinent, b) ongoing systemic treatment for chronic GvHD, need to systemic therapy change (including what type) and systemic therapy discontinuation (including date), c) primary malignancy progression, d) any second primary malignancy (including type), e) return to work or school part-time or full-time. This information will be recorded in the CRF and the participant's medical record.

3.6 STUDY CALENDAR

The study calendar can be found in **Appendix K**.

3.6.1 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 participants in real time, to be able to monitor and collect data, as well as the ability to share the participants' 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 remote visits

may include the following: patient history, verbal exam, symptom reporting, education, and questionnaires.

Telemedicine visits will be scheduled using site-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 the patient's medical record like a normal onsite visit and the note should indicate that this visit was performed virtually.

Remote visits will be conducted in compliance with site guidelines and FDA regulations.

3.6.2 Local Evaluations

A patient may be asked to come to the NIH CC or Washington University for an in-person assessment or be referred to their local provider, if clinically indicated, and at the discretion of the investigator. All physical exams, assessments, labs, and imaging used for follow-up or restaging visits may also be performed with the patient's local physician as determined by the PI. For in-person assessments, physical examinations may be omitted at the discretion of the investigator. For laboratory evaluations conducted with local providers, interlaboratory variability is not a concern. In the case of any visits with participants' local providers, records will be obtained for the research records.

3.7 COST AND COMPENSATION

3.7.1 Costs

3.7.1.1 NIH

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 performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.7.1.2 Participating Sites

Subjects costs will be based on local guidelines as described in the site-specific consent.

3.7.2 Compensation

Participants will not be compensated on this study.

3.7.3 Reimbursement

3.7.3.1 NIH

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.

3.7.3.2 Participating Sites

Reimbursement will be provided per local guidelines.

3.8 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.

3.8.1 Criteria for removal from protocol therapy

- Completion of 6-month course of protocol therapy and no response (PR or CR)
- Chronic GvHD progression by NIH criteria and/or primary physician determination
- Unacceptable toxicity that requires the subject to be off study drug for more than 28 consecutive days in the first six months of the study
- Noncompliance with study medication (defined as missed >20% doses in the first six months of the study for the reason of noncompliance)
- If ibrutinib becomes unavailable
- Principal Investigator discretion
- Participant requested to be withdrawn from active therapy
- Recurrence of underlying malignancy
- Subject becomes pregnant

3.8.2 Off-Study Criteria

- Completed 2-year follow-up period
- Participant request to be withdrawn from the study
- Lost to follow-up
- Death
- Screen failure
- There is significant participant noncompliance
- The investigators decide to end the study
- The investigator's discretion

3.8.3 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

4.1 SYSTEMIC IMMUNOSUPPRESSIVE THERAPY

Participants will be advised to contact the study team before starting any new medications.

4.1.1 Concomitant Systemic Immunosuppression

At enrollment, many subjects will be receiving some immunosuppressive medications that were used to prevent or treat acute GvHD. The dose of these medications must have been stable for 2 weeks. Subjects may continue on stable doses of their immunosuppressive medications with the intent to taper it. Immunosuppression taper may be initiated after 4 weeks on the study treatment. Steroids should be tapered by approximately 20% every 2 weeks. Addition of any new systemic immunosuppressive therapy aimed at controlling chronic GvHD symptoms is prohibited and will be considered treatment failure.

Use of steroids for treatment of adrenal insufficiency will be discussed with PI.

4.1.2 Steroid Pulse for Chronic GvHD Flare

One steroid pulse (prednisone equivalent of 0.5-2 mg/kg/day) is allowed for clinical disease control and stabilization during the first 4 weeks after starting ibrutinib. In case of classic chronic GVHD typical maximal corticosteroid dose for a pulse would be 1mg/kg/day prednisone or equivalent as per usual standard of care. Chronic GVHD manifestations which present simultaneously with acute GVHD signs (chronic GVHD overlap) may require higher doses pulse (up to 2/mg/kg/day) as per usual standard of care. Determination for needing a corticosteroids pulse will be made by the primary practicing clinician and/or PI who will jointly make decision that such intervention would be beneficial to the participant. Subjects may remain on the corticosteroid pulse for up to 2 weeks after which they will begin a taper with the intent of decreasing back to the enrollment steroid dose within 4-6 weeks. More rapid tapering schedule is permitted if clinically appropriate. Rounding of corticosteroid doses is acceptable.

4.2 TOPICAL IMMUNOSUPPRESSIVE THERAPY

Subjects may remain on topical immunosuppressive or symptomatic therapy for chronic GvHD. Addition of new topical immunosuppressive or symptomatic therapy is allowed per NIH Chronic GvHD Ancillary and Supportive Care Working Group standard guidelines, however each such topical intervention must be carefully recorded and reported.

4.3 ANCILLARY THERAPY AND SUPPORTIVE CARE

Ancillary therapy and supportive care for chronic GvHD is permitted and recommended as outlined in the NIH Consensus Development Project 2014 Ancillary Therapy and Supportive Care Working Group Report. Use of topical or organ specific medications to treat or prevent bronchiolitis obliterans (e.g., inhaled steroids/azithromycin/montelukast) or GI acute GvHD (e.g., budesonide or beclomethasone) will not be considered systemic treatment for chronic GvHD; however, each such organ specific or topical intervention must be carefully recorded and reported in the final study data report.

Use of neutrophil growth factors (e.g., filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) is permitted per institutional policy. Transfusions may be given in accordance with institutional policy.

Infection is the most common cause of mortality in participants with chronic GVHD and infection prophylaxis requires special emphasis. The immune defects in chronic GVHD are broad, encompassing macrophage function, antibody production, and T cell function. Prevention, early diagnosis, and prompt treatment of infections are essential to the supportive care of participants with chronic GVHD. Infection disease prevention and management guidelines will be according the NIH Consensus Development Project 2014 Ancillary Therapy and Supportive Care Working Group Report and can be modified by the respective institutional guidelines.

While standard guidelines for aspergillosis prophylaxis in participants on ibrutinib do not exist, we will implement following generally recommended strategy in this protocol:

a) If participant is on more than 0.20 mg/kg prednisone equivalent per day we recommend receiving isavuconazole (or an alternate agent) prophylaxis;

b) If participant is on single agent ibrutinib or lower doses of steroids than 0.20 mg/kg prednisone equivalent +/- any other immunosuppressive agent, the decision will be left to the clinician based on the clinical risk assessment in a given participant.

Clinical vigilance for invasive fungal infections will be pursued in all participants. We recommend checking serum galactomannan at scheduled clinic visits and exert low threshold for imaging studies and early BAL when suspicion exists. We also recommend checking trough isavuconazole levels at each visit if feasible or at least couple times earlier at the protocol driven follow up appointments.

4.4 MEDICATION TO BE USED WITH CAUTION

4.4.1 CYP3A Enzyme Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A4.

A list of common CYP3A inhibitors and inducers is provided in **Appendix C**. For further information, please refer to the current version of the ibrutinib IB and examples of inhibitors, inducers, and substrates can be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates. Avoid concomitant use of strong CYP3A inducers (**Appendix C**). Consider alternative agents with less CYP3A induction and transition to a new agent within 4 weeks of study treatment initiation. Dose modifications for participants on CYP3A4 inhibitors are listed in Section **3.2.1**.

Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A.

4.4.2 Antiplatelet Agents and Anticoagulants

Use ibrutinib with caution in subjects requiring anticoagulants or medications that inhibit platelet function. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen induced platelet aggregation were observed.

Supplements such as fish oil and vitamin E preparations are recommended to be avoided during treatment with ibrutinib.

Bleeding events of any grade, including bruising and petechiae, occurred in subjects treated with ibrutinib. Subjects with congenital bleeding diathesis have not been studied. Ibrutinib should be

held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding (see Section **4.6**).

Subjects requiring the initiation of therapeutic anticoagulation therapy (e.g., atrial fibrillation) should be monitored closely for signs and symptoms of bleeding and the risks and benefits of continuing ibrutinib treatment should be considered.

4.4.3 Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp) but is a mild inhibitor. Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. There is no clinical data available. Therefore, to avoid a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin, should be taken at least 6 hours before or after ibrutinib.

4.5 PROHIBITED CONCOMITANT MEDICATIONS

Use of other investigational agents, chemotherapy, biologic or immunotherapy is prohibited during participation in this study.

4.6 GUIDELINES FOR IBRUTINIB DOSAGE WITH SURGICAL PROCEDURES

Ibrutinib may increase risk of bleeding with invasive procedures or surgery. The following guidance should be applied to the use of ibrutinib in the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib.

4.6.1 Minor Surgical Procedures

For minor procedures (such as a central line placement, skin or needle biopsy, lumbar puncture [other than shunt reservoir access], thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib.

4.6.2 Major Surgical Procedures

For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.

4.6.3 Emergency Procedures

For emergency procedures, ibrutinib should be held as soon as possible and until the surgical site is reasonably healed or for at least 7 days after the urgent surgical procedure, whichever is longer.

5 CORRELATIVE STUDIES FOR RESEARCH

5.1 BIOSPECIMEN COLLECTION

Test/assay	Volume blood (approx.)	Type of tube[Error! Reference source not found.]	Collection point (+/- 48hrs)	Location of specimen Storage
Immune monitoring and Biomarker Studies	50 ml	Five 10 ml green top (heparin) tubes	C1D1, C4D1, C7D1, C12D28	Clinical Pharmacology Blood Processing Core (BPC), Bldg 10 room 5A08.
IHC for myofibroblast markers	oral/skin biopsy (optional), NIH site only	N/A	Baseline, Cycle 7 Day 1, Cycle 12 Day 28	Clinical Pharmacology Blood Processing Core (BPC), Bldg 10 room 5A08.
PK (pre & post)	6 ml	Sodium Heparin	C1D15	Clinical Pharmacology Blood Processing Core (BPC), Bldg 10 room 5A08.
[a] Please note that tubes and media may be substituted based on availability with the permission of the PI or laboratory investigator.				

5.1.1 Immune Monitoring and Biomarker Studies

Peripheral blood will be collected for cGVHD cell phenotypes, gene expression (Section **5.3**) and plasma biomarker assays at 4 time points, concurrent with clinical evaluation of chronic GvHD: at C1D1 (start of ibrutinib treatment), C4D1 (3 months), C7D1 (6 months), and C12D28 (12 months).

At each time point collect 50 ml of blood (e.g., 5, 10 ml green top tubes) in heparinized tubes as plasma. Store plasma at -80° C in at least 4 vials containing aliquots of 1ml of plasma. Process the remaining blood with Lymphocyte Separation Medium to collect PBMC. Aliquot the cells into at least 2 vials at 10 million PBMC/vial (if less than 20 million total cells, divide equally into 2 tubes). Cryopreserve in liquid nitrogen vapor phase.

All vials are to be labeled with a bar code. The bar codes will be linked by participating site to a spreadsheet in which participant biospecimens are identified by Unique Participant Number, study calendar timepoint and either total cell number or plasma volume in each vial. Dates of collection and any relevant notes of the biospecimen collection (such as anti-coagulant, processing delays) will be noted. PBMC and plasma will be sent to NCI for testing at the

completion of accrual for the trial or at intermediate timepoints to be agreed upon. Send to the Clinical Pharmacology Blood Processing Core (BPC) of the National Cancer Institute, NIH in Bethesda MD.

Notify Paula Carter and Trung Pham at least 24 hours prior to shipping cryopreserved materials. Include the spreadsheet of samples to be shipped in the email and in the shipment. Ship cryopreserved cells and plasma on dry ice to: Attention Paula Carter and Trung Pham, BPC Lab, Bldg 10, room 5A08, National Cancer Institute, NIH, Bethesda, MD 20892. Shipments can only be received on Tuesday through Thursday.

Multiparameter flow cytometry assays may include, but not be limited, to the following markers:

1. Assessments of lymphocyte populations including CD3+, CD3+CD4+ and CD3+CD8+ Tcells, CD19+ B cells, and CD3-CD56+ NK cells
2. Assessments of B cell subsets to identify frequencies of transitional, naive, preGC, memory, tissue memory and regulatory subsets: (marker panel will include CD19, CD20, IgD, CD27, CD38, CD21, CD10, CD24, CD3)
3. Assessments of T cell subsets to identify naive, Tscm, central memory, effector memory, TEMRA, regulatory cells (marker panel will include CD3, CD4, CD8, CD25, CD127, CCR7, CD45RA, CD27, CD95)
4. Assessments of T helper lineages by transcription factors (marker panel will include CD3, CD4, CD8, Tbet, RORgt, GATA3, FoxP3).

Plasma biomarker ELISA assays may include but not be limited to the following currently proposed biomarkers of CGVHD: ST2, CXCL10, BAFF, IL-6, TNF, IFNg. Additional or alternative plasma factors will be considered based upon relevant CGVHD biomarkers identified by the end of biospecimen accrual.

5.1.2 Oral/Skin Biopsy

An optional research biopsy of involved or uninvolved skin or oral mucosa will be offered to participants for assessment of sclerotic or lichen-planus like disease by H&E and pathologist evaluation. Immunohistochemistry methods will be applied to look for myofibroblast markers and pSMAD in the sclerotic skin, 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 and stored at the BPC Lab. lab. A biopsy sample will be also sent to the NCI pathology laboratory. Biopsies will only be performed at the NIH site. See the Study Calendar in **Appendix K** for collection timepoints.

5.2 Pharmacokinetic Studies

Blood samples for the determination of sparse steady-state plasma concentrations of ibrutinib will be obtained from each participant on a scheduled visit at the C1D15 visit. Participants will fast the night prior to the visit, have a pre-dose (trough) sample drawn, take the dose, then have another sample drawn 90-min post (+/- 10min) based on a peak that occurs 1-2 hr. post dose (Ibruvica® package insert). Blood will be collected into a 6mL sodium heparin tube (BD, Franklin Lakes, NJ). Bioanalytical measurements on plasma collected at both the NIH site and

participating sites will be conducted on an ultra HPLC-MSMS system using an assay developed and validated by the NCI Clinical Pharmacology Program.

The PK sampling will be used to monitor ibrutinib exposure in order to correlate to clinical response and toxicity.

5.1.2.1 Handling and Processing of Specimens

The samples will be placed immediately on wet ice and refrigerated. The date and exact time of each blood draw should be recorded on the sample tube and the PK sheet. In participants treated at the non-NIH sites, tubes will be centrifuged promptly after collection to separate off plasma. Plasma will be cryopreserved for storage at -80°C. PK samples will be labeled so as to distinguish them from immune monitoring and biomarker samples. At the end of the trial (or at intermediate points to be determined), PK plasma will be shipped on dry ice to the Blood Processing Core of the Clinical Pharmacology Program at the NCI, along with a spreadsheet key identifying protocol, participant, date, stage (pre-dose or 90min), time of draw and time of processing.

Please e-mail NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

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 for NIH. 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 Samples Managed by Dr. Figg's Blood Processing Core (BPC)

5.2.1.1 Sample Data Collection

All samples sent to the Blood Processing Core (BPC) will be barcoded, with data entered and stored in 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 participants without Labmatrix access. The data recorded for each sample includes the participant ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Participant demographics associated with the clinical center participant 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.).

5.2.1.2 Sample Storage

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C 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.

5.2.2 BPC Sample Storage, Tracking and Disposition

Participant blood and tissue samples, collected for the purpose of research under IRB approved protocols of the Blood and Inherited Diseases Cellular Therapy Program (BID-CTP) may be archived by the Clinical Pharmacology Blood Processing Core (BPC), Bldg 10 room 5A08. All data associated with archived clinical research samples is entered into Labmatrix. Access is limited to BPC staff and BID-CTP clinical staff, requiring individual login and password.

The data recorded for each sample includes the participant ID, trial name/protocol number, date drawn, treatment cycle/post-transplant time point, cell source (e.g. peripheral blood, marrow,) as well as box and freezer location. Participant demographics that correlate treatment outcomes and therapies with the samples can be obtained only through the NCI clinical records. As of January 2007, all newly received samples receive a unique bar code number, which is included in the sample record in the BPC database. Only this bar code is recorded on the sample vial and the vials will not be traceable back to participants without authorized access to the BPC database. All non-coded samples previously archived will be stripped of identifiers prior to distribution for any use other than as a primary objective of the protocol under which they were collected.

Samples are stored in freezers. All samples will be labeled solely with a bar code (which includes the date, and serially determined individual sample identifier). The key will be available to a restricted number of BID-CTP investigators and associate investigators on the protocol. Coded samples will be stored frozen at -20°, -80° or liquid nitrogen vapor phase to -180 C according to the stability requirements in a single location under the restricted control of the BPC lab.

These freezers are located onsite at the Clinical Pharmacology Blood Processing Core (BPC) laboratory (5A08) (-85°C freezer) Access to samples from a protocol for research purposes will be by permission of the Principal Investigator of that protocol in order to be used (1) for research purposes associated with protocol objectives for which the samples were collected, or (2) for a new research activity following submission and IRB approval of a new protocol and consent, or (3) for use only as unlinked or coded samples under the OHSRP Exemption Form guidelines stipulating that the activity is exempt from IRB review. Unused samples must be returned to the BPC laboratory. Samples, and associated data, will be stored permanently unless the participant withdraws consent. If researchers have samples remaining once they have completed all studies associated with the protocol, they must be returned to the BPC laboratory.

Once research objectives for the protocol are achieved, researchers can request access to remaining samples, 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 participant consent or an OHSRP exemption indicating that the activity is exempt from IRB review.

The BPC will report to the Principal Investigator any destroyed samples, if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container), lost in transit between facilities or misplaced by a researcher.

5.2.3 Protocol Completion/Sample Destruction

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described in sections above. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed. If the participant withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **7.2**.

5.3 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

Multiplex gene expression assays: Based upon studies utilizing peripheral blood monocytes as 'reporter' cells for the operant processes of CGVHD (53), CD14+ monocytes will be bead sorted from one vial of cryopreserved PBMC, and the isolated RNA will be assessed for expression of a panel of genes to include but not necessarily be limited to the following: Pattern Recognition Receptors (TLR, CLR, NLR and RLR receptors), Interferon-induced genes, genes involved in monocyte migration and genes induced by glucocorticoids. The custom Nanostring probe panels will be assessed using nCounter Systems analyses and analyzed using nSolver software.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The site 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.

The subject's relevant medical history will be collected and recorded. Baseline medical signs and symptoms must be documented to establish baseline severities. A disease history and the date of initial diagnosis should be recorded.

Newly diagnosed moderate or severe chronic GvHD via Chronic GvHD Assessment performed at screening should be documented.

Any clinically significant abnormalities noted at ECG during screening should be documented.

Dose changes must be recorded in the Dose Administration eCRF.

All medications (prescription and non-prescription), including topical chronic GvHD therapies taken throughout the study must be recorded on the appropriate page of the CRF.

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. Grade 1 adverse events will not be recorded as they are not expected to be clinically significant.

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

New malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be recorded for the duration of study treatment and during follow-up period.

An abnormal laboratory value will be recorded in the database as an AE **only** 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 participant'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**.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

Coded, linked human data generated in this research for future research will be shared as follows*:*

- in an NIH-funded or approved public repository clinicaltrials.gov
- in BTRIS (automatic for activities in the Clinical Center)
- with approved outside collaborators under appropriate agreements
- in publication and/or public presentations

at the time of publication or shortly thereafter

6.2.2 Genomic Data Sharing Plan

Not applicable to this protocol as the only planned genomic experiment is RNA evaluation by Nanostring.

6.3 RESPONSE CRITERIA

For the purposes of this study, participants should be evaluated for response at 6 weeks, 3, 6, 9 and 12 months from the start of ibrutinib by the bone marrow transplant physician and/or nurse practitioner trained in chronic GvHD assessments.

Chronic GvHD Organ Specific Staging and Global Scoring (**Appendix D** and **Appendix E**) will occur at screening and at 6 month visit, and will be repeated at 9 and 12 months. Response to treatment with ibrutinib will be assessed and documented in Chronic GvHD Activity Assessment (Clinician) Form A (**Appendix F**) at enrollment, 6 weeks and then 3, 6, 9 and 12 months from the start of ibrutinib. To ensure comparability, baseline and on-study methods for response assessment will be performed using identical grading, scale or techniques.

6.3.1 Response Criteria

Efficacy will be assessed using NIH consensus criteria measuring for therapeutic response in clinical trials for chronic GvHD. The calculations for CR, PR and progressive disease are provided in **Appendix H**.

- **CR** is defined as complete resolution in all of signs and symptoms at all affected organs or tissues.
- **PR** is defined as improvement in ≥ 1 organ or tissue with no progression in any other affected organ or tissue.
- **Stable Disease (SD)** is defined as no change in chronic GvHD.
- **Flare** is defined as exacerbation of chronic GvHD manifestations during withdrawal of immunosuppressive therapy which do not exceed those at the beginning of the trial and improves after reinstatement of previous treatment. For the purpose of this study, any flare which requires change or intensification of systemic therapy beyond the one per protocol allowed steroid pulse within initial four weeks will be considered a therapy failure.
- **Progressive disease (PD)** is defined as failure of therapy to control chronic GvHD. Participants who progress prior to 6 months evaluation will be also evaluable for the primary efficacy endpoint.
- **Mixed response** is defined as an improvement in some organs but worsening in others and will be categorized as progressive disease.

6.3.2 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each participant while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

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/IRB REPORTING

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 (FOR NCI SITE ONLY)

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 should 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 NCI GUIDANCE FOR REPORTING EXPEDITED ADVERSE EVENTS FOR MULTI-CENTER TRIALS

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802: Non-compliance in Human Subjects Research, found at: https://irbo.nih.gov/confluence/display/IRBO/Policies+and+SOPs. Until such time as direct electronic reporting mechanisms are available to participating sites, the site PI must immediately report to the coordinating center PI any deaths possibly related to the research within 24 hours of

PI awareness of the event. The Site PI must also report any other events required by Policy 801 to the coordinating center PI within 7 days of PI awareness.

https://ccrod.cancer.gov/confluence/display/CCRCRO/Templates (**Appendix L**)

Once direct electronic reporting mechanisms are available, these will be utilized. Please also notify the coordinating center PI and study coordinator of your submission at the time you make it.

For IND studies, the site PI will also directly submit reports to the CCR as IND sponsor per section **0.**

7.5 NIH Required Data and Safety Monitoring Plan

7.5.1 Principal Investigator/Research Team

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

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 **Error! Reference source not found.** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each participant 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.

7.5.2 Safety Monitoring Committee (SMC)

This protocol will be periodically reviewed by an intramural Safety Monitoring Committee comprising physicians, biostatisticians and a lay member selected based on experience, area of expertise, reputation for objectivity, absence of conflicts of interest and knowledge of or experience with clinical trial research. Initial review will occur as soon as possible after the annual NIH Intramural IRB continuing review date. In addition, as this study meets CCR SMC review criteria only because it is a multicenter CCR-held IND study, the first SMC review will not take place until at least one external site is activated and has enrolled a participant. Subsequently, each protocol will be reviewed as close to annually as the quarterly meeting schedule permits or more frequently as may be required by the SMC based on the risks presented in the study. For initial and subsequent reviews, protocols will not be reviewed if there is no accrual within the review period.

The SMC review will focus on unexpected protocol-specific safety issues that are identified during the conduct of the clinical trial.

Written outcome letters will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

8 SPONSOR PROTOCOL/SAFETY REPORTING

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a participant 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)
- 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 participant 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 participant 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 5.0.

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.

8.1.6 Adverse Events of Special Interest (AESI)

8.1.6.1 Major Hemorrhage

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic adverse events of Grade 3 or higher*
- Any treatment emergent serious adverse events of bleeding of any grade
- Any treatment-emergent central nervous system hemorrhage / hematoma of any grade

*All hemorrhagic events requiring transfusion of red blood cells should be reported as grade 3 or higher AE per CTCAE v5.0

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 **Error! Reference source not found.**. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor.

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.

All SAE reporting must include the elements described in Section **8.1.6.1**.

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 Safety Reporting Criteria to the Pharmaceutical Collaborators

Reporting will be per the collaborative agreement with Pharmacyclics LLC (CRADA #03211).

8.5 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

8.5.1 Maternal exposure

If a participant 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 becomes 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.

8.5.2 Paternal exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 30 days after the last dose of ibrutinib.

Pregnancy of the participant's partner is not considered to be an AE. However, the outcome of all pregnancies occurring from the date of the first dose until 30 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.

8.6 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 in expedited manner to the FDA in accordance to 21 CFR 312.32. 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.

8.7 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.

Non-NIH participating sites not using the CCR Protocol Deviation Tracking System (PDTS) will report any protocol deviation on the OSRO Site Protocol Non-Adherence/Deviation Log, or a site-generated protocol deviation report approved by OSRO. The Non-Adherence/Deviation Log should be maintained in the site essential documents file and submitted to OSRO via OSROMonitoring@mail.NIH.gov on the **first business day of each month throughout the study**.

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 take place 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

10.1 STATISTICAL HYPOTHESIS

10.1.1 Primary efficacy endpoints

To evaluate the efficacy of ibrutinib as a first-line treatment for persons with newly diagnosed chronic graft-versus-host disease (GvHD) by measuring the overall response rate (complete response [CR] + partial response [PR]) at 6 months, according to the 2014 NIH Consensus Criteria.

10.1.2 Secondary efficacy endpoints

- To evaluate safety of ibrutinib for newly diagnosed chronic GvHD
- To evaluate failure-free survival
- To evaluate 24 months post-treatment follow-up for survival

10.1.3 Exploratory objective(s)

- To evaluate chronic GvHD response rate at 6 weeks, 3 months, 9 months and 1 year
- To evaluate the duration of chronic GvHD response
- To evaluate ability to taper steroids and other systemic immunosuppression
- To evaluate need for steroid pulses
- To evaluate the need for therapy change
- To evaluate subject reported outcome by the NIH Chronic GvHD Activity Assessment-Patient Self Report-Form B

- To evaluate subject reported outcome by Lee Symptom Scale
- To evaluate subject reported outcome by SF36
- To monitor for recurrence of the original malignancy or development of new cancers
- To evaluate changes in T and B regulatory and effector subsets, in patterns of gene expression and in proposed plasma biomarkers to correlate these changes with clinical assessments of chronic GVHD

10.2 SAMPLE SIZE DETERMINATION

The primary objective of this trial is to determine the overall response rate of ibrutinib as a first-line treatment for subjects with newly diagnosed chronic GvHD based on the response at or before 6 months, according to the 2014 NIH Consensus Criteria. In similar subjects who ordinarily would receive steroid treatment, the clinical response rate using NIH criteria may typically be on the order of 30-40%. The goal would be to determine if using ibrutinib would rule out a 20% response rate and target a rate of 45%. For these subjects, the trial will be conducted using an optimal two-stage phase II trial design (Simon R, Controlled Clinical Trials 10:1-10, 1989) in order to rule out an unacceptably low PR+CR rate of 20% (p0=0.20) in favor of an improved response rate of 45% (p1=0.45). With alpha=0.10 (probability of accepting a poor treatment=0.10) and beta = 0.10 (probability of rejecting a good treatment=0.10), this first stage will enroll 14 evaluable subjects, and if 0 to 3 of the 14 have a clinical response, then no further subjects will be accrued. If 4 or more of the first 14 subjects have a response, then accrual would continue until a total of 25 evaluable subjects have been enrolled. As it may take 3 to 6 months to determine if a subject has experienced a response, a temporary pause in the accrual may be necessary to ensure that enrollment to the second stage is warranted. If there are 4 to 7 subjects with a response out of 25 subjects, this would be an uninterestingly low response rate. If there were 8 or more of 25 (32%) who experienced a response, this would be sufficiently interesting to warrant further study in later trials. Under the null hypothesis (20% response rate), the probability of early termination is 69.8%.

It is expected that approximately 1-2 subjects per month may enroll on this trial; thus, it is anticipated that 1.5 to 2 years may be required for accrual of up to 25 evaluable subjects. In order to allow for up to 3 inevaluable subjects and screen failures (screening will occur on this protocol), the accrual ceiling will be set at 40 (3 for inevaluable participants and 12 for screen failures).

10.3 POPULATIONS FOR ANALYSIS

As a modified intention to treat analysis we will report data on participants who received at least one dose of ibrutinib.

10.4 STATISTICAL ANALYSIS

10.4.1 General approach

The proportion of evaluable participants who experience a response will be reported along with a confidence interval.

10.4.2 Analysis of the primary endpoints

The fraction of evaluable participants who experience a response will be determined and reported along with 80% and 95% two-sided confidence intervals.

10.4.3 Analysis of the secondary endpoints

- To evaluate safety of ibrutinib for newly diagnosed chronic GvHD
- To evaluate Failure Free Survival

The secondary objectives will each be evaluated using standard statistical methods, which will largely consist of reporting descriptive statistics and associated 95% confidence intervals. Time to event endpoints such as failure free survival will be determined using a Kaplan-Meier curve.

10.4.4 Safety analyses

Safety of the agent will be assessed by determining the grade of adverse events noted in each participant, and reporting the fraction with grade 3 and grade 4 adverse events. Participants who receive at least one dose of the study treatment will be evaluable for safety. Safety data will be presented in a summary. The safety data will consist of the reporting of all adverse events, and may also include reporting vital signs, physical examination data, and laboratory safety data.

10.4.5 Baseline descriptive statistics

Limited demographic and clinical characteristics of all participants will be reported.

10.4.6 Planned interim analyses

As indicated in the sample size determination section, an interim evaluation of the number of participants who experienced a success in the first stage of the two-stage optimal design will be performed to ensure that enrollment to the second stage is warranted.

10.4.7 Subgroup analyses

None are intended.

10.4.8 Tabulation of individual participant data

No individual participant data is intended to be reported.

10.4.9 Exploratory analyses

The following are the intended exploratory objectives:

- To evaluate chronic GvHD response rate at 6 weeks, 3 months, 9 months, and 1 year
- To evaluate the duration of chronic GvHD response
- To evaluate ability to taper steroids and other systemic immunosuppression
- To evaluate need for steroid pulses
- To evaluate the need for therapy change
- To evaluate subject reported outcome by Lee Symptom Scale
- To evaluate subject reported outcome by SF36

- To evaluate subject reported outcome by the NIH Chronic GvHD Activity Assessment-Patient Self Report-Form B
- To monitor for recurrence of the original malignancy or development of new cancers
- To evaluate changes in T and B regulatory and effector subsets, in patterns of gene expression and in proposed plasma biomarkers to correlate these changes with clinical assessments of chronic GVHD

The Lee scale results, SF36 results, and NIH cGVHD activity assessment form B results after treatment will be compared to the pre-treatment results using a Wilcoxon signed rank test. Any exploratory evaluations which generate quantitative measures will be done using descriptive statistics including confidence intervals when appropriate. Any statistical tests performed for evaluation of exploratory objectives will be done without formal adjustment for multiple comparisons, but in the context of the number of tests performed.

11 COLLABORATIVE AGREEMENTS

11.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)

This study will be conducted under a Collaborative Research and Development Agreement (CRADA) with Pharmacyclics LLC and Washington University in St. Louis (#03211).

11.2 MULTI-INSTITUTIONAL GUIDELINES

Until an electronic submission system is available to participating sites, documents requiring submission to the reviewing IRB per reliance agreement, including local consent documents generated from an approved model consent, should be provided to the coordinating center for submission to the IRB. Thereafter, consents may be submitted directly to the IRB using iRIS.

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 no experience with ibrutinib in children, this study will be limited to subjects age 18 years or older.

12.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

12.3.1 NCI

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 **Error! Reference source not found.**), all subjects ≥ age 18 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) for evaluation to assess ongoing capacity of the subjects and to identify an LAR, as needed..

Please see Section **12.5.1** for consent procedure.

12.3.2 Participating Sites

Participating sites relying on the NIH IRBO should follow local policies for assessing capacity.

Please see Section **12.5.1** for consent procedure.

12.4 Risk/Benefit Assessment

12.4.1 Known Potential Risks

12.4.1.1 Related to Ibrutinib

Potential risks of ibrutinib include the range of toxicities described above, in drug insert, investigational brochure and the consent form. There may also be unexpected side effects. All subjects will be carefully monitored for side effects.

12.4.1.2 Related to Blood Collection

Minor complications including bleeding, pain, and hematoma formation at the site of blood draws, or infections may rarely occur. Up to approximately 135mL of blood will be collected during one visit and no more than 300mL will be collected over an 8-week period.

12.4.1.3 Related to Tissue Biopsy

Skin or oral mucosa biopsy are minor surgical procedures that may be associated with temporary bleeding, hematoma at the site, local infection and postoperative discomfort. These risks are small (generally < 5%) and transient. All bone marrow biopsies on the study will be done only as a part of routine care, and not study-mandatory.

12.4.1.4 Related to Questionnaires

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

12.4.2 Known Potential Benefits

The potential benefit is decreased symptoms that are caused by the cGVHD.

12.4.3 Assessment of Potential Risks and Benefits

Preclinical results demonstrate a substantial therapeutic benefit of ibrutinib treatment to reduce the prolonged effects of chronic GvHD with an acceptable safety profile. Therefore, the benefits outweigh the risks that the participants are exposed to.

12.5 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 site approved remote platforms used in compliance with site policies) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). 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.

The above is for NIH. Please see site specific supplement for electronic signature requirements for participating site (i.e., Wash U).

12.5.1 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 **12.5**.

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, investigators, 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 transmitted to and 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.

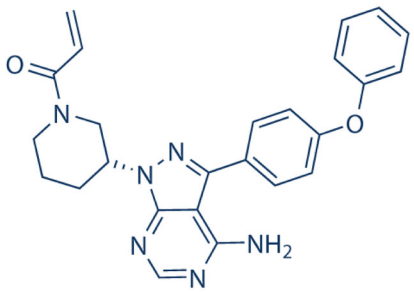
14 PHARMACEUTICAL AND INVESTIGATIONAL DEVICE INFORMATION

14.1 IBRUTINIB (IND # 146697)

14.1.1 Description

Ibrutinib is a small-molecule tyrosine kinase inhibitor with a molecular weight of 440.50 g/mole (anhydrous basis). The CAS name for ibrutinib is 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl) -Hpyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one. The molecular formula of ibrutinib is $C_{25}H_{24}N_6O_2$

Chemical Structure of Ibrutinib:



Ibrutinib is a white to off-white solid. Ibrutinib has a single chiral center and the absolute configuration at the stereocenter is (R).

14.1.2 Source

Pharmacyclics will supply investigational ibrutinib 140 mg capsules. Ibrutinib comes packaged as 92-count and 120-count bottle sizes of 140 mg ibrutinib capsules. All unused capsules at the end of the month will be brought back and disposed.

Pharmacyclics will supply drug free of charge. The initial drug shipment will be sent by Pharmacyclics to the NIH and any participating sites. Each pharmacy will be responsible for all subsequent drug orders.

14.1.3 Formulation and Preparation

Ibrutinib capsules are provided as a hard gelatin capsule containing 140 mg of ibrutinib. All study drug will be dispensed in child-resistant packaging.

14.1.4 Stability and Storage

The PI or their designee is responsible for taking an inventory of each shipment of study drug received and comparing it with the accompanying study drug accountability form. The PI or their designee will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Pharmacyclics.

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access. The study drug should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

14.1.5 Administration procedures

See Section **3.2**.

14.1.6 Expected Toxicities

See Section **1.2.2.4** and **Appendix L**.

14.1.7 Incompatibilities

The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study. Please see table in section **Error! Reference source not found.** for further details on dosing with CYP3A inhibitors.

When anti-fungal agents, that have CYP3A properties are discontinued, the ibrutinib dose should be increased to 420 mg.

14.1.8 Drug Dispensing

Ibrutinib will be dispensed through a qualified healthcare professional (including but not limited to, nurses, pharmacists and physicians) to a participant or Patient Care Unit for self-medication. These healthcare staff will counsel subjects prior to medication being dispensed to ensure that the subject has complied with all requirements including use of birth control and pregnancy testing (FCBP) and that the subject understands the risks associated with ibrutinib.

Ibrutinib comes packaged as 92-count and 120-count bottle sizes of 140 mg ibrutinib capsules. All unused capsules at the end of the month will be brought back and reconciled by the

pharmacy. Participants will be asked to maintain a dairy and bring to the next appointment all remaining capsules.

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16 APPENDICES

16.1 APPENDIX A: DIAGNOSTIC CRITERIA FOR CHRONIC CGVHD (17)

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 sclerosis-like features	□ Depigmentation □ Papulosquamous lesions	□ Sweat impairment □ Ichthyosis □ Keratosis pilaris □Hypopigmentation □Hyperpigmentation	□ Erythema □ Maculopapular rash □ Pruritus
Nails		□ Dystrophy □ Longitudinal ridging, splitting, or brittle features □ Onycholysis □ Pterygium unguis □ Nail loss [5,6]		
Scalp and body hair		□ New onset of scarring or nonscarring scalp alopecia[7] □ Loss of body hair □ Scaling	□ Thinning scalp hair, typically patchy, coarse, or dull [8] □ Premature grey hair	
Mouth	□ Lichen-planus-like changes	□ Xerostomia □ Mucoceles □ Mucosal atrophy □ Pseudomembranes [6] □ Ulcers[6]		□ Gingivitis □ Mucositis □ Erythema □ Pain

Organ or Site	Diagnostic Features[1]	Distinctive Features[2]	Others[3]	Common Features[4]
Eyes		□ New onset dry, gritty, or painful eyes □ Cicatricial conjunctivitis □ Keratoconjunctivitis sicca □ Confluent areas of punctuate keratopathy	□ Photophobia □ Periorbital hyperpigmentation □ Blepharitis	
Genitalia	□ Lichen planus-like features □ Lichen sclerosis-like features □ Vaginal scarring or clitoral/labial agglutination (females) □ Phimosis or urethral/meatus scarring or stenosis (males)	□ Erosions [6] □ Fissures [6] □ Ulcers [6]		
GI tract	□ Esophageal web □ Strictures or stenosis in the upper to mid third of the esophagus		□ Exocrine pancreatic insufficiency	□ Anorexia □ Nausea □ Vomiting □ Diarrhea □ Weight loss □ Failure to thrive
Lung	□ Bronchiolitis obliterans diagnosed with lung biopsy	□ Air trapping and bronchiectasis on chest CT	□ Cryptogenic organizing pneumonia □ Restrictive lung disease	

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

Organ or Site	Diagnostic Features[1]	Distinctive Features[2]	Others[3]	Common Features[4]
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

16.2 APPENDIX B: PERFORMANCE STATUS CRITERIA

Karnofsky Performance Scale	
Percent	Description
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
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.
60	Requires occasional assistance but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

16.3 APPENDIX C: INHIBITORS AND INDUCERS OF CYP3A

Inhibitors of CYP3A are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below. Refer to Section **4.4.1** and **14.1.7** on instructions for concomitant use of CYP3A inhibitors and inducers with study medications.

Inhibitors of CYP3A		**Inducers of CYP3A**
Strong inhibitors: INDINAVIR NELFINAVIR RITONAVIR CLARITHROMYCIN ITRACONAZOLE KETOCONAZOLE NEFAZODONE SAQUINAVIR TELITHROMYCIN **Moderate inhibitors:** aprepitant erythromycin diltiazem flucanazole grapefruit juice Seville orange juice verapamil	**Weak inhibitors:** cimetidine **All other inhibitors:** amiodarone NOT azithromycin chloramphenicol boceprevir ciprofloxacin delavirdine diethyl-dithiocarbamate fluvoxamine gestodene imatinib mibefradil mifepristone norfloxacin norfluoxetine star fruit telaprevir troleandomycin voriconazole	Carbamazepine Efavirenz Nevirapine Barbiturates Glucocorticoids Modafinil Oxcarbazepine Phenobarbital Phenytoin Pioglitazone Rifabutin Rifampin St. John's Wort Troglitazone

Source: http://medicine.iupui.edu/clinpharm/ddis/table.aspx

16.4 APPENDIX D: NIH 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		☐ **S**uperficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Poikiloderma ☐ Severe or generalized pruritus ☐ Hair involvement ☐ Nail involvement ☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

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

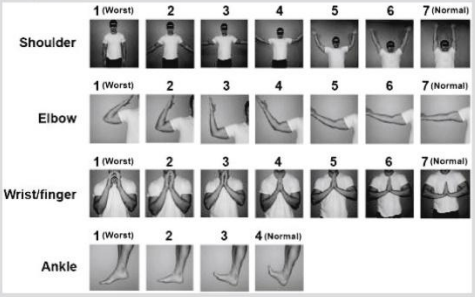
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs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

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

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

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

Photographic Range of Motion (P-ROM)



16.5 APPENDIX E: GLOBAL SCORING OF CHRONIC GVHD

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

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

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

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

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

16.6 APPENDIX F: CHRONIC GVHD ACTIVITY ASSESSMENT (CLINICIAN) FORM A

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):_____				

Chronic GvHD Activity Assessment (Clinician) Form A

	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

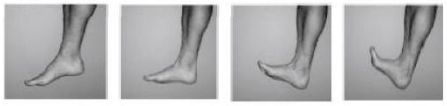
Elbow

❑ Not done

Wrist/finger

❑ Not done

Ankle



❑ Not done

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

16.7 APPENDIX G: PARTICIPANT SELF-ASSESSMENT QUESTIONNAIRES

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

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

	Not at all	Slightly	Moderately	Quite a bit	Extremely
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

	Not at all	Slightly	Moderately	Quite a bit	Extremely
dd. Difficulty sleeping	0	1	2	3	4

Short Form Health Survey (SF-36)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **<u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?**

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking more than a mile	☐ 1	☐ 2	☐ 3
h. Walking several hundred yards	☐ 1	☐ 2	☐ 3
i. Walking one hundred yards	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

16.8 APPENDIX H: 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 Symptom Score 0 after previous involvement	– Increase by 10% predicted absolute value of %FEV1 – If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points	– Decrease by 10% predicted absolute value of %FEV1 – If PFTs not available, increase in NIH Lung Symptom 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

16.9 APPENDIX I: MEDICATION DIARY

Today's date _____ Page 1

Participant Name_____ Participant Study ID_____

INSTRUCTIONS TO THE PARTICIPANT:

1. Complete one form for each cycle.
2. You will take your dose of ibrutinib each day at approximately the same time. Ibrutinib capsules should be swallowed whole, and should not be broken, chewed or opened. You will take ____ ____mg capsules 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 140 mg capsules taken	Comments
	1			
	2			
	3			
	4			
	5			
	6			
	7			
	8			
	9			
	10			
	11			
	12			
	13			
	14			

Participant Name_____ Participant Study ID_____

(*initials acceptable)*

INSTRUCTIONS TO THE PARTICIPANT:

1. Complete one form for each cycle.
2. You will take your dose ibrutinib each day at approximately the same time. Ibrutinib capsules should be swallowed whole, and should not be broken, chewed or opened. You will take ___ ___mg capsules 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 140 mg capsules taken	Comments
	15			
	16			
	17			
	18			
	19			
	20			
	21			
	22			
	23			
	24			
	25			
	26			
	27			
	28			

Participant's Signature: _____ Date: _____

Physician's Office will complete this section:

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

Physician/Nurse/Data Manager's Signature _____

16.10 APPENDIX J: CHILD-PUGH SCORE FOR SUBJECTS WITH LIVER IMPAIRMENT

Measure	1 point	2 points	3 points
Total bilirubin, µmol/L (mg/dL)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/L (g/dL)	>35 (>3.5)	28-35 (2.8-3.5)	<28 (<2.8)
PT/INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Points	Class
5-6	A
7-9	B
10-15	C

16.11 APPENDIX K: STUDY CALENDAR

Procedure	Screening	Baseline	Cycle 1-6 and subsequent cycles[1]												Post Therapy 30 day Follow-up[2]	Annual Telephone Follow-up
			C1 D1	C1 D15	C2 D1	C2 D15	C3D 1	C4 D1	C5 D1	C6 D1	C7 D1 (6m)	C10 D1 (9m)	C12 D28 (12m)	Every 3 cycles after cycle 12 (C15, C18, C21)	C24 D28	
Informed Consent	X															
Confirm Eligibility	X															
Hepatitis Serology	X															
Pregnancy Test	X		X													
ECG[3]	X															
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
History and Physical	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CBC w/ Differential	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Labs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CMV/EBV	X															
Study Drug Accountability				X	X	X	X	X	X	X	X	X	X	X		
Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X	X	
Chronic GvHD Dx Form (**APPENDICES**)	X															
Prior chronic GvHD Thx	X															
Performance Status (Karnofsky) (**Appendix B**)	X	X														
Oral/skin Biopsy[5]		X									X		X		X	
PFTs[6]		X									X		X		X	

Procedure	Screening	Baseline	Cycle 1-6 and subsequent cycles[1]														
			C1 D1	C1 D15	C2 D1	C2 D15	C3D 1	C4 D1	C5 D1	C6 D1	C7 D1 (6m)	C10 D1 (9m)	C12 D28 (12m)	Every 3 cycles after cycle 12 (C15, C18, C21)	C24 D28	Post Therapy 30 day Follow-up[2]	Annual Telephone Follow-up
CT chest Non-contrast[7]		X															
Serum Immunoglobulins		X															
Chronic GvHD 0-3 NIH Organ-Specific & Global Scoring[8] (**Appendix D**, **Appendix E**)	X		X									X	X		X		
Chronic GvHD Activity form (Form A)[9] (**Appendix F**)		X	X			X		X			X	X	X		X		
Patient Self-Assessments[10] (**Appendix G**)			X			X		X			X	X	X		X		
Correlative Immune Monitoring and Plasma Biomarker Studies[11]			X					X			X		X				
PK Studies[12]				X													
Participant Telephone Self Report Status Update																	X[13]

[1] Maximum number of cycles is 24. Scheduled assessments can occur within +/-3 days for cycles 1-3, and +/- 7 days subsequently. Baseline tests need to be done within 7 days prior to administration of the first drug dose. Participants can be also seen for clinical reasons for the duration of the study. At those visits NIH 0-3 organ and global scores are recommended to be documented in the medical and or research record but are not part of the protocol data collection forms.

[2] Efforts should be made to make this visit possible if feasible.

[3] Following screening, ECGs should be performed at the investigator's discretion, particularly in subjects with arrhythmic symptoms (e.g. palpitations, lightheadedness) or new onset of dyspnea. Subjects should be in supine position and resting for at least 10 minutes before study-related ECGs.

[4] Chemistry panels including: Creatinine and potassium (i.e., or Acute Care Panel); calcium and phosphate (i.e., or Mineral Panel); ALT, AST, total bilirubin (i.e., or Hepatic Panel), Lactic dehydrogenase (LDH), uric acid, PT/INR and aPTT As noted under laboratory evaluations in Section **2.2.2.2**).

[5] Optional research biopsy of involved or uninvolved skin or oral mucosa will be offered at baseline and at six month evaluation. This biopsy will only be performed at the NIH site. Additional samples for research may be used from any organ biopsies performed for a clinical indication, as available.

[6] Pulmonary function tests with bronchodilator will be performed at baseline if not performed in previous 3 months of study entry and at six month evaluation (C7D1). Evaluation at 12 months (C12D28) and 24 months (C24D28) are optional.

[7] Non-contrast chest CT will be performed at baseline if clinically indicated and later as clinically indicated (inspiratory and end expiratory BOS preferred).

[8] NIH CGVHD 0-3 Organ-Specific and Global scoring will be done for research purposes only at screening, C1D1, 6 and 12 months.

[9] The CGVHD Activity form (Clinician Assessment, Form A) will be done at all CGVHD evaluation time points:C1D1 ,6 weeks (C2D15), 3 months (C4D1), 6 months (C7D1), 9 months (C10D1) and 12 months (C12D28).

[10] Participant Self-Assessments to include NIH CGVHD Activity Assessment-patient self-report (Form B), Lee CGVHD Symptom Scale, and Short Form Health Survey (SF-36) will be performed at all CGVHD evaluation time points: C1D1 6 weeks (C2D15), 3 months (C4D1), 6 months (C7D1), 9 months (C10D1) and 12 months (C12D28).

[11] Correlative Immune Monitoring and Plasma Biomarker Studies will be performed per Section **Error! Reference source not found.**.

[12] Pharmacokinetics samples pre and post samples will be collected per Section **5.2.1**.

[13] to occur at 12 and 24 months, for a period of two years. See Section **Error! Reference source not found.** for data to be collected during these phone calls.

16.12 APPENDIX L: REPORTABLE EVENT FORM

CCR Reportable Event Forms (REF)

NCI Protocol #: Click or tap here to enter text.	
Protocol Title: Click or tap here to enter text.	
Report version: *(select one)* ☐ Initial Report ☐ Follow-up	
Site Principal Investigator: Click or tap here to enter text.	
Date site PI was notified of the problem: Click or tap to enter a date.	**Date of problem:** Click or tap to enter a date.
If delay in reporting to the coordinating center, please explain: Click or tap here to enter text.	
Location of problem: *(e.g., participant's home, doctor's office)* Click or tap here to enter text.	
Description of Subject Does this problem apply to a subject? ☐ yes ☐ not applicable (more than one subject is involved) **If yes, enter details below:** Subject ID: Click or tap here to enter text. (*do not use medical record number)* Sex: ☐Male ☐ Female Age: Click or tap here to enter text.	

Diagnosis: Click or tap here to enter text.

Name the problem: *(select all that apply)*

☐ Specimen collection issue

☐ Informed consent issue

☐ Ineligible for enrollment

☐ Breach of PII

☐ Other, briefly state the nature of the problem: Click or tap here to enter text.

Detailed Description of the problem: (*Include any relevant treatment, outcomes or pertinent history*): Click or tap here to enter text.

What are you reporting?

☐ **unanticipated problem**

☐ **death**

☐ **non-compliance (other than a protocol deviation)**

☐ **protocol deviation**

☐ **new information that might affect the willingness of subjects to enroll or continue participation in this study**

If interventional or expanded access study, please answer the following questions about your site:

How many participants are still receiving the study intervention? Click or tap here to enter text. How many participants completed study interventions but remain in follow up? Click or tap here to enter text. How many participants are enrolled but not yet receiving study interventions? Click or tap here to enter text.
Have similar problems occurred on this protocol at your site? **☐ Yes ☐ No**
Describe what steps you have already taken or will be taking as a result of this problem: Click or tap here to enter text.

INVESTIGATOR'S SIGNATURE:	**DATE:**

16.13 APPENDIX L: SERIOUS ADVERSE REACTIONS FOR IBRUTINIB CONSIDERED EXPECTED FOR SAFETY REPORTING PURPOSES (RSI STUDY POOL) FOR ADULT POPULATION

System Organ Class	Serious Adverse Reaction (SAR) by Preferred Term	Number of Subjects Exposed to Ibrutinib (N=4791)		Synonymous Medical Terms by Preferred Term[b]
		Frequency n (%)	Frequency Category[a]	
Blood and lymphatic system disorders	Febrile neutropenia	148 (3.1%)	Common	N/A
	Leukocytosis	3 (0.1%)	Uncommon	White blood cell counts increased
	Neutropenia	41 (0.9%)	Uncommon	N/A
	Thrombocytopenia	29 (0.6%)	Uncommon	Platelet production decreased
Cardiac disorders	Atrial fibrillation	110 (2.3%)	Common	N/A
	Cardiac failure	14 (0.3%)	Uncommon	Left ventricular failure
	Cardiac failure congestive	4 (0.1%)	Uncommon	N/A
	Ventricular tachycardia	2 (0.0%)	Rare	N/A
Eye disorders	Eye haemorrhage	2 (0.0%)	Rare	N/A
Gastrointestinal disorders	Diarrhoea	61 (1.3%)	Common	Frequent bowel movements
	Nausea	12 (0.3%)	Uncommon	N/A
	Stomatitis	12 (0.3%)	Uncommon	Aphthous ulcer, Gingival ulceration, Palatal ulcer
	Vomiting	18 (0.4%)	Uncommon	N/A
	Mouth ulceration	2 (0.0%)	Rare	N/A
General disorders and administration site conditions	Pyrexia	69 (1.4%)	Common	Hyperthermia, Body temperature increased
	Oedema peripheral	6 (0.1%)	Uncommon	N/A
Infections and infestations	Pneumonia	235 (4.9%)	Common	N/A
	Sepsis	35 (0.7%)	Uncommon	N/A
	Cellulitis	30 (0.6%)	Uncommon	Skin bacterial infection, Soft tissue infection
	Urinary tract infection	24 (0.5%)	Uncommon	N/A
	Septic shock	18 (0.4%)	Uncommon	N/A
	Pneumocystis jirovecii pneumonia	13 (0.3%)	Uncommon	N/A
	Respiratory tract infection	12 (0.3%)	Uncommon	N/A
	Upper respiratory tract infection	11 (0.2%)	Uncommon	N/A
	Bronchopulmonary aspergillosis	10 (0.2%)	Uncommon	N/A

System Organ Class	Serious Adverse Reaction (SAR) by Preferred Term	Number of Subjects Exposed to Ibrutinib (N=4791)		Synonymous Medical Terms by Preferred Term[b]
		Frequency n (%)	Frequency Category[a]	
	Neutropenic sepsis	10 (0.2%)	Uncommon	N/A
	Pneumonia bacterial	10 (0.2%)	Uncommon	N/A
	Lower respiratory tract infection	8 (0.2%)	Uncommon	N/A
	Pneumonia fungal	6 (0.1%)	Uncommon	N/A
	Bacteraemia	4 (0.1%)	Uncommon	N/A
	Erysipelas	4 (0.1%)	Uncommon	N/A
	Pneumonia viral	4 (0.1%)	Uncommon	N/A
	Skin infection	4 (0.1%)	Uncommon	N/A
	Bacterial sepsis	3 (0.1%)	Uncommon	N/A
	Pneumonia haemophilus	3 (0.1%)	Uncommon	N/A
	Pneumonia klebsiella	3 (0.1%)	Uncommon	N/A
	Sinusitis	3 (0.1%)	Uncommon	Acute sinusitis, Chronic sinusitis, Sinusitis bacterial, Sinusitis fungal, Viral sinusitis
	Staphylococcal bacteraemia	3 (0.1%)	Uncommon	N/A
	Staphylococcal sepsis	3 (0.1%)	Uncommon	N/A
	Urosepsis	3 (0.1%)	Uncommon	N/A
	Atypical pneumonia	2 (0.0%)	Rare	N/A
	Cellulitis orbital	2 (0.0%)	Rare	Periorbital cellulitis
	Enterococcal sepsis	2 (0.0%)	Rare	N/A
	Escherichia sepsis	2 (0.0%)	Rare	N/A
	Folliculitis	2 (0.0%)	Rare	N/A
	Lung abscess	2 (0.0%)	Rare	N/A
	Paronychia	2 (0.0%)	Rare	N/A
	Pneumonia cytomegaloviral	2 (0.0%)	Rare	N/A
	Pneumonia legionella	2 (0.0%)	Rare	N/A
	Pneumonia pseudomonal	2 (0.0%)	Rare	N/A
	Pulmonary tuberculosis	2 (0.0%)	Rare	N/A
	Pseudomonal sepsis	2 (0.0%)	Rare	N/A
	Streptococcal bacteraemia	2 (0.0%)	Rare	Streptococcal sepsis
Injury, poisoning and procedural complications	Subdural haematoma	15 (0.3%)	Uncommon	N/A
	Subdural haemorrhage	2 (0.0%)	Rare	N/A
Investigations	Neutrophil count decreased	10 (0.2%)	Uncommon	N/A
	Platelet count decreased	4 (0.1%)	Uncommon	N/A

System Organ Class	Serious Adverse Reaction (SAR) by Preferred Term	Number of Subjects Exposed to Ibrutinib (N=4791)		Synonymous Medical Terms by Preferred Term[b]
		Frequency n (%)	Frequency Category[a]	
Metabolism and nutrition disorders	Tumour lysis syndrome	14 (0.3%)	Uncommon	N/A
Musculoskeletal and connective tissue disorders	Myalgia	7 (0.2%)	Uncommon	Musculoskeletal discomfort
	Arthralgia	5 (0.1%)	Uncommon	N/A
	Musculoskeletal pain	2 (0.0%)	Rare	N/A
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma	5 (0.1%)	Uncommon	N/A
Nervous system disorders	Cerebrovascular accident	5 (0.1%)	Uncommon	N/A
	Ischaemic stroke	4 (0.1%)	Uncommon	N/A
	Transient ischaemic attack	3 (0.1%)	Uncommon	N/A
	Dizziness	2 (0.0%)	Rare	N/A
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease	11 (0.2%)	Uncommon	Alveolitis, Hypersensitivity pneumonitis, Diffuse alveolar damage
	Pneumonitis	10 (0.2%)	Uncommon	N/A
	Epistaxis	3 (0.1%)	Uncommon	N/A
Skin and subcutaneous tissue disorders	Rash	6 (0.1%)	Uncommon	N/A
	Rash maculo-papular	10 (0.2%)	Uncommon	N/A
	Dermatitis bullous	2 (0.0%)	Rare	N/A
	Drug eruption	2 (0.0%)	Rare	N/A
	Purpura	2 (0.0%)	Rare	N/A
	Urticaria	2 (0.0%)	Rare	N/A
Vascular disorders	Hypertension	8 (0.2%)	Uncommon	Blood pressure increased, Blood pressure diastolic increased, Blood pressure systolic increased, Systolic hypertension, Diastolic hypertension
	Haematoma	2 (0.0%)	Rare	N/A

N/A: not applicable; SAR: serious adverse reaction.

n: number of subjects who experienced a SAR assessed as related.

PTs are coded according to MedDRA version 24.1

a Very common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), based on percentages rounded to 1 decimal place.

b These events would not be subject to expedited reporting

c 0.0% represent < 0.1%