PROTOCOL

TITLE:	A Multicenter Open-Label Phase 1b/2 Study of Ibrutinib in Steroid Dependent or Refractory Chronic Graft Versus Host Disease
PROTOCOL NUMBER:	**PCYC-1129-CA**
STUDY DRUG:	Ibrutinib (PCI-32765)
IND NUMBER:	102,688
SPONSOR MEDICAL MONITOR:	Lori Styles MD Pharmacyclics, LLC Phone: +1 (408) 215-3770 Email: lstyles@pcyc.com
SPONSOR:	Pharmacyclics LLC 995 East Arques Avenue Sunnyvale, CA 94085-4521 United States of America
	Pharmacyclics' protocol developed in collaboration with:
	David B. Miklos, MD PhD Stanford University Stanford, CA 94305-5623
	Samantha Jaglowski, MD MPH Ohio State University Columbus, OH 43210
DATE FINAL:	
Original:	10 April 2014
Amendment 1:	24 June 2015
Amendment 2:	21 October 2015

PROTOCOL APPROVAL PAGE

Study Title:	**A Multicenter Open-label Phase 1b/2 Study of Ibrutinib in Steroid Dependent or Refractory Chronic Graft Versus Host Disease**
Study Number:	**PCYC-1129-CA**
Protocol Date:	**10 April 2014**
Amendment 1:	**24 June 2015**
Amendment 2:	**21 October 2015**

I have carefully read Protocol PCYC-1129-CA entitled "**A Multicenter Open-label Phase 1b/2 Study of Ibrutinib in Steroid Dependent or Refractory Chronic Graft Versus Host Disease**" I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements. Furthermore, I understand that the Sponsor, Pharmacyclics, and the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) must approve any changes to the protocol in writing before implementation.

I agree not to divulge to anyone, either during or after the termination of the study, any confidential information acquired regarding the investigational product and processes or methods of Pharmacyclics. All data pertaining to this study will be provided to Pharmacyclics. The policy of Pharmacyclics LLC requires that any presentation or publication of study data by clinical Investigators be reviewed by Pharmacyclics, before release, as specified in the protocol.

Principal Investigator's Signature Date

Print Name

The following Pharmacyclics LLC representative is authorized to sign the protocol and any amendments:

21 OCT 2015

Medical Monitor's Signature Date

Lori Styles, MD
Clinical Development, Pharmacyclics LLC

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

SYNOPSIS

Study Title:	A Multicenter Open-label Phase 1b/2 Study of Ibrutinib in Steroid Dependent or Refractory Chronic Graft Versus Host Disease
Protocol Number:	PCYC-1129-CA
Study Phase:	1b/2
Study Duration:	Estimated to be 2-3 years
Investigational Product and Reference Therapy:	Ibrutinib will be supplied as 140 mg hard gelatin capsules for oral (PO) administration.
Objectives:	**Phase 1b:** **Primary Objective:** • To evaluate the safety and tolerability of ibrutinib in steroid dependent/refractory chronic graft versus host disease (cGVHD) **Secondary Objectives:** • To evaluate the clinical efficacy of ibrutinib in steroid dependent/refractory cGVHD by measuring: o Best overall cGVHD response (NIH-defined complete response [CR] and partial response [PR]) o Rate of sustained response for at least 5 months o Duration of response (DOR) o Corticosteroid requirement changes over time o Change in symptom burden measured by the Lee cGVHD Symptom Scale **Phase 2:** **Primary Objective:** • To evaluate the clinical efficacy of ibrutinib in steroid dependent/refractory cGVHD by measuring best overall cGVHD response (NIH-defined CR and PR) **Secondary Objectives:** • Rate of sustained response for at least 5 months • Duration of response (DOR) • To evaluate the safety and tolerability of ibrutinib in steroid dependent/refractory cGVHD • To evaluate the impact of ibrutinib on corticosteroid requirement changes over time • To evaluate ibrutinib treatment effect on change in symptom burden measured by the Lee cGVHD Symptom Scale **Exploratory Objectives (Phase 1b and Phase 2):** • To evaluate the clinical efficacy of ibrutinib by measuring failure free survival (FFS) at 6 and 12 months • To evaluate photographic changes in skin and mucocutaneous manifestations with ibrutinib treatment • To determine the pharmacokinetics (PK) of ibrutinib in subjects with cGVHD

	• To determine the alloreactive B cell depletion, T-helper cell composition, and BTK/ITK blockade including: o HY antigen-specific allogeneic B cell depletion in males who receive allo-HCT from a female donor. o Quantification of HY IgG and IgM alloreactive antibodies in males who receive allo-HCT from a female donor. o BTK and ITK binding site occupation. o B cell depletion, flow cytometric analysis of T-helper cell composition, T and B cell cytokine analysis, and phosphoflow analysis of CD4+ T-cell ITK blockade.
Study Design:	This is a Phase 1b/2 open-label study designed to evaluate the safety and efficacy of ibrutinib in treating subjects with steroid dependent/refractory chronic GVHD. Phase 1b will begin with the evaluation of the safety of standard dose (420 mg) ibrutinib with the potential for subsequent dose reductions if dose limiting toxicities (DLTs) are detected. A modified 3+3+3 design will be used to determine a safe dose to carry forward to Phase 2 of the study (recommended Phase 2 dose [RP2D], see Section 3.3.1). Between 6-27 subjects will be evaluated in Phase 1b depending on the frequency of DLTs and need for dose reductions. Phase 2 will evaluate the efficacy of the RP2D of ibrutinib determined in Phase 1b. Subjects will be given ibrutinib continuously along with their pre-existing immunosuppressants for cGVHD and followed for signs of progression/resolution of cGVHD. Approximately 34 subjects will be enrolled in Phase 2 to reach approximately 40 subjects (Phase 1b + Phase 2 subjects) treated at the RP2D. Subjects not experiencing a DLT in the Phase 1b portion of the study are permitted to continue undergoing Phase 2 procedures and follow up at their Phase 1 dose.
Population:	Steroid dependent or refractory chronic graft versus host disease.
Centers:	Multiple, US
Key Inclusion Criteria: *Refer to Section 4 for the complete and detailed list of inclusion/exclusion criteria.*	1. Steroid dependent/refractory classic chronic GVHD defined at any time post-HCT as: a) Dependent disease - Persistent cGVHD manifestations requiring a glucocorticoid dose ≥ prednisone 0.25 mg/kg/day (0.5 mg/kg orally every other day or equivalent) for at least 12 weeks. b) Refractory disease - Progressive cGVHD manifestations despite treatment with a glucocorticoid dose ≥ prednisone 0.5 mg/kg/day (1 mg/kg orally every other day or equivalent) for at least 4 weeks. 2. No more than 3 previous treatments for cGVHD. Treatment with glucocorticoids is considered a treatment for cGVHD and should be included in determining the number of previous treatments. Participants may have received pre-transplant ibrutinib for other reasons besides cGVHD such as for the treatment of leukemia or lymphoma.

	3. Participants must be receiving baseline systemic glucocorticoid therapy for cGVHD at study entry. The dose of steroids must be stable for 28 days prior to starting ibrutinib. 4. At the time of trial enrollment, participants may be receiving other immunosuppressive therapies in addition to glucocorticoids. Immunosuppressant doses must be stable for 28 days prior to starting ibrutinib. Monoclonal T and B cell antibodies must be discontinued at least 56 days before starting ibrutinib. 5. Chronic GVHD manifestations (Appendix B) that can be followed on physical or laboratory exam including at least one of the following criteria: • >25% body surface area (BSA) NIH-defined criteria "Erythematous rash" • >4 total mouth score by NIH-defined criteria 6. Clinically stable or worsening cGVHD between Screening and Day 1 cGVHD response assessments (see Section 7.1.3) 7. ≥18 years of age 8. Life expectancy ≥6 months 9. Karnofsky performance status ≥60 (see Appendix C) 10. Adequate hepatic and renal function as defined as: a) Serum creatinine ≤1.5 x ULN b) AST, ALT and Alkaline phosphatase ≤3 x ULN or of non-hepatic origin, such as hemolysis c) Total bilirubin ≤2 x ULN (unless bilirubin rise is due to Gilbert's syndrome) d) Estimated Creatinine Clearance ≥30 mL/min (Cockcroft-Gault formula) 11. Adequate hematological function defined as: a) Absolute neutrophil count ≥1.0 x 10^9/L and off growth factor support for 7 days b) Platelets ≥30 x 10^9/L and no transfusion support for 7 days c) Hemoglobin ≥8 g/dL and no transfusion or growth support for 7 days 12. PT/INR <1.5 x ULN and PTT (aPTT) <1.5 x ULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder). 13. ≤6 stools per day 14. Oxygen saturation after exertion maintained at ≥88% on room air. If not, FEV1 ≥50% on pulmonary function tests performed within 6 months of study entry. 15. Ability to understand and willingness to sign a written informed consent form. 16. Myeloablative or non-myeloablative allogeneic hematopoietic cell transplant for underlying hematological disease.

Exclusion Criteria:	Subjects are excluded if any of the following criteria are met: 1. Known or suspected active acute GVHD. 2. Received any investigational agents ≤28 days before starting ibrutinib. 3. Current treatment with sirolimus AND either cyclosporine or tacrolimus. 4. History of treatment with a tyrosine kinase inhibitor (eg, imatinib), purine analogs or other cancer chemotherapy in the 4 weeks prior to starting ibrutinib. 5. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to randomization. 6. Any uncontrolled active systemic infection or infection requiring systemic treatment that was completed ≤7 days before the first dose of ibrutinib. 7. Progressive underlying malignant disease including post-transplant lymphoproliferative disease. 8. History of other malignancy (not including the underlying malignancy that was the indication for transplant), with the following exceptions: • Malignancy treated with curative intent and with no evidence of active disease present for more than 3 years prior to Screening and felt to be at low risk for recurrence by treating physician; • Adequately treated nonmelanomatous skin cancer or lentigo maligna melanoma without current evidence of disease; • Adequately treated cervical carcinoma in situ without current evidence of disease. 9. Subject is pregnant, breast-feeding, or of childbearing potential without a negative serum or urine pregnancy test within 7 days of enrollment. Male or female patients of childbearing potential unwilling to use effective contraceptive precautions throughout the trial. 10. Subject not willing to comply with treatment or response evaluation. 11. Moderate or severe hepatic impairment (Child-Pugh classification). 12. Subject has a concurrent illness which in the opinion of the investigator may interfere with the treatment and evaluation of the patient. 13. Concomitant use of warfarin or other Vitamin K antagonists 14. Subject has a known allergy or hypersensitivity to ibrutinib. 15. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of ibrutinib. 16. Known bleeding disorders (eg, von Willebrand's disease or hemophilia). 17. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.

	18. Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded. 19. Major surgery within 4 weeks of first dose of study drug. 20. Concurrent use of a strong cytochrome P450(CYP) 3A inhibitor (Appendix I) 21. Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.
Study Treatment:	Ibrutinib will be dosed daily and will continue as long as the subject is deriving clinical benefit and the subject is not experiencing unacceptable toxicity. **Phase 1b:** Three dose levels of ibrutinib may be tested: 140 mg/day, 280 mg/day and 420 mg/day. The starting dose will be 420 mg/day and the dose will be modified based on the occurrence of dose limiting toxicities (DLTs). Phase 1b will follow a modified 3+3+3 design with 6-9 subjects at each dose level. The dose will be selected as the RP2D if the subject incidence of DLTs during the first 28 days of study treatment is <33%. Before determining the RP2D, 6 subjects in any given cohort must have completed the DLT observation period which is defined as 28 days of therapy. Using the modified 3+3+3 design, the maximum tolerated dose (MTD) is exceeded when ≥3 out of 9 subjects in a dose level experience a DLT. If there are 3 DLTs at a dose level, the MTD is exceeded and the next lower dose level will be enrolled. Enrollment in a dose level cohort will proceed as follows: • If no DLT is observed during the DLT observation period in the initial 3 subjects of a dose level, then a second group of 3 subjects will be enrolled at the same dose level for a total of 6 subjects. If 0-1 DLT occur out of 6 subjects, then this dose will be the RP2D. If 2 DLTs occur out of 6, then the dose level cohort will be expanded to enroll a total of 9 subjects. If no further DLTs occur then this dose will be the RP2D. • If 1 DLT is observed in the initial 3 subjects, the dose level will be expanded to enroll 3 additional subjects at the same dose level for a total of at least 6 subjects. If no further DLT(s) are observed, then this dose will be the RP2D. If 2 DLTs are observed out of 6 subjects, then the dose level cohort will be expanded to enroll a total of 9 subjects. If no further DLTs are observed in this group of subjects then this dose will be the RP2D. • If 2 DLTs are observed in the initial 3 subjects, then enrollment to this dose level will be stopped. A DLT review will occur to determine if the dose should be lowered.

	• If 3 DLTs are observed, then the dose level will be stopped and the next lower dose will be assessed. If a subject experiences a DLT during the DLT observation window, the subject will discontinue treatment and not be replaced in that dose level. The decision to proceed with a RP2D or to dose reduce will be made in a Dose Level Review Meeting by the Sponsor in conjunction with representative investigators after consideration of all available safety and laboratory information. A dose limiting toxicity (DLT) is defined as any drug-related hematologic or non-hematologic toxicity Grade 3 or higher, with the following exceptions: • Grade 4 nausea, vomiting, or diarrhea or Grade 3 diarrhea defined by ≥7 stools/day persisting for 3 days despite best supportive care • Grade 4 neutropenia or Grade 3 neutropenia persisting for 14 days or Grade 3 neutropenia of any duration with fever • For subjects with Grade 2 rash at entry, DLT will be progression to Grade 3 AND a doubling of % BSA involvement • For subjects with Grade 3 rash at entry, DLT will be progression to Grade 4 OR a doubling of % BSA involvement **Phase 2:** Following the establishment of the RP2D, the Phase 2 portion of the study will begin accruing additional subjects. Approximately 40 subjects (cumulative from both Phase 1b and Phase 2) will be treated with the RP2D.
Concomitant Therapy:	Refer to Section 6 for information on concomitant therapy.
Safety Plan:	This study will be monitored in accordance with the Sponsor's Pharmacovigilance Committee procedures. Adverse events (AEs) and serious adverse events (SAEs) will be reviewed by the Sponsor on an ongoing basis to identify safety concerns per the Medical Monitoring Plan.
Statistical Methods and Data Analysis:	**Phase 1:** Designed to determine the RP2D and toxicity profile of ibrutinib using the modified 3+3+3 design. Up to 3 dose levels will be explored. In observing ≤2 DLTs in 9 subjects, RP2D is determined. The Phase 1b efficacy data for subjects with RP2D will be combined with Phase 2 efficacy data. **Phase 2** **Primary Efficacy Analysis:** Best overall cGVHD response rate is defined as the proportion of subjects who achieve a NIH-defined complete response (CR) or partial response (PR) during the study over all subjects who got RP2D from either Phase 1b portion or Phase 2 portion. The cGVHD response rate along with its 95% exact binomial confidence interval will be presented. **Secondary Efficacy Analyses:** Secondary efficacy variables including sustained response rate, DOR,

	corticosteroid requirement changes over time, and change in symptom burden as measured by the Lee cGVHD Symptom Scale will be analyzed descriptively. Efficacy analyses will be performed on all subjects who are enrolled for RP2D from either Phase 1b portion or Phase 2 portion. **Safety Analysis:** All subjects are to be monitored for adverse events during the study. Other safety measurements include clinical laboratory tests and vital signs. Descriptive statistics will be use to summarize safety data (adverse events [AEs], clinical laboratory tests and vital signs) for all subjects receiving ibrutinib. Summary statistics will include means, standard deviations, and medians for continuous variables and proportions for categorical variables.
Interim Analysis	Not applicable.

ABBREVIATIONS

AE	adverse event
aGVHD	acute GVHD
Allo-HCT	alogenic hematopoietic cell transplant
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASBMT	American Society for Blood and Marrow Transplantation
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
BAFF	B cell activating factor
BCR	B-cell receptor
BSA	body surface area
Btk	Bruton's tyrosine kinase
CFR	US Code of Federal Regulations
cGVHD	chronic GVHD
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CRF	case report form
CR	complete response
CTCAE v. 4.03	Common Terminology Criteria for Adverse Events version 4.03
CYP	cytochrome P450
DLT	dose limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECP	extracorporeal photopheresis
eCRF	Electronic case report form
EDC	electronic data capture
EMR	electronic medical records
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FFS	failure free survival
GCP	Good Clinical Practice
GVHD	graft versus host disease
GVT	graft versus tumor
HCT	hematopoietic cell transplantation
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC50	half maximal inhibitor concentration
ICF	Informed consent form
ICH	International Conference on Harmonization

IEC	Independent Ethics Committee
IGH	immunoglobin heavy chain
IL	Interleukin
INR	international normalized ratio
IRB	Institutional Review Board
ITK	IL-2 Inducible T-cell kinase
IV	Intravenous
KPS	Karnofsky performance status
MCL	mantle cell lymphoma
mHAs	minor histocompatibility antigens
MMF	mycophenolate mofetil
MTD	maximum tolerated dose
NIH	National Institutes of Health
NRM	non-relapse mortality
PCI-32765	ibrutinib or Imbruvica®
PCR	polymerase chain reaction
PCYC	Pharmacyclics LLC
PFTs	pulmonary function tests
PK	Pharmacokinetic
PR	partial response
aPTT	activated partial thromboplastin time
PT	prothrombin time
QoL	Quality of life
QTc	Corrected QT interval
REB	Research Ethics Board
RP2D	recommended phase 2 dose
SAE	serious adverse event
SCT	stem cell transplant
SD	stable disease
SOP	standard operating procedures
$t_{1/2}$	half life
TCR	T cell receptor
TFKs	Tec family kinases
T_{max}	median time to maximum plasma concentration
ULN	upper limit of normal

1. BACKGROUND

1.1. Chronic Graft Versus Host Disease

Since its first report in 1957, allogeneic hematopoietic cell transplant (HCT) has been refined from a dismal failure to a standard therapy for hematologic malignancies and hematopoietic progenitor cell disorders (Thomas 1957). Allogeneic HCT can cure patients with chemotherapy resistant malignancies through graft versus tumor effects generated by the donor's immune system against the recipient's tumor (Appelbaum 2001). However, just as the donor's immune system can sense and attack the recipient's malignant cells, so can it sense and attack the recipient's normal tissues resulting in graft versus host disease (GVHD).

Chronic GVHD (cGVHD) is a serious and life threatening impediment to the otherwise curative potential of allogeneic hematopoetic stem cell transplantation (allo-HCT) (Baird 2006; Lee 2003; Pidala 2011; Arai 2011). It is the most common long-term complication following allo-HCT, affecting 30-70% of patients who survive past the first 100 days (Lee 2010), and it is a leading cause of non-relapse mortality (NRM) (Lee 2008). Chronic GVHD is an important cause of late morbidity and mortality after allogeneic HCT (Socie 1999; Lee 2002). Patients with active cGVHD are more likely to report adverse general health, mental health, functional impairments, and pain than allo-HCT survivors without cGVHD (Fraser 2006). Chronic GVHD is also associated with decreased quality of life (QoL) and the continued need for immunosuppressive medications (Fraser 2006; Sutherland 1997; Lee 2003; Lee 2006). Chronic GVHD can appear as early as 3 months following stem cell transplant (SCT), although its manifestations may take much longer to appear, and any organ system can be affected (Mohty 2008). The distinct cGVHD findings are collagen-vascular changes involving the skin, mouth, genitalia, gastrointestinal tract, lung, muscle fascia, and joints (Filipovich 2005). Pathologically, cGVHD is characterized by fibrosis and inflammation of affected organs (Shulman 2006).

Risk factors for developing cGVHD include older patient age, use of peripheral blood stem cells versus bone marrow, and lack of T-cell depletion (Lee 2008). While limited progress related to prevention or treatment of cGVHD has been made, the development of the National Institutes of Health (NIH) Consensus Criteria for grading and staging cGVHD represents a significant advancement, providing a clinically useful severity measure for use in clinical trials (Filipovich 2005). Therapy for cGVHD is limited to broad-spectrum immune inhibitors which, in addition to lacking efficacy, increase the risk of tumor relapse by inhibiting graft versus tumor (GVT) immunity (Holler 2007). The initial treatment is corticosteroids, but half of patients require second-line treatment, for which there is no standard of care. NRM increases from 12% to 27% for patients requiring a therapy change within 4 months of the start of treatment (Flowers 2008b). The median treatment duration is 2-3 years, contributing further to morbidity (Syrjala 2012). There is a direct clinical need for new therapies which suppress the autoimmune and fibrotic cascades yet preserve GVT and immunity against infection.

1.2. Pathogenesis of Chronic Graft Versus Host Disease

The immunopathology underlying development of cGVHD is poorly understood. Mouse models typically involve three main mechanisms: autoantibody production, pro-fibrotic pathways, and defective thymic function (Schroeder 2011). Thymic damage results in dysfunctional negative selection of autoreactive T cells. Recipient B cells are activated by minor antigens and Th2 cytokines, and present processed antigens to donor $CD4^+$ T cells, which co-stimulate B cells to produce autoantibodies and additional stimulatory cytokines (Morris 1990; Shimabukuro-Vornhagen 2009). T and B cells then clonally expand, forming memory and effector cells which traffic to target organ sites, mediating damage through cytokine-mediated fibrosis. Activated T and B cells release inflammatory and fibrosing cytokines, such as IL-13, IL-10, and IL-3. In addition, activated macrophages produce transforming growth factor-β (TGF-β), stimulating collagen production from fibroblasts which leads to a scleroderma-like syndrome (Schroeder 2011). T cells are known to be critically important in the development of cGVHD. Higher rates of cGVHD are seen in recipients of colony-stimulating factor mobilized peripheral blood grafts compared with marrow grafts and in patients who receive a higher T cell dose (Anasetti 2011). *In vivo* T cell depletion with anti-thymocyte globulin or alemtuzumab can reduce the incidence of cGVHD, but at the cost of higher rates of viral or opportunistic infections and relapse (Hale 2012; Perez-Simon 2002). More recently, alloreactive B cell have been implicated in the development of cGVHD (Miklos 2005; Miklos 2004).

1.3. B Cells and the Development of cGVHD

Alloreactive B cells are associated with cGVHD and, in particular, antibodies against minor histocompatibility antigens (mHAs) correlate with cGVHD incidence (Miklos 2005; Miklos 2004). HY antibodies develop in male patients who receive their HCT from a female donor. HY IgG positive patients have a cGVHD incidence of 89% and 0% relapse at 5-years post-transplant while those without HY IgG have a 31% incidence of cGVHD and 48% relapse at 5 years (Miklos 2005; Miklos 2004). HY antigens are mHAs found on the Y chromosome with homologous proteins on the X chromosome (Ofran 2010) and by looking at the HY antigens in sex-mismatched transplants an allo-immune response representing cGVHD was studied. The rationale is that lymphocytes from the female donor graft, which lack a Y chromosome, recognize the HY mHAs as foreign, thus producing HY specific antibodies. This coordinated HY antibody response in the context of cGVHD suggests that specific anti-B cell therapy may be effective in treating cGVHD. In support of this hypothesis, rituximab infused 2-3 months after allo-HCT in male patients with female donors, prevents development of HY antigen-specific alloreactive B cells and IgM antibody (Arai 2012).

B-cell depletion therapy using rituximab in newly diagnosed cGVHD is steroid sparing, but cGVHD frequently recurs as alloreactive B cells recur 9–12 months after rituximab treatment. The Miklos group reported at the American Society for Blood and Marrow Transplantation (ASBMT) 2013 Meeting a Phase 2 study testing the efficacy of rituximab and corticosteroids in 35 patients with new onset cGVHD (Sahaf 2013). The clinically significant primary endpoint of

achieving NIH partial and complete responses and prednisone taper <0.25 mg/kg/day were seen in 15/35 patients (43%, 13 complete response [CR]; 2 partial response [PR]) at 6 months and remained 15/35 (43%, 11 CR, 4 PR) through 1 year. However, in contrast to prophylactic rituximab treatment 2-3 months post allogeneic HCT, the new onset cGVHD study showed that allogeneic HY-specific B cells and antibodies were depleted but uniformly recurred 9–12 months after rituximab (Sahaf 2013).

In addition to the production of alloantibodies, B cells contribute to the immune response via antibody-independent processes, such as antigen presentation, cytokine and chemokine production, and immunoregulatory function (Sahaf 2013). Following activation via the B-cell receptor (BCR) signaling pathways, B cells become potent antigen-presenting cells. Activated B cells produce a variety of inflammatory cytokines, and antigen presentation by autoreactive B cells is critical in autoimmune disorders (Shimabukuro-Vornhagen 2009). Dysfunctional B cells have been identified in cGVHD, where patients have a relatively higher number of activated memory B cells, higher levels of B cell-activating factor of the tumor necrosis family (BAFF), and donor-derived alloantibodies (Sarantopoulos 2009). Immunoglobin heavy chain (IGH) diversity, as evaluated by high-throughput sequencing, is decreased at 30 and 90 days following SCT among patients who subsequently develop GVHD, suggesting impaired B cell clonotype diversification (Logan 2013).

1.4. Other Lymphocytes and the Development of cGVHD

The Ohio State group recently evaluated the influence of lymphocyte reconstitution at days 30 and 100 following allogeneic SCT on subsequent development of cGVHD through use of an extensive immune reconstitution flow cytometric “immunome” assay. Patients who developed cGVHD had a larger increase in $CD4^+$ T cells and a smaller increase in $CD8^+$ T cells over time compared with patients who did not, suggesting a selective expansion of $CD4^+$ T cells. Further, an increase in percentages of activated B cells was noted. An increase in $CD4^+$ cells is associated with an inflammatory phenotype, and a Th2-skewed proinflammatory response may contribute to B cell activation. The presence of increased $CD4^+/CD193^+$ cells among patients with cGVHD supports the notion of a Th2-skewed phenotype, as CCR3 is preferentially expressed on Th2 cells. While a Th2-skewed phenotype has been demonstrated in mouse models of cGVHD, this has not been definitively established in humans (Jaglowski, 2012).

1.5. Current Therapies for cGVHD

Corticosteroids are the primary therapy for cGVHD. An early double-blind, randomized trial compared prednisone and placebo with prednisone and azathioprine as early treatment for standard risk cGVHD (Sullivan 1988). Non-relapse mortality was significantly lower (21% vs. 40%, p=0.003) and overall survival significantly higher (61% vs. 47%, p=.03) in the prednisone and placebo arm, establishing prednisone as the primary therapy for cGVHD. Corticosteroid treatment may require several months before the full benefits are seen. During this time, patients may experience the side effects of corticosteroids: more frequent infections, avascular necrosis,

adrenal insufficiency, cataracts, altered mental states, and disturbed sleep patterns (Sullivan 1988). Koc et al. tested the addition of cyclosporine to prednisone as a steroid-sparing agent and observed fewer complications such as avascular necrosis from steroid use (Koc 2002). However, the relapse rate was increased resulting in no overall survival benefit compared to the prednisone only arm.

Second line therapy for cGVHD patients who fail corticosteroids is not well established. The addition of mycophenolate mofetil (MMF) was compared to standard therapy in a double blind randomized trial (Martin 2009). This trial was stopped early because of decreased survival in the MMF arm, leading the investigators to recommend against adding MMF to cGVHD therapy. A randomized trial comparing the addition of extracorporeal photopheresis (ECP) to standard therapy demonstrated a small but significant benefit (improvement in 4/48 vs. 0/47 patients, p=0.04) (Flowers 2008a). However, ECP requires a motivated patient to endure 3-4 hours vascularly connected to a pheresis pump on a weekly to monthly basis and may not be feasible for all patients. Other therapeutic options include thalidomide (Parker 1995; Kulkarni 2003), hydroxychloroquine (Gilman 2000), sirolimus (Couriel 2005; Johnston 2005), and rituximab (Ratanatharathorn 2003; Cutler 2006; Canninga-van Dijk 2004). These have complete response rates ranging from 10-35% and none has been shown to be clearly superior.

A recently published single institution study developed a new approach for evaluating clinical trial endpoints for testing therapies for second-line treatment of cGVHD (Inamoto 2013). The primary study endpoint was failure free survival (FFS) defined as the absence of a third line therapy, NRM, and recurrent malignancy. This was a retrospective study of 312 patients at the Fred Hutchinson Cancer Research Center who had received systemic steroids for the treatment of cGVHD at a dose of at least 0.5 mg/kg/day before second line treatment, were on systemic immunosuppressive therapy when the second line therapy was initiated, and had received second line therapy due to cGVHD progression after at least one week of initial therapy or due to lack of improvement after at least two weeks of initial therapy. FFS was reported at 56% at 6 months and at 45% at 12 months from the start of second line therapy (Inamoto 2013). With 48 months of follow-up, only 15% of patients were able to successfully withdraw from all immuno-suppressive therapy. The major cause of FFS was treatment change (ie, need for third line therapy) and the study results have set a benchmark for second line cGVHD therapy (Inamoto 2013).

1.6. Ibrutinib Overview

Ibrutinib (IMBRUVICA®) is a first-in-class, potent, orally administered covalently-binding inhibitor of Bruton's tyrosine kinase (Btk) co-developed by Pharmacyclics LLC and Janssen Research & Development LLC (collectively referred to as the Sponsor) for the treatment of B-cell malignancies.

Ibrutinib has been approved in many regions including the US and EUfor indications covering the treatment of patients with mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL) who have received at least one prior therapy, first-line treatment of patients with CLL with a deletion of the short arm of chromosome 17 (del17p) or a *TP53* mutation, and patients with Waldenström's macroglobulinemia. Ibrutinib is currently under investigation in various indications as a single agent and in combinations.

B cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B-cells express cell surface immunoglobulins comprising the B-cell receptor (BCR), which is activated by binding to antigen. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways (Bishop 2003).

For the most comprehensive nonclinical and clinical information regarding ibrutinib background, safety, efficacy, and in vitro and in vivo preclinical activity and toxicology of ibrutinib, refer to the latest version of the ibrutinib Investigator's Brochure.

1.7. Summary of Nonclinical Data

For the most comprehensive nonclinical and clinical information regarding ibrutinib, please refer to the current version of the Investigator's Brochure.

1.7.1. Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor of the Btk (Pan 2007). In vitro, ibrutinib is a potent inhibitor of Btk activity (IC50 = 0.39 nM). The irreversible binding of ibrutinib to cysteine-481 in the active site of Btk results in sustained inhibition of Btk catalytic activity and enhanced selectivity over other kinases that do not contain a cysteine at this position. When added directly to human whole blood, ibrutinib inhibits signal transduction from the B-cell receptor and blocks primary B-cell activation (IC50 = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression (Herman 2011).

For more detailed and comprehensive information regarding nonclinical pharmacology and toxicology, please refer to the current Investigator's Brochure.

1.7.2. Toxicology

In safety pharmacology assessments, no treatment-related effects were observed in the central nervous system (CNS) or respiratory system in rats at any dose tested. Further, no treatment-related corrected QT interval (QTc) prolongation effect was observed at any tested dose in a cardiovascular study using telemetry-monitored dogs.

Based on data from rat and dog including general toxicity studies up to 13 weeks duration, the greatest potential for human toxicity with ibrutinib is predicted to be in lymphoid tissues (lymphoid depletion) and the gastrointestinal tract (soft feces/diarrhea with or without inflammation). Additional toxicity findings seen in only one species with no observed human correlate in clinical studies to date include pancreatic acinar cell atrophy (rat), minimally decreased trabecular and cortical bone (rat) and corneal dystrophy (dog).

In vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. In a rat embryo-fetal toxicity study ibrutinib administration was associated with fetal loss and malformations (teratogenicity) at ibrutinib doses that result in approximately 6 times and 14 times the exposure (AUC) in patients administered the dose of 560 mg daily, respectively.

1.7.2.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ibrutinib.

Ibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an in vivo bone marrow micronucleus assay in mice at doses up to 2000 mg/kg.

Fertility studies with ibrutinib have not been conducted in animals. In the general toxicology studies conducted in rats and dogs, orally administered ibrutinib did not result in adverse effects on reproductive organs.

1.8. Summary of Clinical Data

For the most comprehensive clinical information regarding ibrutinib, please refer to the current version of the Investigator's Brochure.

1.8.1. Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging from 1.25 to 12.5 mg/kg/day as well as fixed dose levels of 420, 560, and 840 mg/day, exposure to ibrutinib increased as doses increased with substantial intersubject variability. The mean half life ($t_{1/2}$) of ibrutinib across 3 clinical studies ranged from 4 to 9 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Administration of 420 mg ibrutinib with a high-fat breakfast in subjects with CLL approximately doubled the mean systemic exposure compared to intake after overnight fasting with median time to T_{max} delayed from 2 to 4 hours. Ibrutinib was extensively metabolized to the dihydrodiol metabolite PCI-45227, a reversible inhibitor of Btk, with approximately 15 times lower inhibitory potency compared to ibrutinib. The metabolite-to-parent AUC ratio ranged from 0.7 to 3.4. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure.

The results of human mass balance study of [^{14}C]-ibrutinib conducted in six healthy male subjects demonstrated that less than 10% of the total dose of [^{14}C]-ibrutinib is renally excreted, whereas approximately 80% is recovered in feces. Subjects with mild and moderate renal insufficiency (creatinine clearance >30 mL/min) were eligible to enroll in Study PCYC-1102-CA in which pharmacokinetic (PK) assessments were included. No dose adjustment is needed for mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). There is no data in patients with severe renal impairment or patients on dialysis. In a hepatic impairment study, data showed an increase in ibrutinib exposure. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. The safety of ibrutinib has not been evaluated in patients with hepatic impairment.

1.8.2. Summary of Clinical Safety

A brief summary of safety data from monotherapy and combination therapy studies is provided in below. For more comprehensive safety information please refer to the current version of the IB. Additional safety information may be available for approved indications in regional prescribing labels where the study is conducted (eg, USPI, SmPC).

1.8.2.1. Monotherapy Studies

Pooled safety data for a total of 1071 subjects treated with ibrutinib monotherapy from 9 studies in B-cell malignancies, which includes subjects from 2 randomized-control studies who crossed over from comparator treatment or placebo to receive ibrutinib monotherapy, are summarized below.

Most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N=1071):

Most frequently reported TEAEs >10%	Most frequently reported Grade 3 or 4 TEAEs >2%	Most frequently reported Serious TEAEs >1%
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Febrile neutropenia
Cough	Anemia	Pyrexia
Anemia	Hypertension	
Pyrexia	Atrial fibrillation	
Neutropenia		

1.8.3. Risks

1.8.3.1. 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 some major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria. 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. See Section 6.2.4 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 6.4 for guidance on ibrutinib management with surgeries or procedures.

1.8.3.2. Cytopenia

Treatment-emergent grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib.

1.8.3.3. Atrial Fibrillation

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 5.3.1.4).

1.8.3.4. 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. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (see Section 5.3.1.4).

1.8.3.5. Infections

Fatal and non-fatal infections have occurred with ibrutinib therapy. At least 25% of subjects with MCL and 35% of subjects with CLL had grade 3 or greater infections per NCI Common Terminology Criteria for Adverse Events (CTCAE v.4.03). The most commonly reported infections include pneumonia, cellulitis, urinary tract infection and sepsis. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib.

1.8.3.6. Second primary Malignancies

Second primary malignancies, most frequently skin cancers, have occurred in subjects treated with ibrutinib. Second primary malignancies including non-skin carcinomas have occurred in

patients treated with ibrutinib. The most frequent second primary malignancy was non-melanoma skin cancer.

1.8.3.7. Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. In a randomized Phase 3 study (PCYC-1112-CA), rash occurred at a higher rate in the ibrutinib arm than in the control arm. Most rashes were mild to moderate in severity.

1.9. Study Rationale

1.9.1. Ibrutinib (Btk Inhibitor) Targets of Interest in cGVHD

Ibrutinib is a first-in-class, potent, orally administered covalently-binding inhibitor of Bruton's tyrosine kinase (Btk) and may be a more potent B cell malignancy drug than rituximab (Advani 2012; Byrd 2013). Btk is a critical intermediate in BCR signaling (Mohamed 2009). It is a non-receptor tyrosine kinase belonging to the Tec family of kinases (TFKs), and critical for B cell processes effected by the BCR (Mohamed 2009). Individuals who lack functioning Btk lack circulating B cells and are unable to produce immunoglobulins or mount humoral immune responses (Satterthwaite 2000). BCR ligation leads to Btk activation which subsequently phosphorylates phospholipase Cγ2 (PLCγ2) triggering a series of downstream events including transcriptional regulation involving NF-κB and NFAT (Mohamed 2009). Btk appears to regulate B cell survival by triggering the classical pathway in response to BAFF under both BCR and BAFF-R signaling (Shinners 2007).

Ibrutinib is also an irreversible inhibitor of interleukin-2 inducible kinase (ITK). ITK is involved in proximal T-cell receptor (TCR) signaling which activates the signaling cascade that includes NFAT, NFkB, and MAPK pathways resulting in T cell activation. ITK has a dominant role in the activation of Th2 cells, but not in Th1 cells.

This is an exploratory study and other than anecdotal reports there is no clinical data on the use of ibrutinib in cGVHD.

1.9.2. Ibrutinib in Murine cGVHD Models

Investigators at Ohio State University and University of Minnesota have studied cGVHD in mouse models (unpublished data; manuscript submitted). In the LP/J→C57BL/6 model of sclerodermatous cGVHD, symptoms become apparent between days 20-25 and peak between days 37–47 after HCT. Ibrutinib, vehicle, or cyclosporine treatment was initiated on randomized cohorts at day 25, after the majority (72%) of mice had clinical signs of cGVHD. By day 39, ibrutinib treated mice displayed a profound lack of signs of cGVHD that were observed in both the vehicle and cyclosporine treatment groups including hair loss, hunched posture, and dermal lesions. Mice were blindly assessed using a scale which quantitatively grades cGVHD on a scale

from 0 to 19. Using this scale, it was documented that mice treated with ibrutinib had significantly fewer manifestations of cGVHD compared with vehicle treatment (p=0.0184). In addition, ibrutinib significantly extended median time to progression by 14 days; 33% (6 of 18) of ibrutinib treated mice did not progress as compared to 12% (2 of 18) of mice receiving vehicle and 10% (1 of 11) of mice receiving cyclosporine 10mg/kg/day (p<0.02).

In addition to the sclerodermatous cGVHD model, these investigators also evaluated ibrutinib in a murine model of alloantibody driven multi-organ system cGVHD (MHC disparate, C57BL/6→B10.BR). This murine model includes evidence of bronchiolar obliterans (BO). Ibrutinib treatment in this model restored pulmonary function defects, reduced germinal center reactions, and reversed lung and liver fibrosis.

1.9.3. Justification of Study Design and Dose Rationale

While rituximab has shown efficacy in a prophylactic role against cGHVD, rituximab used with corticosteroids has provided only partial efficacy in steroid-refractory or new onset cGVHD. Furthermore, rituximab alone does not deplete alloreactive B cells once cGVHD has developed. Ibrutinib has the potential to improve upon the efficacy of rituximab due to its unique mechanism of action on B cells in combination with its potential to reverse ITK polarization, thus causing a skewing away from a Th2 cytokine profile.

Btk occupancy >95% has been demonstrated in all patients who received Ibrutinib dosed 2.5 mg/kg/day or higher. Modest toxicity has been reported at 420 and 840 mg daily. Common AEs reported were gastrointestinal upset (diarrhea, nausea, vomiting), fatigue, respiratory infections, and rash. Because these AEs may overlap with cGVHD manifestations, a conservative dose of 420 mg will be used as the starting does for this trial. This dose is currently approved for use in relapsed/refractory CLL with an acceptable safety profile. At 420 mg daily, Dubovsky et al. (2013) reported 40-80% ITK occupancy (Dubovsky 2013). If the 420 mg dose demonstrates unacceptable toxicity in the cGVHD population then the dose will be lowered to 280 mg/day which is also expected to produce full BTK occupancy. If further dose reduction is required due to toxicity, a dose of 140 mg daily will be used and is the lowest dose recommended in the FDA package insert for ibrutinib.

2. STUDY OBJECTIVE

2.1. Primary Objective

Phase 1b:

To evaluate the safety and tolerability of ibrutinib in steroid dependent/refractory cGVHD.

Phase 2:

To evaluate the clinical efficacy of ibrutinib in steroid dependent/refractory cGVHD by measuring best overall cGVHD response (NIH-defined complete [CR] and partial response [PR]).

2.2. Secondary Objectives

Phase 1b:

- To evaluate the clinical efficacy of ibrutinib in steroid dependent/refractory cGVHD by measuring:
  - Best overall cGVHD response (NIH-defined CR and PR)
  - Rate of sustained response for at least 5 months
  - Duration of response (DOR)
  - Corticosteroid requirement changes over time
  - Change in symptom burden measured by the Lee cGVHD Symptom Scale

Phase 2:

- Rate of sustained response for at least 5 months
- Duration of response (DOR)
- To evaluate the safety and tolerability of ibrutinib in steroid dependent/refractory cGVHD
- To evaluate the impact of ibrutinib on corticosteroid requirement changes over time
- To evaluate ibrutinib treatment effect on change in symptom burden measured by the Lee cGVHD Symptom Scale

2.3. Exploratory Objective(s)

Phase 1b and Phase 2:

- To evaluate the clinical efficacy of ibrutinib by measuring failure free survival (FFS) at 6 and 12 months
- To evaluate photographic changes in skin and mucocutaneous manifestations with ibrutinib treatment
- To determine the pharmacokinetics (PK) of ibrutinib in subjects with cGVHD
- To determine the alloreactive B cell depletion, T-helper cell composition, and BTK/ITK blockade including:
  - HY antigen-specific allogeneic B cell depletion in males who receive allo-HCT from a female donor.
  - Quantification of HY IgG and IgM alloreactive antibodies in males who receive allo-HCT from a female donor.
  - BTK and ITK binding site occupation.
  - B cell depletion, flow cytometric analysis of T-helper cell composition, T and B cell cytokine analysis, and phosphoflow analysis of $CD4^+$ T-cell ITK blockade.

3. STUDY DESIGN

3.1. Overview of Study Design

The primary objective of this Phase 1b/2 study is to evaluate the safety and efficacy of ibrutinib in treating subjects with steroid dependent/refractory cGVHD.

The study will be conducted in two phases.

Phase 1b will be an open-label, safety study to determine the proper dose to take into the Phase 2 safety and efficacy study. The study will begin with a standard dose of ibrutinib (420 mg) but includes potential dose reduction(s) (to 280 mg and 140 mg) if dose limiting toxicities (DLTs) are detected (see Section 5.2.2 below). Depending on the incidence of DLTs, between 6-27 subjects will be enrolled in the Phase 1b portion of the study. Once the recommended Phase 2 dose (RP2D) is determined, Phase 2 will commence.

Phase 2 will be an open-label study using the RP2D determined in Phase 1b. Enrollment will continue until a total of approximately 40 subjects (from both Phase 1b and Phase 2) receive the RP2D dose.

Subjects will be treated continuously with ibrutinib and efficacy will be evaluated including:

- Best overall cGVHD response according to NIH-defined CR and PR
- Rate of sustained response for at least 5 months
- Duration of response (DOR)
- Corticosteroid requirement changes over time
- Change in symptom burden measured by the Lee cGVHD Symptom Scale
- Photographic changes in skin and mucocutaneous manifestations

Both Phase 1b and 2 will include a Screening Phase, Treatment Phase and a Follow-Up Phase.

The Screening Phase assessments will be performed within 42 days prior to study treatment. Eligible subjects will have clinically determined cGVHD and are dependent on or been refractory to steroids. Subjects may have had no more than 3 previous therapies for cGVHD and must have GVHD involvement in at least one of the following categories:

- >25% body surface area (BSA) NIH-defined criteria “Erythematous rash”
- >4 total mouth score by NIH-defined criteria

Study subjects must have a stable or worsening cGVHD assessment for a minimum of 14 days before starting ibrutinib.

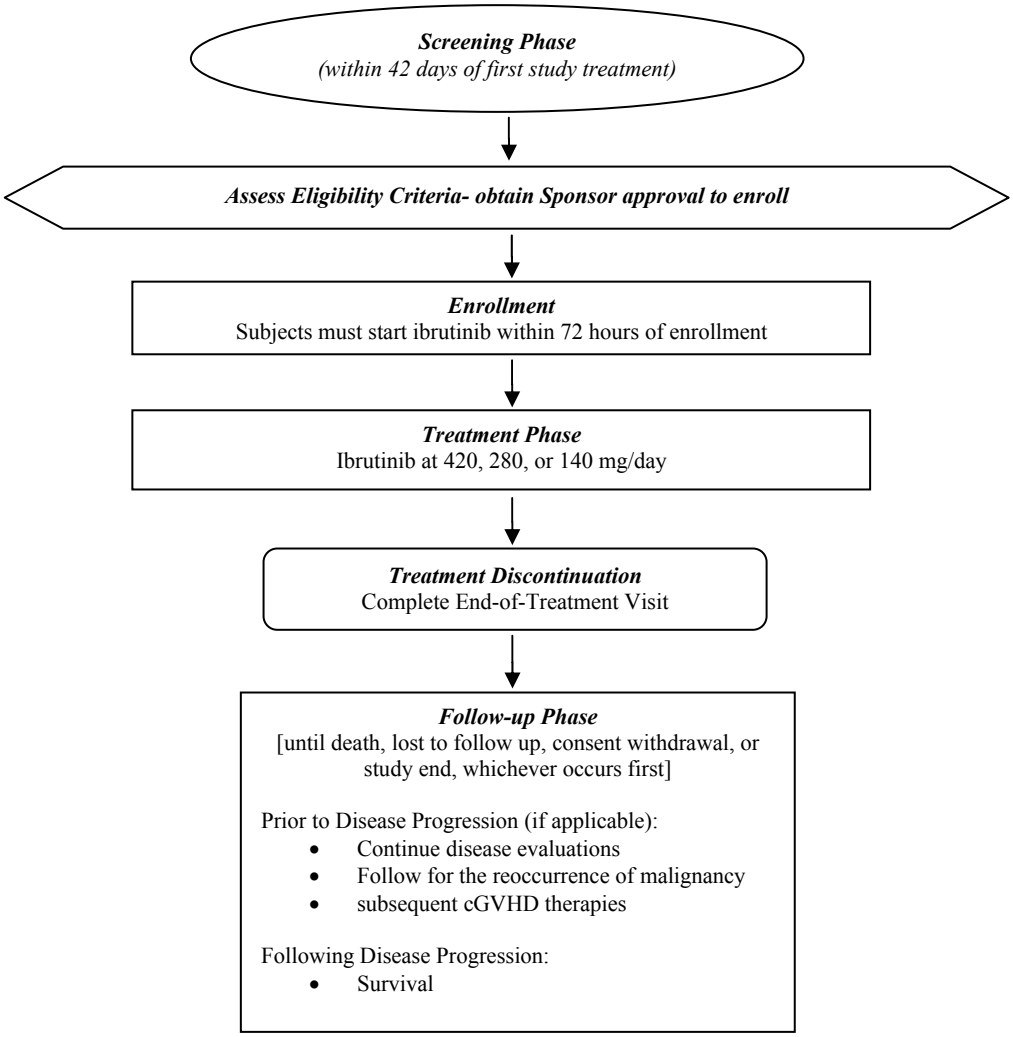
The Treatment Phase will extend from first dose of study treatment until DLT in Phase 1b or until disease progression, unacceptable toxicity, recurrence of underlying malignancy, or study

closure in Phase 2. During the Treatment Phase, efficacy and safety evaluations will be performed according to the Schedule of Assessments in Appendix A.

The Post-treatment Follow-up Phase will begin once a subject discontinues ibrutinib treatment:

- Subjects who discontinue for reasons other than disease progression (ie, for adverse event or Investigator decision), will complete an End-of-Treatment Visit (30 ± 3 days from the last dose of ibrutinib) and will be followed until death, lost to follow-up, consent withdrawal, or study end, whichever occurs first:
  - Continued disease evaluations
  - Follow-up for recurrence of malignancy
  - Follow-up for new cGVHD treatments
- Subjects who discontinue due to disease progression will complete an End-of-Treatment Visit and be followed for survival status.

3.2. Study Schema

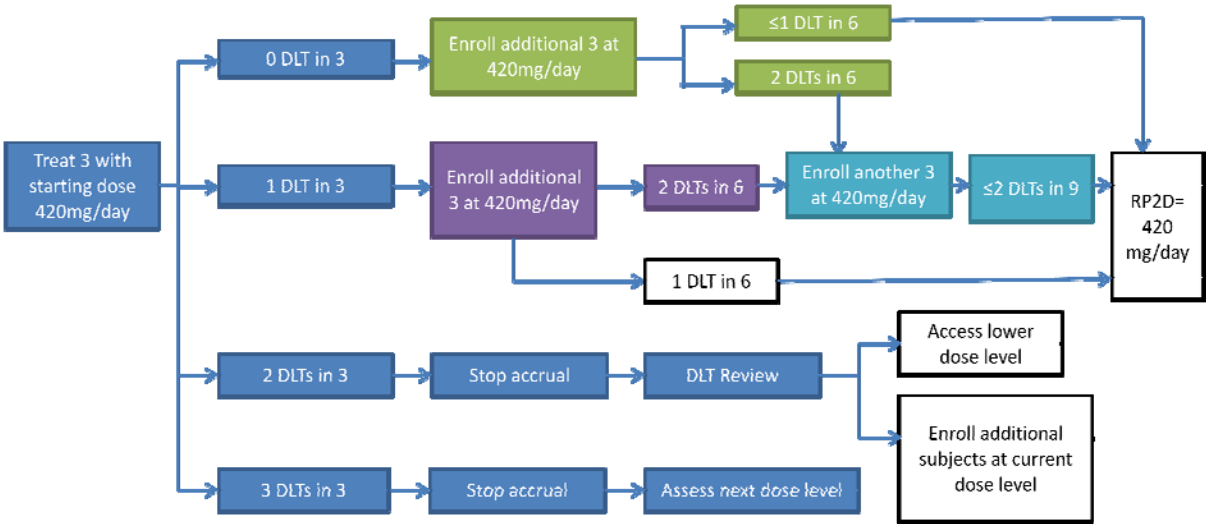


3.3. Phase 1b Safety/DLT Assessment

Phase 1b will be conducted with up to 27 subjects enrolled depending on the occurrence of DLTs. The starting dose will be 420 mg and a modified 3+3+3 design will be used (see Section 5.2.1 and Section 3.3.1) to assess DLTs. If DLTs are unacceptably high then the dose of ibrutinib may be reduced sequentially to 280 mg or 140 mg. After completion of Phase 1b, further enrollment into Phase 2 will commence after the RP2D is identified and the initial safety and efficacy data are evaluated as favorable by the Sponsor. Subjects who have not experienced a DLT in Phase 1b (after 4 weeks of ibrutinib treatment) may continue into Phase 2 without interruption at their initial Phase 1b dose.

The decision to proceed with a RP2D or to dose reduce will be made in a Dose Level Review Meeting by the Sponsor in conjunction representative investigators after careful consideration of all available safety and laboratory information.

3.3.1. Phase 1b DLT Schema



4. SUBJECT SELECTION

4.1. Inclusion Criteria

To be enrolled in the study, each potential subject must satisfy all of the following inclusion criteria.

1. Steroid dependent/refractory classic cGVHD defined at any time post-HCT as:
   a) Dependent disease – Persistent cGVHD manifestations requiring a glucocorticoid dose ≥ prednisone 0.25 mg/kg/day (0.5 mg/kg orally every other day or equivalent) for at least 12 weeks.

b) Refractory disease - Progressive cGVHD manifestations despite treatment with a glucocorticoid dose ≥ prednisone 0.5 mg/kg/day (1 mg/kg orally every other day or equivalent) for at least 4 weeks.

2. No more than 3 previous treatments for cGVHD. Treatment with glucocorticoids is considered a treatment for cGVHD and should be included in determining the number of previous treatments. Participants may have received ibrutinib pre-transplant for other reasons besides cGVHD such as for the treatment of leukemia or lymphoma.
3. Participants must be receiving baseline systemic glucocorticoid therapy for cGVHD at study entry. The dose of steroids must be stable for 28 days prior to starting ibrutinib
4. At the time of trial enrollment, participants may be receiving other immunosuppressive therapies in addition to glucocorticoids. Immunosuppressant doses must be stable for 28 days prior to starting ibrutinib. Monoclonal T and B cell antibodies must be discontinued at least 56 days before starting ibrutinib.
5. Chronic GVHD manifestations (Appendix B) that can be followed on physical or laboratory exam including at least one of the following criteria:
   - >25% BSA NIH-defined criteria "Erythematous rash"
   - >4 total mouth score by NIH-defined criteria
6. Clinically stable or worsening cGVHD between Screening and Day 1 cGVHD response assessment (see Section 7.1.3 for details).
7. ≥18 years of age
8. Life expectancy ≥6 months
9. Karnofsky performance status ≥60 (see Appendix C).
10. Adequate hepatic and renal function as defined as:
    a) Serum creatinine ≤1.5 x ULN
    b) Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase ≤3 x ULN or of non-hepatic origin, such as hemolysis
    c) Total bilirubin ≤2 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)
    d) Estimated Creatinine Clearance ≥30 mL/min (using Cockcroft-Gault formula)
11. Adequate hematological function defined as:
    a) Absolute neutrophil count (ANC) ≥1.0 x 10^9/L and off growth factor support x 7 days
    b) Platelets ≥30 x 10^9/L and no transfusion support x 7 days
    c) Hemoglobin ≥8 g/dL and no transfusion or growth support x 7 days
12. PT/INR <1.5 x ULN and PTT (aPTT) <1.5 x ULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder).
13. ≤6 stools per day

14. Oxygen saturation after exertion maintained at ≥88% on room air. If not, forced expiratory volume in 1 second (FEV1) ≥50% on pulmonary function tests performed within 6 months of study entry.
15. Ability to understand and willingness to sign a written informed consent form (ICF).
16. Myeloablative or non-myeloablative allogeneic hematopoietic cell transplant for underlying hematological disease.
17. Female subjects who are of non-reproductive potential (ie, post-menopausal by history - no menses for ≥1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy). Female subjects of reproductive potential must have a negative serum pregnancy test upon study entry.
18. Male and female subjects of reproductive potential who agree to use highly effective methods of birth control (eg, condoms, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence[1], or sterilized partner) during the period of therapy and for 90 days after the last dose of ibrutinib.

4.2. Exclusion Criteria

To be enrolled in the study, potential subjects must meet NONE of the following exclusion criteria:

1. Known or suspected active acute GVHD
2. Received any investigational agents ≤28 days before starting ibrutinib.
3. Current treatment with sirolimus AND either cyclosporine or tacrolimus.
4. History of treatment with a tyrosine kinase inhibitor (eg imatinib) purine analogs, or other cancer chemotherapy in the 4 weeks prior to starting ibrutinib.
5. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to randomization.
6. Any uncontrolled active systemic infection or infection requiring systemic treatment that was completed ≤7 days before the first dose of ibrutinib.
7. Progressive underlying malignant disease including post-transplant lymphoproliferative disease.
8. History of other malignancy (not including the underlying malignancy that was the indication for transplant), with the following exceptions:

[1] Complete abstinence is a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01 About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

- Malignancy treated with curative intent and with no evidence of active disease present for more than 3 years prior to screening and felt to be at low risk for recurrence by treating physician;
- Adequately treated nonmelanomatous skin cancer or lentigo maligna melanoma without current evidence of disease;
- Adequately treated cervical carcinoma in situ without current evidence of disease.

9. Subject is pregnant, breast-feeding, or of childbearing potential without a negative serum or urine pregnancy test within 7 days of enrollment. Male or female patients of childbearing potential unwilling to use effective contraceptive precautions throughout the trial.
10. Subject not willing to comply with treatment or response evaluation.
11. Moderate or severe hepatic impairment (Child-Pugh classification, see Appendix K).
12. Subject has a concurrent illness which in the opinion of the investigator may interfere with the treatment and evaluation of the patient.
13. Concomitant use of warfarin or other Vitamin K antagonists
14. Subject has a known allergy or hypersensitivity to ibrutinib.
15. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of ibrutinib.
16. Known bleeding disorders (eg, von Willebrand's disease or hemophilia).
17. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
18. Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.
19. Major surgery within 4 weeks of first dose of ibrutinib.
20. Concurrent use of a strong cytochrome P450 (CYP) 3A inhibitor (Appendix I).
21. Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.
22. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).

5. TREATMENT OF SUBJECTS

5.1. Treatment Allocation and Blinding

This is an open label study and no randomization will occur.

5.2. Study Treatment

5.2.1. Phase 1b Dose Selection and Stopping Rules

Three dose levels of ibrutinib may be tested: 140 mg/day, 280 mg/day and 420 mg/day. The starting dose will be 420 mg/day and the dose will be modified based on the dose limiting toxicities (DLTs).

Phase 1b will follow a modified 3+3+3 design with 6-9 subjects at each dose level. The dose will be selected as the RP2D if the subject incidence of DLTs during the first 28 days of study treatment is <33%. Before determining the RP2D, 6 subjects in any given cohort must have completed the DLT observation period which is defined as 28 days of therapy. Using the modified 3+3+3 design, the maximum tolerated dose (MTD) is exceeded when ≥3 out of 9 subjects in a dose level experience a DLT. If there are 3 DLTs at a dose level, the MTD is exceeded and then the next lower dose level will be enrolled.

Enrollment in a dose level will proceed as follows:

- If no DLT is observed during the DLT observation period in the initial 3 subjects of a dose level, then a second group of 3 subjects will be enrolled at the same dose level for a total of 6 subjects. If 0-1 DLT occur out of 6 subjects, then this dose will be the RP2D. If 2 DLTs occur out of 6, then the dose level cohort will be expanded to enroll a total of 9 subjects. If no further DLTs occur then this dose will be the RP2D.
- If 1 DLT is observed in the initial 3 subjects, the dose level will be expanded to enroll 3 additional subjects at the same dose level for a total of at least 6 subjects. If no further DLT(s) are observed, then this dose will be the RP2D. If 2 DLTs are observed out of 6 subjects, then the dose level will be expanded to enroll a total of 9 subjects. If no further DLTs are observed in this group of subjects then this dose will be the RP2D.
- If 2 DLTs are observed in the initial 3 subjects, then enrollment to this dose level will be stopped. A DLT review will occur to determine if the dose should be lowered.
- If 3 DLTs are observed, then the dose level will be stopped and the next lower dose will be assessed.

If a subject experiences a DLT during the DLT observation window, the subject will discontinue treatment.

The decision to proceed with a RP2D or to dose reduce will be made in a Dose Level Review Meeting by the Sponsor in conjunction with the investigators after careful consideration of all available safety and laboratory information.

5.2.2. Definition of Dose Limiting Toxicities

The following DLT criteria apply only to Phase 1b of the study. After completing the DLT period (28 days), Phase 1b subjects will be evaluated by standard safety reporting.

A DLT is defined as any drug-related hematologic or non-hematologic toxicity Grade 3 or higher, with the following exceptions:

- Grade 4 nausea, vomiting, or diarrhea or Grade 3 diarrhea defined by ≥7 stools/day persisting for greater than 3 days despite best supportive care
- Grade 4 neutropenia or Grade 3 neutropenia persisting for greater than 14 days or Grade 3 neutropenia of any duration with fever
- For subjects with Grade 2 rash at entry, DLT will be progression to Grade 3 AND a doubling of % BSA involvement
- For subjects with Grade 3 rash at entry, DLT will be progression to Grade 4 OR a doubling of % BSA involvement

5.2.3. Phase 2

Following the establishment of the RP2D, the Phase 2 portion of the study will begin accruing additional subjects. Approximately 40 subjects (cumulative from both Phase 1b and Phase 2) will be treated with the RP2D. Subjects enrolled in the Phase 2 part of the study will have met the same inclusion/exclusion criteria as Phase 1b subjects and will be treated with the RP2D. Subjects continuing from Phase 1b and subjects enrolled in Phase 2 will continue to be treated unless they have intervening unacceptable toxicity or meet other criteria for subject discontinuation (see Section 9).

5.3. Study Medication

5.3.1. Ibrutinib

5.3.1.1. Formulation/Packaging/Storage

Ibrutinib capsules are provided as a hard gelatin capsule containing 140 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib Investigator's Brochure for a list of excipients.

The ibrutinib capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All ibrutinib capsules drug will be dispensed in child-resistant packaging.

Refer to the Pharmacy Manual for additional guidance on study drug storage, dispensing and handling.

Study drug labels will contain information to meet the applicable regulatory requirements.

5.3.1.2. Dose and Administration

Ibrutinib is administered orally once daily. The capsules are to be taken around the same time each day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and patients should not attempt to open capsules or dissolve them in water. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study (Appendix J).

If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subjects should not take extra capsules to make up the missed dose.

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 except Week 1 Day 2 and Week 2. Unused ibrutinib must be returned to the site and drug accountability records (Section 12.8) updated at each visit. Returned capsules must not be redispensed to anyone.

5.3.1.3. Overdose

Any dose of study drug administered in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any Serious Adverse Event criterion must be reported as a Serious Adverse Event in the appropriate time frame and documented as clinical sequelae to an overdose.

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

Refer to Section 11.4 for further information regarding AE reporting.

5.3.1.4. Dose Modification for Adverse Reactions

During Phase 1b, ibrutinib will be stopped according to DLT rules in Section 5.2.1 during the 28 day DLT window. Thereafter, subjects enrolled in Phase 1b will have ibrutinib modified or discontinued according to the guidelines in Table 1.

For Phase 2, the dose of ibrutinib should be modified according to the dose modification guidelines in Table 1 if any of the following toxicities occur:

- Grade 3 ANC (<1,000/µL) with an associated temperature ≥38.5°C
- Grade 4 ANC (<500/µL) for more than 7 days. Refer to Section 6.1.1 for instruction regarding the use of growth factor support
- Grade 3 thrombocytopenia (<50,000/µL) in the presence of Grade ≥2 bleeding events
- Grade 4 thrombocytopenia (<25,000/µL)

- Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic and/or anti-diarrheal therapy
- Any other Grade 4 or unmanageable Grade 3 toxicity attributed to ibrutinib

Table 1: Ibrutinib Dose Modifications

Hematologic Adverse Events	
Occurrence	**Action to be Taken**
First	Withhold ibrutinib until recovery to an ANC ≥750 or platelets >25,000 with no evidence of Grade ≥2 bleeding; may restart at original dose level
Second	Withhold ibrutinib until recovery to an ANC ≥750 or platelets >25,000 with no evidence of Grade ≥2 bleeding; may restart at 1 dose level lower
Third	Withhold ibrutinib until recovery to an ANC ≥750 or platelets >25,000 with no evidence of Grade ≥2 bleeding; may restart at 1 dose level lower
Fourth	Discontinue ibrutinib[a]
Non-Hematologic 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 lower
Third	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower
Fourth	Discontinue ibrutinib[a]

[a.] If ibrutinib is discontinued for toxicity, subject will end the Treatment Phase of the study.

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 (Section 6.2.4).

Dose changes must be recorded in the Dose Administration eCRF. At the Investigator's discretion, the dose of ibrutinib may be re-escalated after 8 weeks of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction.

5.3.1.5. Dose Modification for Hepatic Impaired Subjects

Ibrutinib is metabolized in the liver. For subjects who develop mild liver impairment while on study (Child-Pugh class A), the recommended dose reduction for ibrutinib/placebo is to a level of 280 mg daily (two capsules). For subjects who develop moderate liver impairment (Child-Pugh class B), the recommended dose reduction is to a level of 140 mg daily (one capsule). Subjects who develop severe hepatic impairment (Child-Pugh class C) must hold study drug until resolved to moderate impairment (Child-Pugh class B) or better, and could be re-treated according to resolved hepatic conditions (ie, 140 mg or 280 mg for moderate or mild impairment, respectively). Monitor subjects for signs of toxicity and follow dose modification guidance as needed (refer to Appendix K).

5.3.2. Management of Immunosuppression

Participants may be receiving other immunosuppressive therapies (including extra-corporeal photopheresis [ECP]) in addition to glucocorticoids. In addition, due to potential drug-drug interactions with ibrutinib, drug levels for immunosuppressant agents such as cyclosporine, tacrolimus, and/or sirolimus are highly recommended during the clinical trial. The doses for these immune-suppressants should be adjusted per institutional practices based on the measured drug level. Changes in immunosuppressive medications being used for the treatment of cGVHD should not be altered during the DLT window unless levels are documented to be at sub-therapeutic or toxic levels. Concurrent use of sirolimus and a calcineurin inhibitor (tacrolimus or cyclosporine) are prohibited.

5.3.3. Management of Steroids

Systemic steroids may be decreased at the treating physician's discretion. The initial taper of steroids may begin two weeks following initiation of ibrutinib if a clinical response is seen. The recommendation is to not taper below 50 percent of the original dose by the 12-week assessment period unless there is a documented medical reason for steroid reduction below 50 percent (eg, uncontrolled diabetes, infection). A specific steroid taper schedule will not be mandated.

Because cGVHD by its nature is a protean disease with clinical manifestations that wax and wane over time, closely spaced clinical evaluations will detect temporary exacerbations of cGVHD manifestations but may not accurately reflect the long term trajectory of a subject's cGVHD and response to treatment. Therefore, in the event a participant experiences a flare of cGVHD, a temporary increase in steroids will be allowed until symptoms return to baseline or criteria are met for progressive cGVHD. If criteria are met for progressive cGVHD, the participant will be scored as a treatment failure and removed from the study.

Non-absorbable oral steroids will be allowed and recorded.

5.3.4. Prophylaxis for Infections

Prophylaxis for infections will be managed according to institutional guidelines.

6. CONCOMITANT MEDICATIONS/PROCEDURES

Concomitant therapies must be recorded throughout the study beginning 60 days prior to the start of the first dose of ibrutinib until 30 days after the last dose of study drug.

6.1. Concomitant Medications

6.1.1. Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell

growth factors (erythropoietin) is permitted per institutional policy and in accordance with the ASCO guidelines (Smith 2006). Transfusions may be given in accordance with institutional policy.

6.2. Medications to be Used with Caution

6.2.1. CYP3A Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong CYP3A (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, and nefazadone) or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. If a strong CYP3A inhibitor must be used, reduce ibrutinib dose to 140 mg or withhold treatment temporarily for the duration of the inhibitor use. Subjects should be monitored for signs of ibrutinib toxicity. If a moderate CYP3A inhibitor must be used, reduce ibrutinib to 140 mg for the duration of the inhibitor use. No dose adjustment is required in combination with mild inhibitors. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A (see Section 5.3.1.2).

Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

A list of common CYP3A inhibitors or inducers is provided in Appendix J; a comprehensive list of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/table.aspx. This website is continually revised and should be checked frequently for updates.

For the most comprehensive effect of CYP3A inhibitors or inducers on ibrutinib exposure, please refer to the current version of the IB.

6.2.2. 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 (with an IC_{50} of 2.15 μg/mL). 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.

6.2.3. QT Prolonging Agents

Any medications known to cause QT prolongation should be used with caution; periodic ECG and electrolyte monitoring should be considered.

6.2.4. Antiplatelet Agents and Anticoagulants

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring anticoagulants or medications that inhibit platelet function. 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 6.4).

Subjects requiring the initiation of therapeutic anticoagulation therapy (eg, atrial fibrillation), (other than warfarin or a vitamin K antagonist) during the course of the study should have treatment with ibrutinib held, and ibrutinib should not be restarted until the subject is clinically stable. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

6.3. Prohibited Concomitant Medications

Any chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy are prohibited while the subject is receiving ibrutinib treatment.

Localized, hormonal, or bone sparing treatment may be considered with prior approval of the Medical Monitor.

The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.4. Guidelines for Ibrutinib Management with Surgeries or 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 patients who require surgical intervention or an invasive procedure while receiving ibrutinib.

6.4.1. Minor Surgical Procedures

For minor procedures (such as a central line placement, needle biopsy, 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 for these procedures.

6.4.2. 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.

6.4.3. Emergency Procedures

For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

7. STUDY EVALUATIONS

7.1. Description of Procedures

7.1.1. Screening/Administrative

All screening clinical and laboratory assessments must be performed within 42 days of first dose of study drug (some exceptions apply).

7.1.2. Informed Consent

The subject must read, understand, and sign the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) approved informed consent form (ICF) confirming his or her willingness to participate in this study before any study-specific screening procedures are performed. Subjects must also grant permission to use protected health information per the Health Insurance Portability and Accountability Act (HIPAA). In addition, subjects must sign all approved ICF amendments per the site IRB/REB/IEC guidelines during the course of the study.

7.1.3. Confirm Eligibility

All necessary procedures and evaluations must be performed to document that the subject meets all of the inclusion criteria and none of the exclusion criteria (Section 4). Each subject must have an eligibility checklist completed by the site and reviewed/approved by the Sponsor Medical Monitor, prior to enrollment.

Clinical assessment of cGVHD must be clinically stable or worsening for a minimum of 14 days between screening and first dose of ibrutinib. If cGVHD assessment shows clinical improvement during this period, subject may be re-assessed at least 14 days later. If cGVHD assessment is stable or worsening between the last 2 assessments then the subject may receive first dose of ibrutinib. Please contact the medical monitor for any questions concerning eligibility.

7.1.4. Medical History and Demographics

The subject's complete history through review of medical records and by interview will be collected and recorded. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of initial diagnosis and list of all prior cGVHD therapies, transplant history, dates administered, and responses and duration of response to these treatments, also will be recorded.

7.1.5. Prior and Concomitant Medications

All medications from 60 days prior to the first dose through 30 days after the last dose of study drug will be documented. If a subject discontinues study treatment without evidence of progressive disease, receipt of all subsequent anti-cGVHD therapies will be collected until death, subject withdrawal of full consent, loss to follow-up, or study termination by Sponsor, whichever comes first.

7.1.6. Adverse Events

The accepted regulatory definition for an adverse event is provided in Section 11.1. The occurrence of AE at the time the ICF is signed until first dose should be recorded under medical history in the eCRF form. All medical occurrences after the first dose with study drug until 30 days after the last dose of study drug that meet the adverse event definition must be recorded as AEs in the eCRF. Laboratory abnormalities designated clinically significant by the Investigator will also be documented as adverse events. Additional important requirements for adverse event and serious adverse event reporting are explained in Section 11.4.

7.1.7. Physical Examination

The complete physical examination will be performed at time points specified in the Schedule of Assessments (Appendix A) and will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes and fundi, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system. Please refer to Efficacy Evaluations (Section 7.2) for the description of NIH cGVHD and Lee Symptom Assessments.

On Weeks 2, 9, 13, 17, 21, and 25 visits, only a limited symptom-directed physical examination is required. Review of symptoms should include inquiry of ocular symptoms; subjects should be referred to an ophthalmologist for a formal examination if any grade ≥2 symptoms are reported.

7.1.8. Imaging

Photographic images of the skin and oral cavities will be captured at time points specified in the Schedule of Assessments (Appendix A) and sent to an independent central repository.

7.1.9. Karnosky Performance Status

The Karnosky Performance Status (KPS) index is provided in Appendix C. The performance status will be assessed at time points specified in the Schedule of Assessments (Appendix A).

7.1.10. Vital Signs

Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature and will be assessed at time points specified in the Schedule of Assessments (Appendix A).

Vital signs should be obtained after the subject has been resting in the sitting position for at least 3 minutes. Height and weight will also be measured at Screening.

7.1.11. Laboratory

7.1.11.1. Hematology

Hematology parameters performed at local laboratory will include a complete blood count: white blood cells, red blood cells, hemoglobin, hematocrit, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils and bands (if reported).

7.1.11.2. Chemistry (Serum)

Serum chemistry parameters performed at local laboratory will include sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), phosphate, uric acid, magnesium and bicarbonate.

7.1.11.3. Coagulation Studies

Measurement of prothrombin time (PT)/INR, and activated partial thromboplastin time (aPTT) will be performed at local laboratory at Screening.

7.1.11.4. Hepatitis Serologies

Hepatitis serologies include hepatitis C antibody, hepatitis B surface antigen, and hepatitis B core antibody and will be evaluated. If hepatitis B core antibody, hepatitis B surface antigen or hepatitis C antibody is positive, then PCR to quantitate hepatitis B or C DNA must be performed and must be negative prior to randomization /enrollment.

7.1.11.5. Donor/Host Chimerism

Donor/host chimerism for the evaluation of engraftment status of the stem cell transplantation will be evaluated at local laboratory at time points specified in the Schedule of Assessments (Appendix A).

7.1.11.6. Immunosuppressant Level

Measurement of immunosupressant levels at local laboratory will be obtained if clinically indicated.

7.1.11.7. Pregnancy Test

Serum pregnancy tests are required at Screening by local laboratory and only for women of childbearing potential. A urine pregnancy test will also be performed on Day 1 prior to first dose.

If positive, pregnancy must be ruled out by ultrasound to be eligible. This test may be performed more frequently if required by local regulatory authorities.

7.1.11.8. Quantitative Serum Immunoglobulins

Testing for IgA, IgG and IgM levels will be performed at a local laboratory (time points specified in the Schedule of Assessments [Appendix A]).

7.1.12. Diagnostics/Procedures

7.1.12.1. ECG

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

Subjects should be in supine position and resting for at least 10 minutes before study-related ECGs. During visits in which both ECGs and blood draws are performed, ECGs should be performed first.

At Screening, 12-lead ECGs will be done in triplicate (≥1 minute apart); the calculated QTcF average of the 3 ECGs must be <470 msec for eligibility.

Any clinically significant abnormalities noted at Screening should be included in the medical history.

7.1.12.2. Oxygen Saturation/Pulmonary Function Tests (PFTs)

Subjects should be evaluated for oxygen saturation or have PFTs at Screening, if not performed within 6 months of study entry.

Evaluation of oxygen saturation by pulse oximeter is acceptable after exertion (eg, brisk walk, marching in place, climbing stairs). If oxygen saturation is not done at Screening, then a Pulmonary Function Test with a FEV1≥50% performed within 6 months of enrollment is acceptable.

7.1.13. Pharmacokinetics/Biomarkers

7.1.13.1. Pharmacokinetics

Plasma concentrations of ibrutinib and PCI-45227 will be determined using a validated analytical method. Other potential metabolites of ibrutinib may be explored. Refer to the Schedule of Assessments (Appendix A) and the Pharmacokinetic Sample Schedule (Table 2).

Table 2: Pharmacokinetic Sampling Schedule

Week	Study Day of Study Week	Predose	Time After Dosing[a]			
			1h ± 15 min	2 h ± 15 min	4 h ± 30 min	6 h (± 1 h)
1	1	x	x	x	x	x
1	2	x[b]				
2	1	x	x	x	x	x

a. Record actual time of sample collection.
b. Sample collected 24 hours (± 2 hours) after Day 1 dose and prior to dosing on Day 2.

Pharmacokinetics Sample Collection for Subjects Treated with a Concomitant CYP3A Inhibitor While on Ibrutinib Treatment

For subjects who have a dose reduction due to toxicity or who start a moderate or strong CYP3A inhibitor while on treatment with ibrutinib, additional PK blood samples for evaluation of ibrutinib exposure is requested at the following scheduled visit after concomitant CYP3A inhibitor has started and is still in use. PK samples will be collected at:

- Pre-dose (If possible, sample should be obtained 22-24 hours post the previous day's dose and before dosing on the day of the scheduled visit)
- 1 hour ± 15 min
- 2 hours ± 15 min
- 4 hours ± 30 min
- 6 hours ± 1 h

Refer to the Laboratory Manual for instructions on collecting and processing these samples. On the day of the sampling visit, the clinical staff will instruct the subject not to take a dose before arrival at the clinic. Study drug intake will be observed by clinic staff. The actual time (versus requested time) that each sample is drawn must be recorded using a 24 hour format. The same clock should be used for recording the time of dosing.

7.1.13.2. Biomarkers and Pharmacodynamic (PD) Studies

Samples collected may be used for pharmacodynamic and biomarker assessments including BTK and other kinase activity and signaling, expression analysis, sequencing, flow cytometry and secreted protein analyses. Fluids including blood collected during the course of the study may be used for, but not limited to, pharmacodynamics and biomarker assessments as noted above.

Studies will be conducted at specialty laboratories to determine alloreactive B cell depletion, T-helper cell composition, and BTK and ITK occupancy. Specifically, the following studies will be conducted:

a) **Biomarker Study[a]:** HY antigen-specific allogeneic B cell depletion in males who receive HCT from a female donor.

b) **Biomarker Study[a]:** Quantification of HY IgG and IgM alloreactive antibodies males who receive HCT from a female donor .

c) **Pharmacodynamics Study:** BTK and ITK binding site occupation (Pharmacyclics, LLC [PCYC]) (Table 3).

d) **Other Studies[a]:** B cell depletion, flow cytometric analysis of T-helper cell composition, T and B cell cytokine analysis, and phosphoflow analysis of $CD4^+$ T-cell ITK blockade.

[a.] Performed at designated central laboratory, refer to Laboratory Manual.

Table 3: PD (BTK and ITK Occupancy) Sampling Schedule (collection for PCYC)

Week	Study Day of Study Week	Predose[a]	Time After Dosing[a]
			4 h ± 30 min
1	1	x	x
1	2	x[b]	
2	1	x[b]	x
9	1	x[b]	x
13	1	x[b]	x

[a.] Record actual time of sample collection.
[b.] Sample collected 24 hours (± 2 hours) after Day 1 dose and prior to dosing on the study day.

After samples are collected, samples will be processed onsite before shipping to PCYC for final storage/analysis. Please refer to Laboratory Manual for instructions.

7.1.13.3. T/B/NK Counts

The blood sample(s) for T/B/NK cell count ($CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD16/56^+$) must be collected at the time points specified in the Schedule of Assessments (Appendix A) and the T/B/NK Sampling Schedule (Table 4).

Table 4: T/B/NK Sampling Schedule (collection for PCYC)

Week	Study Day of Study Week	Predose[a]	Time After Dosing[a]
			4 h ± 30 min
Screening		X	
1	1	X	x
1	2	x[b]	
2	1	x[b]	x
9	1	x[b]	x
13	1	x[b]	x

[a.] Record actual time of sample collection.
[b.] Sample collected 24 hours (± 2 hours) after Day 1 dose and prior to dosing on the study day.

After samples are collected, samples will be processed onsite before shipping to PCYC for final storage/analysis. Please refer to laboratory manual for instructions.

7.2. Efficacy Evaluations

7.2.1. NIH Response Criteria (see Appendix F and Appendix G)

All subjects in the study will have their response assessed using the NIH cGVHD Response assessment (Pavletic 2006; Measurement of Therapeutic Response, ASBMT Web site) at baseline, at week 5, and after every 12 weeks of therapy. Response will be determined by the following criteria:

1. Complete Response – Complete resolution of all reversible manifestations of cGVHD. Irreversible manifestations will be defined by NIH consensus criteria (Pavletic 2006) (eg, ocular xerosis, esophageal stricture, and bronchiolitis obliterans).
2. Partial Response – At least a 25% absolute or 50% relative change (whichever is greater) when comparing start and end measurements in one cGVHD domain without worsening in the other domains (Appendix H).
3. Stable Disease – No worsening in baseline cGVHD manifestations.
4. Progressive Disease – Worsening in any one cGVHD domain by at least an absolute change of 25% from baseline unless baseline values are within 25% of the scale used to score cGVHD. In addition, a new cGVHD manifestation also counts as progression (Appendix H).

7.2.2. Lee cGVHD Symptom Scale

All subjects in the study will complete the Lee Symptom scale (Appendix E) after every 12 weeks of study treatment. A change in >7 points on the Lee cGVHD Symptom Scale will be considered clinically significant and relates to improvement in quality of life (Lee 2006).

7.2.3. Failure Free Survival

Failure free survival will be defined as no death, no relapse of underlying malignancy, and no new immunosuppressive therapy. FFS will be assessed every 6 months starting with beginning of therapy. FFS with corticosteroid requirements at 6 months and 12 months on therapy will be assessed as described in Inamato et al. (Inamato 2013).

7.3. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in source documents for transcription to the eCRF or laboratory requisition form. Refer to the Schedule of Assessments (Appendix A) for the timing and frequency of all sample collections.

Instructions for the collection, handling, and shipment of samples are found in the Laboratory Manual.

8. STUDY PROCEDURES

Each of the phases (1b or 2) in this study is divided into 3 sub-phases: Screening Phase, a Treatment Phase, and a Follow-up Phase. The Schedule of Assessments (Appendix A) summarizes the frequency and timing of efficacy, PK, PD, biomarker, and safety measurements applicable to this study. All subjects enrolled will undergo the same study procedures throughout the study unless otherwise noted.

Details for each part are presented below and can be found on the Schedule of Assessments (Appendix A).

8.1. Screening Phase

The Screening period can occur up to 42 days prior to the first dose of ibrutinib. All subjects must first read, understand, and sign the IRB/REB/IEC approved ICF before any study-specific screening procedures are performed. Standard of care follow-up per institutional practices do not require prior consent (eg, routine laboratory testing). All study tests and procedures should be performed at the study center at which the subject was enrolled and will be receiving treatment. After signing the ICF, screening, and being deemed eligible for entry, subjects will be enrolled in the study after review and approval of screening inclusion/exclusion records by the Sponsor Medical Monitor.

8.1.1. Screening Visit

The following procedures will be performed at the Screening Visit within 42 days prior to first dose of study drug and randomization unless otherwise noted:

- Obtain signed, written informed consent
- Medical history including demographic information
- Collection of transplant history
- Evaluation of KPS performance status
- Complete physical exam including height and weight (may use prior height measurement if available in source documents).
- Record adverse events since signing the ICF
- Record concomitant medication history including over-the-counter drugs, vitamins and herbs
- cGVHD assessment (eg, NIH assessments [Appendix F and Appendix G])
- Lee cGVHD Symptom Scale (Appendix E)
- Obtain vital signs (including blood pressure, heart rate, respiratory rate, and body temperature) after the subject has rested in the sitting position for ≥3 minutesObtain blood specimens for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Coagulation studies: PT/INR, aPTT

- Hepatitis serologies/PCR
- Quantitative serum immunoglobulins (IgA, IgG, and IgM)

- Donor/host Chimerism testing
- T/B/NK sampling for PCYC
- Perform oxygen saturation and/or PFT (if O_2 not assessed within 6 months of study entry)
- Obtain triplicate 12-lead ECG (≥1 minute apart) after the subject has been in a supine position and resting for at least 10 minutes
- Immunosuppressant level – if applicable
- Obtain serum pregnancy test for women of childbearing potential only
- Complete enrollment-eligibility checklist and submit to Sponsor for review and approval prior to enrollment

8.2. Treatment Phase

Following completion of the Screening Visit and once eligibility has been confirmed, subjects are enrolled. Enrollment should occur as close to the time of the expected first dose as possible, ie, not more than 3 business days prior to expected first dose with study drug.

During the treatment/follow-up period, DLT assessment will occur over a 28-day period. DLTs are defined in Section 5.2.2. Local labs will be used to guide all dosing-related decisions.

Week 1 Day 1

Predose

- Complete physical exam including weight.
- Vital signs and performance status (KPS)
- cGVHD assessment per NIH (Appendix F and Appendix G). This assessment must be a minimum of 14 days after the prior response assessment unless the subject's cGVHD is worsening. If the subject's cGVHD is clinically improved from the prior response assessment, then the first dose must be delayed and subject will need to be re-assessed at least 14 days later to confirm stable or worsening cGVHD. Please contact the Medical Monitor for any questions related to eligibility.
- Lee cGVHD Symptom Scale (Appendix E)
- Photographic imaging of cGVHD
- Hematology
- Serum chemistry
- Urine pregnancy test for women of childbearing potential
- Review of baseline adverse events and concomitant medications (including corticosteroid requirements)
- Review of inclusion and exclusion criteria to confirm subject eligibility prior to first dosing
- Pharmacokinetic sampling (pre-dose)

- Pharmacodynamic sampling for PCYC (pre-dose)
- T/B/NK sampling for PCYC (pre-dose)
- Biomarkers sampling
- Immunosuppressant level – if applicable

Post Dose

- Administer ibrutinib at specified dose level, and then dispense remaining amount to subject for at-home dosing
- Provide drug diary and dosing instructions to subject
- Pharmacokinetic sampling for PCYC at 1, 2, 4, and 6 hours post-dose
- Pharmacodynamic sampling for PCYC (4 hours after first dose administration)
- T/B/NK sampling for PCYC (4 hours after first dose administration)
- Review adverse events

Week 1 Day 2

Predose

- [a.] Pharmacokinetic sampling for PCYC (pre-dose before Day 2 drug administration)
- [a.] Pharmacodynamic sampling for PCYC (pre-dose before Day 2 drug administration)
- [a.] T/B/NK sampling (pre-dose)

[a.] Within 24 hours of the first ibrutinib dose.

Week 2

Predose

- Symptom-directed physical examination
- Hematology
- Serum chemistry
- Vital signs
- Immunosuppressant level – if applicable
- Review adverse events and concomitant medications (including corticosteroid requirements)
- Pharmacokinetic sampling for PCYC (pre-dose)
- Pharmacodynamic sampling for PCYC (pre-dose)
- T/B/NK sampling for PCYC (pre-dose before Day 2 drug administration)

During and Post Dose

- Administer ibrutinib at specified dose level
- Pharmacokinetic sampling for PCYC at 1, 2, 4, and 6 hours post-dose
- Pharmacodynamic sampling for PCYC (4 hours after first dose administration)
- T/B/NK sampling for PCYC (4 hours after drug administration)

Week 5, 9, 13, 17, 21, 25 (± 3 days)

Predose

- DLT assessment period ends (Phase 1b Week 5 only)
- Symptom-directed physical examination
- Vital signs and performance status (KPS)
- Photographic imaging of cGVHD (Weeks 5, 13 and 25)
- Hematology
- Serum chemistry
- cGVHD assessment per NIH (Weeks 5, 13 and 25) (Appendix F and Appendix G)
- Lee cGVHD Symptom Scale (Weeks 5, 13 and 25) (Appendix E)
- Donor/host chimerism testing (Weeks 13 and 25)
- Quantitative serum immunoglobulins (IgA, IgG, and IgM) (Weeks 13 and 25)
- Biomarker sampling (Weeks 5, 12 and 25)
- Pharmacodynamic sampling for PCYC (pre-dose on Weeks 9 and 13)
- T/B/NK sampling for PCYC (pre-dose on Weeks 9 and 13)
- Immunosuppressant level – if applicable
- Review returned subject dosing diary
- Review adverse events and concomitant medications (including corticosteroid requirements)

Post Dose

- Administer ibrutinib at specified dose level, and then dispense remaining amount to subject
- Pharmacodynamic sample collection (4 hours after drug administration on Weeks 9 and 13)
- T/B/NK sampling for PCYC (4 hours after drug administration on Weeks 9 and 13)

Week 37 and every 12 weeks thereafter

Predose

- Complete physical examination
- Vital signs and performance status (KPS)
- Photographic imaging of cGVHD
- Hematology
- Serum chemistry
- cGVHD assessment per NIH (Appendix F and Appendix G)
- Lee cGVHD Symptom Scale (Appendix E)
- Donor/host chimerism testing
- Quantitative serum immunoglobulins (IgA, IgG, and IgM)
- Biomarker sampling (Weeks 37 and 49)

- Immunosuppressant level – if applicable
- Review returned subject dosing diary
- Review adverse events and concomitant medications (including corticosteroid requirements)

Post Dose

- Administer ibrutinib at specified dose level, and then dispense remaining amount to subject

8.2.1. Progressive Disease Visit

Progressive Disease visit should be performed at any time during the study, if based on clinical and/or laboratory evaluation, the Investigator suspects progressive disease, or if the subject discontinues treatment for any other reason. If possible, the visit should be performed within 24 hours after the subject's previous dose.

- Complete physical examination
- Vital signs and performance status (KPS)
- Hematology
- Serum chemistry
- Donor/host chimerism testing
- Immunosuppressant level – if applicable
- cGVHD NIH Form assessment (Appendix F and Appendix G)
- Lee cGVHD Symptom Scale (Appendix E)
- Photographic imaging of cGVHD
- Quantitative serum immunoglobulins (IgA, IgG, and IgM)
- Review adverse events and concomitant medications (including corticosteroid requirements)
- Review returned subject dosing diary
- Final drug accountability

8.2.2. End-of-Treatment Visit

An End-of-Treatment visit should occur 30 days (± 7 days) from the last dose of study drug or prior to the start of a new cGVHD treatment. If the subject starts a new cGVHD treatment less than 7 days after the Progressive Disease visit, only those procedures not conducted at the Progressive Disease visit should be performed at the End-of-Treatment visit.

The following procedures will be performed at the End-of-Treatment visit:

- Complete physical examination
- Vital signs and performance status (KPS)
- Hematology

- Serum chemistry
- Donor/host chimerism testing Lee cGVHD Symptom Scale (Appendix E)
- cGVHD NIH Form assessment (Appendix F and Appendix G)
- Photographic imaging of cGVHD
- Immunosuppressant level – if applicable
- Quantitative serum immunoglobulins (IgA, IgG, and IgM)
- Review returned subject dosing diary
- Review adverse events and concomitant medications (including corticosteroid requirements and any new cGVHD treatment if applicable)
- Final drug accountability
- Biomarker sampling

8.3. Follow-up Phase

Once a subject has completed the End-of-Treatment Visit they will enter the Follow-Up Phase (Visits every 12 Weeks).

8.3.1. Response Follow-up

Subjects who discontinue the study for reasons other than progressive disease will be followed every 12 weeks (±7 days) by clinic visit until progressive disease. During this period, the following procedures will be performed:

- Symptom-directed physical examination
- Vital signs and performance status (KPS)
- Hematology
- Serum chemistry
- Donor/host chimerism testingcGVHD NIH Form assessment (Appendix F and Appendix G)
- Lee cGVHD Symptom Scale (Appendix E)
- Photographic imaging of cGVHD
- Review corticosteroid requirements and any new cGVHD treatment if applicable

8.3.2. Long-Term Follow-up

Once subjects progress (for subjects who have not withdrawn consent), they will be contacted approximately every 3 months (±14 days) by clinic visit or telephone to assess survival. Subjects will be contacted until death, subject withdrawal, lost to follow-up, or study termination by the Sponsor, whichever occurs first.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Completion

A subject will be considered to have completed the study if he or she has died before the end of the study, has not been lost to follow up, or has not withdrawn consent before the end of study.

9.2. Withdrawal from Study Treatment

Study treatment will be discontinued in the event of any of the following events:

- cGVHD progression (see definition in Section 7.2.1)
- Unacceptable toxicity: an intercurrent illness or AE that prevents further ibrutinib administration.
- Noncompliance with study medication.
- Investigator's decision (such as chronic noncompliance, significant protocol deviation, or best interest of the subject)
- Withdrawal of consent for treatment by subject
- Malignancy progression/relapse.
- Subject's condition no longer requires study treatment.
- Subject becomes pregnant
- Study termination by Sponsor
- Death

All subjects, regardless of reason for discontinuation of study treatment will undergo an End-of-Treatment Visit and be followed for progression and survival.

9.3. Withdrawal from Study

Withdrawal from study (including all follow-up) will occur under the following circumstances:

- Withdrawal of consent for follow-up observation by the subject
- Lost to follow-up
- Study termination by Sponsor
- Death

If a subject is lost to follow-up, every reasonable effort should be made by the study site personnel to contact the subject. The measures taken to follow up should be documented.

When a subject withdraws before completing the study, the following information should be documented in the source documents:

- Reason for withdrawal;
- Whether the subject withdraws consent (ie, withdraws consent to treatment and all further contact) or withdraws consent to treatment but agrees to participate in follow-up visits.

10. STATISTICAL METHODS AND ANALYSIS

Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

The primary analysis for all efficacy and safety endpoints will be conducted at approximately 12 months after the last subject's first dose of study drug.

10.1. Subject Information

The following definitions will be used for the safety and efficacy analysis, respectively:

- **Safety population:** All enrolled subjects who receive at least one dose of study drug.
- **Efficacy population:** All enrolled subjects who receive at least one RP2D of study drug.

Additional analysis populations, which might be used for sensitivity analyses and biomarker studies, are defined in the SAP.

10.2. Endpoints

10.2.1. Primary Endpoints

Phase 1b:

Safety and Tolerability

Drug toxicity will be described and graded according to CTCAE v. 4.03 criteria. Dose limiting toxicities are defined in Section 5.2.2. Only toxicities which occur during the first 28 days on ibrutinib will count towards the assessment of DLTs.

Toxicities which occur after the first 28 days for Phase 1b subjects will be described and graded according to CTCAE v. 4.03 criteria and presented in tabulated form. This will also be performed for subjects enrolled in the Phase 2 portion of the study.

Phase 2:

The primary efficacy endpoint is the best overall cGVHD response rate. Best overall cGVHD response rate is defined the proportion of subjects who achieve a NIH-defined complete response or partial response.

Please refer to Section 7.2.1 for the definition of overall cGVHD response.

10.2.2. Secondary Efficacy Endpoints

10.2.2.1. Rate of Sustained Response for at Least 5 Months

Sustained response for at least 5 months is defined as NIH-defined complete response or partial response that was sustained for at least 5 months.

10.2.2.2. Duration of Response (DOR)

Duration of response is defined as the interval between the date of initial documentation of a response, and the date of first documented evidence of progressive disease, death, or date of censoring if applicable, for responders only. Percentage of subjects with sustained response and its 95% confidence interval will be calculated using normal approximation to the binomial distribution. Subjects who stop the study drug and start new GVHD treatment before documentation of disease progression will be censored on the date of the last adequate disease assessment that is on or before the start date of new GVHD therapy. Responders are subjects who achieve a NIH-defined complete response or partial response during the study. Non-responders will be excluded from the analysis for DOR.

10.2.2.3. Corticosteroid Requirement Changes Over Time

Corticosteroid requirement will be monitored cross the study. The decrease of corticosteroid need will be viewed as the benefit of the ibrutinib.

10.2.2.4. Change in cGVHD Symptom Scale

Subject reported improvement in symptom burden. The symptom burden will be measured according to the Lee cGVHD Symptom Scale. A change in >7 points on the Lee cGVHD Symptom Scale will be considered significant and relates to improvement in quality of life (Lee 2006).

10.2.3. Safety Endpoints

Safety assessments will consist of monitoring and recording AEs and SAEs; measurements of protocol-specified hematology, clinical chemistry, urinalysis, and other laboratory variables; measurement of protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

10.2.4. Exploratory Endpoints

10.2.4.1. Photographic Changes in Skin and Mucocutaneous Manifestations.

Skin and mucocutaneous manifestations will be monitored across the study. The decrease of area with skin and mucocutaneous manifestations will be view as the benefit of the ibrutinib.

10.2.4.2. Pharmacokinetic Analysis

Plasma concentrations of ibrutinib and metabolite PCI-45227 will be determined using a validated analytical method. Other potential metabolites of ibrutinib may be explored.

Bioanalytical data from this study will be used in noncompartmental PK analysis and also may be combined with data from other studies performed with ibrutinib in subjects with hematologic malignancies as part of a population PK analysis using nonlinear mixed effects models. For the population PK analysis, covariates that could potentially correlate with plasma PK parameters will be evaluated. The results of the population PK analyses (if performed) will be presented in a separate report.

10.2.4.3. Biomarker and Pharmacodynamic Studies

Pharmacodynamic studies will be conducted to determine alloreactive B cell depletion, T-helper cell composition, BTK occupancy and ITK blockade. Specifically, the following PD studies will be conducted:

- HY antigen-specific allogeneic B cell depletion in males who receive HCT from a female donor.
- Quantification of HY IgG and IgM alloreactive antibodies males who receive HCT from a female donor.
- BTK and ITK binding site occupation (PCYC).
- B cell depletion, flow cytometric analysis of T-helper cell composition, T and B cell cytokine analysis, and phosphoflow analysis of CD4+ T-cell ITK blockade.

10.2.4.4. Failure Free Survival

Failure free survival is defined as no death, no relapse of malignancy, and no new immunosuppressive therapy for GVHD.

10.3. Sample Size Determination

With a sample size of 40 subjects and assuming an best overall cGVHD response rate of approximately 50%, it is expected to have at least 90% power to show the efficacious treatment effect (the lower bound of 95% CI of the response rate >0.25).

10.4. Efficacy Analysis

Best overall cGVHD response rate and its 95% confidence interval will be calculated with the exact test for binomial distribution.

The secondary efficacy endpoint rate of sustained response for at least 5 months will be evaluated in the same manner as best overall cGVHD response rate.

The distribution (median and Kaplan-Meier curves) and estimates of DOR will be provided using Kaplan-Meier estimates for responders.

Other secondary endpoints, such as on corticosteroid requirement changes over time, change in symptom burden measured by the Lee cGVHD Symptom Scale will be summarized by descriptive statistics.

Exploratory endpoints will be will be summarized by descriptive statistics.

10.5. Safety Analysis

The safety variables to be analyzed include adverse events, clinical laboratory test results (hematology and chemistry), and other safety measurements. They will be summarized by descriptive statistics. No formal statistical testing is planned.

Exposure to ibrutinib first dose and reasons for discontinuation from study treatment will be tabulated.

Adverse Events

Adverse event parameters to be evaluated are the type, incidence, and intensity of adverse events; the relationship of adverse events to ibrutinib; and the action taken with respect to ibrutinib treatment due to adverse events.

The verbatim terms used in the eCRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent adverse events are those adverse events occurring after the first dose of study drugs and within 30 days following the last dose of study drug; any adverse event that is considered study drug-related regardless of the start date of the event; or any adverse event that is present at baseline but worsens after the first administration of study drug in severity or is subsequently considered drug-related by the Investigator. All treatment-emergent adverse events will be included in the analysis.

For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized. The number and percent of subjects with treatment-emergent adverse events will be summarized according to intensity (NCI CTCAE v. 4.03) and drug relationship as well as categorized by system organ class and preferred term. Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

All laboratory values will be converted to standard international units and will be graded using the NCI CTCAE v. 4.03.

A summary of the shifts in selected laboratory hematology and serum chemistry parameters from baseline to the worst toxicity grade during the study will be tabulated.

11. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

11.1. Definitions

11.1.1. Adverse Events

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational study drug, whether or not considered related to the study drug (ICH-E2A, 1995).

For the purposes of this clinical study, AEs include events which are either new or represent detectable exacerbations of pre-existing conditions.

The term “disease progression” should not be reported as an adverse event term. As an example, "worsening of underlying disease" or the clinical diagnosis that is associated with disease progression should be reported.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms provided by the patient and/or observed by the Investigator or study staff including laboratory abnormalities of clinical significance.
- Any AEs experienced by the patient through the completion of final study procedures.
- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with cGVHD that were not present before the AE reporting period
- Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies).

The following are NOT considered AEs:

- **Pre-existing condition:** A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Pre-planned or elective hospitalization:** A hospitalization planned before signing the informed consent form is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.
- **Diagnostic Testing and Procedures:** Testing and procedures should not to be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.

11.1.2. Serious Adverse Events

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death (ie, the AE actually causes or leads to death).
- Is life-threatening. Life-threatening is defined as an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the Investigator or the Sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening.
- Requires in-patient hospitalization >24 hours or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the patient's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not result in death, be immediately life-threatening or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the patient or patient may require intervention to prevent one of the other outcomes listed in this definition. Examples of such events are intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsion that does not result in hospitalization; or development of drug dependency or drug abuse.

Given that the Investigator's perspective may be informed by having actually observed the event, and the Sponsor is likely to have broader knowledge of the drug and its effects to inform its evaluation of the significance of the event, if either the Sponsor or the Investigator believes that the event is serious, the event will be considered serious.

11.1.3. Severity Criteria (Grade 1-5)

Definitions found in the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v. 4.03) will be used for grading the severity (intensity) of AEs. The CTCAE v. 4.03displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a patient experience any AE not listed in the CTCAE v. 4.03, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the patient's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the patient, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the patient's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the patient to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in patient death

11.1.4. Causality (Attribution)

The Investigator is to assess the causal relation (ie, whether there is a reasonable possibility that the study drug caused the event) using the following definitions:

Not Related:	Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.
Unlikely:	The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely.
Possibly Related:	There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.
Related:	The AE is clearly related to use of the investigational product.

11.2. Unexpected Adverse Events

An "unexpected" AE is an AE that is not listed in the Investigator's Brochure/package insert or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be "unexpected" (by virtue of greater severity) if the Investigator's Brochure referred only

to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be “unexpected” (by virtue of greater specificity) if the Investigator's Brochure/package insert listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

11.3. Special Reporting Situations

Special reporting situation on a Sponsor study may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of any study drug
- Suspected abuse/misuse of a study drug
- Inadvertent or accidental exposure to a study drug
- Medication error involving a product (with or without subject/patient exposure to the study drug, eg, name confusion)

Occurrence of any special reporting situations should be recorded in the eCRF. If any special reporting situation meets the criteria of an adverse event, it should be recorded on the adverse events eCRF. If the adverse event is considered serious, it should be recorded on the adverse events eCRF as serious and should be reported on the Serious Adverse Event Report Form. The SAE Report Form should be sent via email or fax to Pharmacyclics Drug Safety or designee within 24 hours of awareness.

11.4. Documenting and Reporting of Adverse Events and Serious Adverse Events by Investigators

11.4.1. Assessment of Adverse Events

Investigators will assess the occurrence of adverse events and serious adverse events at all subject evaluation timepoints during the study. All adverse events and serious adverse events whether volunteered by the subject, discovered by study personnel during questioning, detected through physical examination, clinically significant laboratory test, or other means, will be recorded in the subject’s medical record and on the Adverse Event CRF and, when applicable, on the Serious Adverse Event Report Form.

Each recorded adverse event or serious adverse event will be described by its duration (ie, start and end dates), severity, regulatory seriousness criteria (if applicable), suspected relationship to the investigational product, and any actions taken.

11.4.2. Adverse Event Reporting Period

All AEs whether serious or non-serious, will be documented in the source documents from the time signed and dated ICF is obtained until 30 days following the last dose of study drug. SAEs will be reported to the Sponsor from the time of ICF signing. Both serious and non-serious AEs will be recorded in the eCRF from the first dose of study drug until 30 days after the last dose of study drug.

Serious adverse events reported after 30 days following the last dose of study drug should also be reported if considered related to study drug. Resolution information after 30 days should be provided.

Progressive disease should NOT be reported as an event term, but instead symptoms/clinical signs of disease progression may be reported.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study drug, investigator's evaluation of its relationship to the study drug, and the event outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to Sponsor instructions.

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to the Sponsor, or designee, as outlined above.

If a death occurs within 30 days after the last dose of study drug, the death must be reported to the Sponsor as a serious adverse event.

11.4.3. Expediting Reporting Requirements for Serious Adverse Events

All serious adverse events (initial and follow-up information) will be reported on the Serious Adverse Event Report Form and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of the discovery of the event or information. Pharmacyclics may request follow-up and other additional information from the Investigator (eg, hospital admission/discharge notes and laboratory results). The contact information (phone, email and fax) for Pharmacyclics Drug Safety can be found on the Serious Adverse Event Report Form and instructions.

All serious adverse events that have not resolved by the end of the study, or that have not

resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts)

The Sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities and governing bodies according to the local regulations.

The investigator (or Sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

11.4.4. Adverse Events of Special Interest (AESI)

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities by the Sponsor. These events (regardless of seriousness) should be reported on the Serious Adverse Event Report Form and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of awareness.

11.4.4.1. Major Hemorrhage

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic AEs 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 v4.03.

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 11.4.4 above.

11.4.5. Pregnancy

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy. However, should a pregnancy occur in a female study subject, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.

A female subject must immediately inform the Investigator if she becomes pregnant from the time of consent to 30 days after the last dose of study drug. A male subject must immediately inform the Investigator if his partner becomes pregnant from the time of consent to 3 months after the last dose of study drug. Any female subjects receiving study drug(s) who become pregnant must immediately discontinue study drug. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. Any pregnancy occurring in a subject or subject's partner from the time of consent to 30 days after the last dose of study drug must be reported. Any occurrence of pregnancy must be recorded on the Pregnancy Report Form Part I and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of learning of the event. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. For pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing the Pregnancy Report Form Part II. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

11.4.6. Other Malignancies

In addition to all routine AE reporting, all new malignant tumors including solid tumors, skin malignancies and hematologic malignancies are to be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival. If observed, enter data in the corresponding eCRF.

12. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

12.1. Regulatory and Ethical Compliance

This clinical study was designed and will be implemented in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practices, with applicable local regulations (including US Code of Federal Regulations [CFR] Title 21 and European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

12.2. Institutional Review Board (IRB), Research Ethics Board (REB) and Independent Ethics Committee (IEC) Approval

The Investigator will submit this protocol, the ICF, IB, and any other relevant supporting information (eg, all advertising materials or materials given to the subject during the study) to the appropriate IRB/REB/IEC for review and approval before study initiation. Amendments to the protocol and informed consent form must also be approved by the IRB/REB/IEC before the implementation of changes in this study.

The Investigator is responsible for providing the IRB/REB/IEC with any required information before or during the study, such as SAE expedited reports or study progress reports.

The IRB/REB/IEC must comply with current United States (US) regulations (§21 CFR 56) as well as country-specific national regulations and/or local laws.

The following documents must be provided to Pharmacyclics or its authorized representative before entering subjects in this study: (1) a copy of the IRB/REB/IEC letter that grants formal approval; and (2) a copy of the IRB/REB/IEC-approved ICF.

12.3. Informed Consent

The ICF and process must comply with the US regulations (§ 21 CFR Part 50) as well as country specific national regulations and/or local laws. The ICF will document the study-specific information the Investigator or his/her designee provides to the subject and the subject's agreement to participate.

The Investigator or designee (designee must be listed on the Delegation of Authority log), **must** explain in terms understandable to the subject the purpose and nature of the study, study procedures, anticipated benefits, potential risks, possible AEs, and any discomfort participation in the study may entail. This process must be documented in the subject's source record. Each subject must provide a signed and dated ICF before any study-related (nonstandard of care) activities are performed. The original and any amended signed and dated consent forms must remain in each subject's study file at the study site and be available for verification by study monitors at any time. A copy of each signed consent form must be given to the subject at the time that it is signed by the subject.

12.4. Quality Control and Quality Assurance

Sponsor shall implement and maintain quality control and quality assurance procedures to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulatory requirements. This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2008) and all revisions thereof, and in accordance with FDA regulations (21 CFR Parts 11, 50, 54, 56, and 312, Subpart D – Responsibilities of Sponsors and Investigators) and with the ICH guidelines on GCP (ICH E6).

12.5. Protected Subject Health Information Authorization

Information on maintaining subject confidentiality in accordance to individual local and national subject privacy regulations must be provided to each subject as part of the informed consent process (refer to Section 12.3), either as part of the ICF or as a separate signed document (for example, in the US, a site-specific HIPAA consent may be used). The Investigator or designee **must** explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Pharmacyclics and its designees, regulatory agencies, and IRBs/REBs/IECs. As the study Sponsor, Pharmacyclics will not use the subject's protected health information or disclose it to a third party without applicable

subject authorization. It is the Investigator's or designee's responsibility to obtain written permission to use protected health information from each subject. If a subject withdraws permission to use protected health information, it is the Investigator's responsibility to obtain the withdrawal request in writing from the subject **and** to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

During the review of source documents by the monitors or auditors, the confidentiality of the subject will be respected with strict adherence to professional standards and regulations.

12.6. Study Files and Record Retention

The Investigator must keep a record of all subjects in the study. For those subjects subsequently excluded from enrollment, the reason(s) for exclusion is to be recorded.

The Investigator/study staff must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Essential documentation includes, but is not limited to, the IB, signed protocols and amendments, IRB/REB/IEC approval letters (dated), signed Form FDA 1572 and Financial Disclosures, signed ICFs (including subject confidentiality information), drug dispensing and accountability records, shipping records of investigational product and study-related materials, signed (electronically), dated and completed CRFs, and documentation of CRF corrections, SAE forms transmitted to Pharmacyclics and notification of SAEs and related reports, source documentation, normal laboratory values, decoding procedures for blinded studies, curricula vitae for study staff, and all relevant correspondence and other documents pertaining to the conduct of the study.

All essential documentation will be retained by the Investigator for at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated and until there are no pending or contemplated marketing applications; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after formal discontinuation of clinical development of the drug.

The Investigator must notify Pharmacyclics and obtain written approval from Pharmacyclics before destroying any clinical study documents or images (eg, scan, radiograph, ECG tracing) at any time. Should an Investigator wish to assign the study records to another party or move them to another location, advance written notice will be given to Pharmacyclics. Pharmacyclics will inform the Investigator of the date that study records may be destroyed or returned to Pharmacyclics.

Pharmacyclics must be notified in advance of, and Pharmacyclics must provide express written approval of, any change in the maintenance of the foregoing documents if the Investigator wishes to move study records to another location or assign responsibility for record retention to another party. If the Investigator cannot guarantee the archiving requirements set forth herein at

his or her study site for all such documents, special arrangements must be made between the Investigator and Pharmacyclics to store such documents in sealed containers away from the study site so that they can be returned sealed to the Investigator for audit purposes.

12.7. Case Report Forms and Record Maintenance

CRFs will be used to collect the clinical study data and must be completed for each enrolled subject with all required study data accurately recorded such that the information matches the data contained in medical records (eg, physicians' notes, nurses' notes, clinic charts and other study-specific source documents). Authorized study site personnel (ie, listed on the Delegation of Authority log) will complete CRFs designed for this study according to the completion guidelines that will be provided. The Investigator will ensure that the CRFs are accurate, complete, legible, and completed within a reasonable period of time. At all times, the Investigator has final responsibility for the accuracy and authenticity of all clinical data.

The CRFs exist within an electronic data capture (EDC) system with controlled access managed by Pharmacyclics or its authorized representative for this study. Study staff will be appropriately trained in the use of CRFs and application of electronic signatures before the start of the study and before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The Investigator attests that the information contained in the CRFs is true by providing electronic signature within the EDC system. After database lock, the Investigator will receive a copy of the subject data (eg, paper, CD, or other appropriate media) for archiving at the study site.

12.8. Investigational Study Drug Accountability

Ibrutinib must be kept in a locked limited access room. The study drug must not be used outside the context of the protocol. Under no circumstances should the Investigator or other site personnel supply PCI-32765 or comparator to other Investigators, subjects, or clinics or allow supplies to be used other than as directed by this protocol without prior authorization from Pharmacyclics.

Accountability records for ibrutinib and any comparator must be maintained and readily available for inspection by representatives of Pharmacyclics and are open to inspections by regulatory authorities at any time.

An Investigational Drug Accountability Log must be used for drug accountability. For accurate accountability, the following information must be noted when drug supplies are used during the study:

1. Study identification number (PCYC-1129-CA)
2. Subject identification number

3. Lot number(s) of ibrutinib or comparator dispensed for that subject
4. Date and quantity of drug dispensed
5. Any unused drug returned by the subject

At study initiation, the monitor will evaluate and approve the site's procedure for investigational product disposal/destruction to ensure that it complies with Pharmacyclics' requirements. If the site cannot meet Pharmacyclics' requirements for disposal/destruction, arrangements will be made between the site and Pharmacyclics or its representative, for return of unused investigational product. Before disposal/destruction, final drug accountability and reconciliation must be performed by the monitor and/or two authorized study site personnel.

All study supplies and associated documentation will be regularly reviewed and verified by the monitor.

12.9. Study Monitoring/Audit Requirements

Representatives of Pharmacyclics or its designee will monitor this study until completion. Monitoring will be conducted through personal visits with the Investigator and site staff, remote monitoring, as well as any appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure that the study is conducted in compliance with the protocol, standard operating procedures (SOPs), and other written instructions and regulatory guidelines, and to ensure the quality and integrity of the data. This study is also subject to reviews or audits.

To assure the accuracy of data collected in the CRFs, it is mandatory that the monitor/auditor have access to all original source documents, including all electronic medical records (EMR) at reasonable times and upon reasonable notice. During the review of source documents, every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the Investigator agrees to allow the IRB/REB/IEC, representatives of Pharmacyclics, its designated agents and authorized employees of the appropriate Regulatory Authority to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

Pharmacyclics or its authorized representative may perform an audit at any time during or after completion of this study. All study-related documentation must be made available to the designated auditor. In addition, a representative of the FDA or other Regulatory Agencies may choose to inspect a study site at any time before, during, or after completion of the clinical study. In the event of such an inspection, Pharmacyclics will be available to assist in the preparation. All pertinent study data should be made available as requested to the Regulatory Authority for verification, audit, or inspection purposes.

12.10. Investigator Responsibilities

A complete list of Investigator responsibilities are outlined in the clinical trial research agreement and the Statement of Investigator Form FDA 1572, both of which are signed by the Investigator before commencement of the study. In summary, the Investigator will conduct the study according to the current protocol; will read and understand the IB; will obtain IRB/REB/IEC approval to conduct the study; will obtain informed consent from each study participant; will maintain and supply to the Sponsor or designee, auditors and regulatory agencies adequate and accurate records of study activity and drug accountability for study-related monitoring, audits, IRB/REB/IEC reviews and regulatory inspections; will report SAEs to the Sponsor or designee and IRB/ REB/IEC according to the specifics outlined in this protocol; will personally conduct or supervise the study; and will ensure that colleagues participating in the study are informed about their obligations in meeting the above commitments.

12.11. Sponsor Responsibilities

A complete list of the Sponsor responsibilities is outlined in the clinical trial research agreement and in the laws and regulation of the country in which the research is conducted. In summary, the Sponsor will select qualified Investigators, provide them with the information they need to properly conduct the study, ensure adequate monitoring of the study, conduct the study in accordance with the general investigational plan and protocols and promptly inform Investigators, health and regulatory agencies/authorities as appropriate of significant new adverse effects or risks with respect to the drug.

12.12. Financial Disclosure

A separate financial agreement will be made between each Principal Investigator and Pharmacyclics or its authorized representative before the study drug is delivered.

For this study, each Investigator and Subinvestigator (as designated on the Form FDA1572) will provide a personally signed Financial Disclosure Form in accordance with § 21 CFR 54. Each Investigator will notify Pharmacyclics or its authorized representative of any relevant changes in financial disclosure information during the conduct of the study and for 1 year after the study has been completed.

12.13. Liability and Clinical Trial Insurance

In the event of a side effect or injury, appropriate medical care as determined by the Investigator/designee will be provided.

If a bodily injury is sustained, resulting directly from the use of the study drug, Pharmacyclics will reimburse for reasonable physician fees and medical expenses necessary for treatment of only the bodily injury which is not covered by the subject's medical or hospital insurance, provided that the injury is not due to a negligent or wrongful act or omission by the Investigator/

study staff. The ICF will include a description of this reimbursement policy, incorporating country-specific national regulations and/or local laws. Financial compensation for lost wages, disability or discomfort due to the study is not available.

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

12.14. Protocol Amendments

Pharmacyclics will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB/REB/IEC together with, if applicable, a revised model ICF. Written documentation of IRB/REB/IEC and required site approval must be received by Pharmacyclics before the amendment may take effect at each site. Additionally under this circumstance, information on any change in risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand and sign each revised ICF confirming willingness to remain in the trial.

No other significant or consistent change in the study procedures, except to eliminate an immediate hazard, shall be effected without the mutual agreement of the Investigator and Pharmacyclics.

12.15. Publication of Study Results

Pharmacyclics may use the results of this clinical study in registration documents for Regulatory Authorities in the US or abroad. The results may also be used for papers, abstracts, posters, or other material presented at scientific meetings or published in professional journals or as part of an academic thesis by an Investigator. In all cases, to avoid disclosures that could jeopardize proprietary rights and to ensure accuracy of the data, Pharmacyclics reserves the right to preview all manuscripts and abstracts related to this study, allowing Pharmacyclics sufficient time to make appropriate comments before submission for publication.

In most cases, the Investigators at the sites with the highest accruals of eligible subjects shall be listed as lead authors on manuscripts and reports of study results. The Medical Monitor, study director and/or lead statistician may also be included in the list of authors. This custom can be adjusted upon mutual agreement of the authors and Pharmacyclics and in accordance with current standards for authorship as recorded in professional conference and journal submission instructions.

12.16. Study Discontinuation

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, both the Sponsor and the Investigator will arrange discontinuation procedures. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

13. REFERENCES

Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. J Clin Oncol 2012;31:88-94.

Measurement of Therapeutic Response in Chronic Graft-versus-Host Disease. American Society for Blood and Marrow Transplantation (ASBMT) Web site. http://www.asbmt.org/?29. Accessed April 9, 2014.

Anasetti C, Logan BR, Lee SJ, et al. Increased incidence of chronic graft-versus-host disease (GVHD) and no survival advantage with filgrastim-mobilized peripheral blood stem cells (PBSC) compared to bone marrow (BM) transplants from unrelated donors: results of Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Protocol 0201, a Phase III, prospective, randomized trial. ASH Annual Meeting Abstracts 2011;118: Abstract 1.

Appelbaum FR, Haematopoietic cell transplantation as immunotherapy. Nature 2001; 411:385-9.

Arai S, Jagasia M, Storer B, et al. Global and organ-specific chronic graft-versus-host disease severity according to the 2005 NIH Consensus Criteria. Blood. 2011;118:4242-49.

Arai S, Sahaf B, Narasimhan B, et al. Prophylactic rituximab after allogeneic transplantation decreases B-cell alloimmunity with low chronic GVHD incidence. Blood 2012;119:6145-6154.

Baird K, Pavletic SZ. Chronic graft versus host disease. Curr Opin Hematol. 2006;13:426-435.

Bishop GA, Haxhinasto SA, Stunz LL, et al. Antigen-specific B-lymphocyte activation. Crit Rev Immunol 2003;23:165–197.

Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia. N Engl J Med 2013;369:32-42.

Canninga-van Dijk MR, van er Straaten HM. Fijnheer R, et al. Anti-CD20 monoclonal antibody treatment in 6 patients with therapy-refractory chronic graft-versus-host diseae. Blood. 2004; 104:2603-2606.

Child CG, Turcotte JG. “Surgery and portal hypertension”. In Child CG. The liver and portal hypertension. Philadelphia:Saunders. 1964. pp. 50-64. Chronic GVHD Activity Assessment-Clinician. Source: http://asbmt.affiniscape.com/associations/11741/files/ResponseCriteriaAPPENDIXAFormA.pdf

Chronic GVHD Activity Assessment - Patient Self Report. Source: http://asbmt.affiniscape.com/associations/11741/files/ResponseCriteriaAPPENDIXBFormB.pdf

Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03, Published June 14, 2010.

Couriel DR, Saliba R, Escalón MP, et al. Sirolimus in combination with tacrolimus and corticosteroids for the treatment of resistant chronic graft-versus-host disease. Br J Haematol 2005;130:409-17.

Cutler C, Miklos D, Kim HT et al. Rituximab for steroid-refractory chronic graft-vs.-host disease. Blood 2006;108:756-762.

Dubovsky JA, Beckwith KA, Natarajan G, et al. Ibrutinib is an irreversible molecular inhibitor of ITK driving a Th1 selective pressure in T-lymphocytes. Blood. 2013;122:2539-49.

Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant 2005;11:945-956.

Flowers ME, Apperley JF, van Besien K, et al. A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. Blood 2008a; 112: 2667-74.

Flowers ME, Storer B, Carpenter P, et al. Treatment change as a predictor of outcome among patients with classic chronic graft-versus-host disease. Biol Blood Marrow Transplant. 2008b;14:1380-1384.

Fraser CJ, Bhatia S, Ness K, et al. Impact of chronic graft-versus-host disease on the health status of hematopoietic cell transplantation survivors: a report from the Bone Marrow Transplant Survivor Study. Blood 2006; 108: 2867-73.

Gilman AL, Chan KW, Mogul A, et al. Hydroxychloroquine for the treatment of chronic graft-versus-host disease. Biol Blood Marrow Transplant 2000;6:327-34.

Hale GA, Shrestha S, Le-Rademacher J, et al. Alternate donor hematopoietic cell transplantation (HCT) in non-Hodgkin lymphoma using lower intensity conditioning: A Report from the CIBMTR. Biol Blood Marrow Transplant 2012;18:1036-1043.

Herman SE, Gordon AL, Hertlein E, et al. Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by PCI-32765. Blood. 2011;117:6287-96.

Holler E. Risk assessment in haematopoietic stem cell transplantation: GvHD prevention and treatment. Best Pract Res Clin Haematol. 2007;20:281-294.

ICH-E2A, Federal Register, Vol 60, No.40, March, 1995.

Inamoto, Y, Storer, BE, Lee, SJ et al. Failure-free survival after second-line systemic treatment of chronic graft-versus-host disease. Blood 2013;121:2340-6.

Investigator's Brochure. Ibrutinib. Version 9: 30June 2015. Pharmacyclics LLC; Janssen Research & Development, LLC.

Jaglowski SM, Vasu S, Geyer S, et al. Immune Reconstitution at Days 30 and 100 following allogeneic stem cell transplant and association with subsequent development of chronic graft-versus-host disease. ASH Annual Meeting Abstracts;2012;120:1949.

Johnston LJ, Brown J, Shizuru JA, et al. Rapamycin (sirolimus) for treatment of chronic graft-versus-host disease. Biol Blood Marrow Transplant 2005;11:47-55.

Koc S, Leisenring W, Flowers ME, et al. Therapy for chronic graft-versus-host disease: a randomized trial comparing cyclosporine plus prednisone versus prednisone alone. Blood 2002;100:48-51.

Kulkarni S, Powles R, Sirohi B, et al. Thalidomide after allogeneic haematopoietic stem cell transplantation: activity in chronic but not in acute graft-versus-host disease. Bone Marrow Transplant 2003;32:165-70.

Lee cGVHD Symptom Scale. http://www.uniklinikum-regensburg.de/imperia/md/content/kliniken-institute/haematologie-onkologie/gvhd/deutsch/lee-symptom_scale.pdf

Lee JW, Deeg HJ. Prevention of chronic GVHD. Best Pract Res Clin Haematol. 2008;21:259-270.

Lee SJ, Kim HT, Ho VT, et al. Quality of life associated with acute and chronic graft-versus-host disease. Bone Marrow Transplant 2006;38:305-10.

Lee SJ, Klein JP, Barrett AJ, et al. Severity of chronic graft-versus-host disease: association with treatment-related mortality and relapse. Blood 2002;100: 406-14.

Lee SJ, Vogelsang G, Flowers ME. Chronic graft-versus-host disease. Biol Blood Marrow Transplant. 2003;9:215-233.

Lee SJ. Have we made progress in the management of chronic graft-vs-host disease? Best Pract Res Clin Haematol. 2010;23:529-535.

Logan A, Sahaf B, Zhang B, et al. Impaired B Cell clonotype diversification after allogeneic hematopoietic cell transplantation predicts graft-versus-host disease. Biol Blood Marrow Transplant 2013;19:S148-S149.

Martin PJ, Storer BE, Rowley SD, et al. Evaluation of mycophenolate mofetil for initial treatment of chronic graft-versus-host disease. Blood 2009;113:5074-82.

Miklos DB, Kim H, Zorn E, et al. Antibody Response to DBY minor histocompatibility antigen is induced after allogenic stem cell transplantation and in normal female donors. Blood 2004;103:353-359.

Miklos DB, Kim HT, Miller KH et al. Antibody responses to H-Y minor histocompatibility antigens correlate with chronic graft-versus-host disease and disease remission. Blood 2005;105:2973-2978.

Mohamed AJ, Yu L, Backesjo CM, et al. Bruton's tyrosine kinase (Btk): function, regulation, and transformation with special emphasis on the PH domain. Immunol Rev. 2009;228:58-73.

Mohty M, Marchetti N, El-Cheikh J, et al. Rituximab as salvage therapy for refractory chronic GVHD. Bone Marrow Transplant 2008;41:909-911.

Morris SC, Cheek RL, Cohen PL, Eisenberg RA. Allotype-specific immunoregulation of autoantibody production by host B cells in chronic graft-versus host disease. J Immunol. 1990;144:916-922.

Ofran Y, Kim HT, Brusic V, et al. Diverse patterns of T cell response against multiple newly identified human Y chromosome encoded minor histocompatibility epitopes. Clin Cancer Res 2010; 16: 1642-51.

Pan Z, Scheerens H, Li SJ, et al. Discovery of selective irreversible inhibitors for Bruton's tyrosine kinase. ChemMedChem 2007;2:58-61.

Parker PM, Chao N, Nademanee A, et al. Thalidomide as salvage therapy for chronic graft-versus-host disease. Blood 1995; 86:3604-9.

Pavletic SZ, Martin P, Lee SJ, et al. Measuring therapeutic response in chronic graft-versus-host-disease: national institutes of health consensus development project on criteria for clinical trials in chronic graft-versus-host-disease: IV. Response criteria working group report. Biol. Blood Marrow Transplant. 2006;12:252-66.

Perez-Simon JA, Kottaridis PD, Martino R, et al. Nonmyeloablative transplantation with or without alemtuzumab: comparison between 2 prospective studies in patients with lymphoproliferative disorders. Blood. 2002;100:3121-3127.

Pidala J, Kurland B, Chai X, et al. Patient-reported quality of life is associated with severity of chronic graft-versus-host disease as measured by NIH criteria: report on baseline data from the Chronic GVHD Consortium. Blood. 2011;117:4651-4657.

Pugh RN, Murray-Lyon IM, Dawson L, Pietroni MC, Williams R . "Transection of the oesophagus for bleeding oesophageal varices". *The British journal of surgery*, 1973;60: 646-9.

Ratanatharathorn V, Ayash L, Reynolds C, et al. Treatment of chronic graft-versus-host disease with anit-CD20 chimeric monoclonal antibody. Biol Blood Marrow Transplant. 2003;9:505-511.

Response Criteria for Partial Response and Progression in cGVHD. http://asbmt.affiniscape.com/associations/11741/files/ResponseCriteriaAPPENDIXC_DCalculations.pdf

Sahaf B, Arai S, Otani J, et al. Rituximab Provides Steroid-Sparing Therapy in New-Onset Chronic Graft-Versus-Host Disease. ASBMT 2013 (manuscript in preparation).

Sarantopoulos S, Stevenson KE, Kim HT, et al. Altered B-cell homeostasis and excess BAFF in human chronic graft-versus-host disease. Blood. 2009;113:3865-3874.

Satterthwaite AB, Witte ON. The role of Bruton's tyrosine kinase in B cell development and function: a genetic perspective. Immunol Rev 2000;175:120-7.

Schroeder MA, DiPersio JF. Mouse models of graft-versus-host disease: advances and limitations. Dis Model Mech;2011;4:318-333.

Shimabukuro-Vornhagen A, Hallek MJ, Storb RF, von Bergwelt-Baildon MS. The role of B cells in the pathogenesis of graft-versus-host disease. Blood. 2009;114:4919-4927.

Shinners NP, Carlesso G, Castro I, et al. Bruton's Tyrosine Kinase Mediates NF-kappa B Activation and B Cell Survival by B Cell-Activating Factor Receptor of the TNF-R Family. The Journal of Immunology. 2007;179:3872-3880.

Shulman HM, Kleiner D, Lee SJ, et al. Histopathologic diagnosis of chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: II. Pathology Working Group Report. Biol Blood Marrow Transplant 2006;12:31-47.

Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline. J Clin Oncol 2006;24:3187-205.

Socie G, Stone JV, Wingard JR, et al. Long-term survival and late deaths after allogeneic bone marrow transplantation. Late Effects Working Committee of the International Bone Marrow Transplant Registry. N Engl J Med. 1999;341:14-21.

Sullivan KM, Witherspoon RP, Storb R, et al. Prednisone and azathioprine compared with prednisone and placebo for treatment of chronic graft-v-host disease: prognostic influence of prolonged thrombocytopenia after allogeneic marrow transplantation. Blood 1988;72:546-54.

Sutherland HJ, Fyles GM, Adams G et al. Quality of life following bone marrow transplantation: a comparison of patient reports with population norms. Bone Marrow Transplant. 1997;19:1129-1136.

Syrjala KL, Martin PJ, Lee SJ. Delivering care to long-term adult survivors of hematopoietic cell transplantation. J Clin Oncol. 2012;30:3746-51.

Thomas ED, Lochte HL Jr, Lu WC, Ferrebee JW. Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. N Engl J Med 1957; 257:491-6.

14. APPENDICES

Appendix A. Schedule of Assessments

	Screening Phase	Treatment Phase								Post-Treatment/ Follow-up Phase	
Study Weeks		**1**	**1**	**2**	**5**	**9, 13, 17, 21, 25 q4 weeks**	**37 and every 12 weeks thereafter**	**Progressive Disease Visit**	**End-of-Treatment Visit (30 days from last dose of study drug)**	**Response Follow-up Visits (Until progressive disease) q12 weeks**	**Survival Follow-up q12 weeks**
Study Day of study week		1	2	1	1	1	1				
Study Windows	*-42 days*	*On time*		*±3 days*				*anytime*	*± 7 days*	*± 7 days*	*± 7 days*
Study Drug Administration											
ibrutinib 420mg/280mg/140mg dispensing		x			x	x	x				
ibrutinib administration		*Continuous daily dosing*									
Administrative Procedures											
Informed consent	x										
Confirm eligibility/enrollment checklist	x	x									
Medical history and Demographics	x										
GVHD/Transplant History	x										
Safety Assessments											
DLT Assessment (Phase 1b)					x						
Physical exam (height at Screening only)	x[a]	x[a]		x[b]	x[a]	x[b]	x[a]	x[a]	x[a]	x[b]	
KPS status	x	x			x	x	x	x	x	x	
Vital signs	x	x		x	x	x	x	x	x	x	
Oxygen saturation/PFT[c]	x										
Survival											x
ECG [d]	x	If clinically indicated (eg, subjects with palpitations, lightheadedness)									
Clinical Laboratory Assessments											
Hematology	x	x		x	x	x	x	x	x	x	
Serum Chemistry	x	x		x	x	x	x	x	x	x	
Coagulation (PT, INR, and aPTT)	x										
Pregnancy test [e]	x	x									
Hepatitis serologies	x										
Donor/host chimerism	x					Weeks 13, 25	x	x	x	x	
Quantitative serum immunoglobulins (IgA, IgG and IgM)	x					Weeks 13, 25	x	x	x		
Immunosupressant Levels	x	As needed during treatment									
PK		x[g]	x[g]	x[g]							
PD		x[h]	x[h]	x[h]		Week 9, 13					

	Screening Phase	Treatment Phase								Post-Treatment/ Follow-up Phase	
Study Weeks		**1**	**1**	**2**	**5**	**9, 13, 17, 21, 25 q4 weeks**	**37 and every 12 weeks thereafter**	**Progressive Disease Visit**	**End-of-Treatment Visit (30 days from last dose of study drug)**	**Response Follow-up Visits (Until progressive disease) q12 weeks**	**Survival Follow-up q12 weeks**
Study Day of study week		1	2	1	1	1	1				
Study Windows	*-42 days*	*On time*			*±3 days*			*anytime*	*± 7 days*	*± 7 days*	*± 7 days*
Efficacy Assessments											
cGVHD Assessment (NIH Form)	x	x			x	Weeks 13, 25	x	x	x	x	
Lee cGVHD Symptom Scale [f]	x	x			x	Weeks 13, 25	x	x	x	x	
Photographic imaging of cGVHD symptoms		x			x	Weeks 13, 25	x	x	x	x	
Corticosteroid Requirements	x	x		x	x	x	x	x	x	x	
Ongoing Subject Assessments											
Concomitant medications	x	Continuous from Informed Consent to 30 days after last dose of study drug									
Adverse events	x	Continuous from Informed Consent to 30 days after last dose of study drug									
Biomarkers											
T/B/NK cell counts	x[i]	x[i]	x[i]	x[i]		Week 9, 13					
Biomarkers		x			x	Weeks 13, 25	Weeks 37, 49		x		

Abbreviations: AEs=adverse events; aPTT=activated partial thromboplastin time; ECG=electrocardiogram; KPS=Karnofsky Performance Status; EOT=end-of-treatment; INR=international normalized ration; PD=pharmacodynamic; PK=pharmacokinetics; PO=orally; PT=prothrombin time; q4 weeks=every 4 weeks; q12 weeks=every 12 weeks

Footnote:

a. Physical Examination includes: general appearance of subject, examination of skin, eyes and fundi, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system.

b. Only a limited symptom-directed physical examination is required. Review of symptoms should include inquiry of ocular symptoms; subjects should be referred to an ophthalmologist for a formal examination if any Grade ≥2 symptoms are reported.

c. Oxygen saturation by pulse oximeter is permitted. If not done, then PFT with FEV1 required within 6 months of Screening.

d. ECG's may be performed at the Investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset of dyspnea.

e. Women of childbearing potential only. Serum pregnancy test required at Screening and urine pregnancy test required at Day 1 prior to first dose. If the test result is positive, the pregnancy must be ruled out by ultrasound to be eligible.

f. Lee cGVHD Symptom Scale should be completed prior to any assessments, and before being clinically evaluated by the study nurse or physician.

g. Pharmacokinetic (PK) samples will be drawn for all subjects according to the schedule in Section 7.1.13.1. Additional PK samples will be collected for subjects treated with concomitant a moderate or strong CYP3A inhibitors while on ibrutinib treatment according to the schedule in Section 7.1.13.1.

h. Pharmacodynamic (PD) sampling for PCYC will be performed on selected days at predose and post-dose. Refer to Table 3 for more details.

i. T/B/NK sampling for PCYC will be performed on selected days at predose and post-dose. Refer to Table 4 for more details.

Appendix B. NIH Defined Diagnostic or Distinctive Features of Chronic GVHD

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive (Seen in Chronic GVHD, but Insufficient Alone to Establish a Diagnosis of Chronic GVHD)	Other Features*	Common (Seen with Both Acute and Chronic GVHD)
Skin	Poikiloderma Lichen planus-like features Sclerotic features Morphea-like features Lichen sclerosus-like features	Depigmentation	Sweat impairment Ichthyosis Keratosis pilaris Hypopigmentation Hyperpigmentation	Erythema Maculopapular rash Pruritus
Nails		Dystrophy Longitudinal ridging, splitting, or brittle features Onycholysis Pterygium unguis Nail loss (usually symmetric; affects most nails)†		
Scalp and body hair		New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) Scaling, papulosquamous lesions	Thinning scalp hair, typically patchy, coarse, or dull (not explained by endocrine or other causes) Premature gray hair	
Mouth	Lichen-type features Hyperkeratotic plaques Restriction of mouth	Xerostomia Mucocele Mucosal atrophy Pseudomembranes† Ulcers†		Gingivitis Mucositis Erythema Pain
Eyes		New onset dry, gritty, or painful eyes‡ Cicatricial conjunctivitis Keratoconjunctivitis sicca‡ Confluent areas of punctate keratopathy	Photophobia Periorbital hyperpigmentation Blepharitis (erythema of the eyelids with edema)	
Genitalia	Lichen planus-like features Vaginal scarring or stenosis	Erosions† Fissures† Ulcers†		
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 (infants and children)
Liver				Total bilirubin, alkaline phosphatase >2 ULN† ALT or AST >2 ULN†
Lung	Bronchiolitis obliterans diagnosed with lung biopsy	Bronchiolitis obliterans diagnosed with PFTs and radiology‡		BOOP

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive (Seen in Chronic GVHD, but Insufficient Alone to Establish a Diagnosis of Chronic GVHD)	Other Features*	Common (Seen with Both Acute and Chronic GVHD)
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures secondary to sclerosis	Myositis or polymyositis‡	Edema Muscle cramps Arthralgia or arthritis	
Hematopoietic and immune			Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hypergammaglobulinemia Autoantibodies (AIHA and ITP)	
Other			Pericardial or pleural effusions Ascites Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality or cardiomyopathy	

GVHD indicates graft-versus-host disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BOOP, bronchiolitis obliterans organizing pneumonia; PFTs, pulmonary function tests; AIHA, autoimmune hemolytic anemia; ITP, idiopathic thrombocytopenic purpura.

* Can be acknowledged as part of the chronic GVHD symptomatology if the diagnosis is confirmed.

† In all cases, infection, drug effects, malignancy, or other causes must be excluded.

‡ Diagnosis of chronic GVHD requires biopsy or radiology confirmation (or Schirmer test for eyes).

Source: Filipovich 2005

Appendix C. Karnofsky Performance Status Scores

%	Karnofsky Performance Status
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	Care for self. Unable to carry on normal activity or do active work.
60	Requires occasional assistance but is able to care for most of his or her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled; hospitalization is indicated though death not imminent.
20	Hospitalization necessary; very sick; active supportive treatment necessary.
10	Moribund; fatal processes progressing rapidly.
0	Dead.

Appendix D. Non-Investigational Treatments for cGVHD

Medications or procedures not considered to be investigational for the treatment of chronic graft-versus-host disease.

Cellcept
Cyclosporine
Etanercept or other FDA-approved TNFα inhibitors
Extracorpeal photophoresis (ECP)
Imatinib
Methotrexate
Pentostatin
Rituximab
Sirolimus
Tacrolimus

Appendix E. Lee cGVHD Symptom Scale

Identification (Name):_____ Date:_____

chronic GVHD Symptom Scale

By circling one (1) number per line, please indicate how much you have been bothered by the following problems in the past month:

SKIN:		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
1.	Abnormal skin color……..	0	1	2	3	4
2.	Rashes……	0	1	2	3	4
3.	Thickened skin…… ……...	0	1	2	3	4
4.	Sores on skin…….	0	1	2	3	4
5.	Itchy skin…….	0	1	2	3	4
EYES AND MOUTH:		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
6.	Dry eyes…….	0	1	2	3	4
7.	Need to use eye drops frequently..	0	1	2	3	4
8.	Difficulty seeing clearly……	0	1	2	3	4
9.	Need to avoid certain foods due to mouth pain…….	0	1	2	3	4
10.	Ulcers in mouth…….	0	1	2	3	4
11.	Receiving nutrition from an intravenous line or feeding tube....	0	1	2	3	4
BREATHING:		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
12.	Frequent cough…….	0	1	2	3	4
13. .	Colored sputum……	0	1	2	3	4
14.	Shortness of breath with exercise..	0	1	2	3	4
15.	Shortness of breath at rest……...	0	1	2	3	4
16.	Need to use oxygen……..	0	1	2	3	4

EATING AND DIGESTION:		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
17.	Difficulty swallowing solid foods….	0	1	2	3	4
18.	Difficulty swallowing liquids…….	0	1	2	3	4
19.	Vomiting…….	0	1	2	3	4
20.	Weight loss……	0	1	2	3	4
MUSCLES AND JOINTS:		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
21.	Joint and muscle aches.....….	0	1	2	3	4
22.	Limited joint movement…....…….	0	1	2	3	4
23.	Muscle cramps……..	0	1	2	3	4
24.	Weak muscles……...	0	1	2	3	4
Energy:		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
25.	Loss of energy…….	0	1	2	3	4
26.	Need to sleep more/take naps…..	0	1	2	3	4
27.	Fevers……	0	1	2	3	4
MENTAL AND EMOTIONAL:		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
28.	Depression……	0	1	2	3	4
29.	Anxiety……...	0	1	2	3	4
30.	Difficulty sleeping…….	0	1	2	3	4

Source:
http://www.uniklinikum-regensburg.de/imperia/md/content/kliniken-institute/haematologie-onkologie/gvhd/deutsch/lee-symptom_scale.pdf

Appendix F. Chronic GVHD Activity Assessment – Clinician

Guidelines for completing the Chronic GVHD Activity Assessment – Clinician Form:

EYES- If Schirmer's Tear test is not performed please complete the NIH eye score.

LUNGS-Complete full PFTs if possible but FEV1 is required.

--If FEV1 is normal at baseline, repeat assessment not required unless progression is suspected. Complete NIH lung score in place of FEV1 at each visit.

--If FEV1 is abnormal at baseline then reassessment Q12 weeks is required.

GRIP STRENGTH-Not necessary to complete

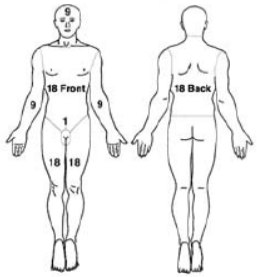
2 MIN WALK TEST-Complete only at baseline

RANGE OF MOTION—Complete photographic ROM score and NIH joint/fascia score

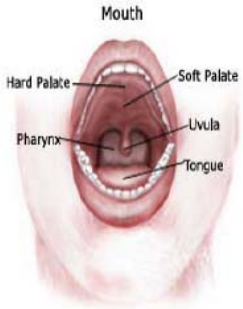
** If a change in score is considered to be due to a cause other than cGVHD please note and mark NE (not evaluable) for cGVHD score.

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

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN

Component	Findings	Scoring (see skin score worksheet)
Skin 	**Erythematous rash of any sort**	**% BSA (max 100%)**
	Moveable sclerosis	**% BSA (max 100%)**
	Non-moveable sclerosis (hidebound/non-pinchable) or subcutaneous sclerosis/fasciitis	**% BSA (max 100%)**
	Ulcer(s): select the largest ulcerative lesion, and measure its largest dimension in cm and mark location of ulcer	**Location: _____** **Largest dimension: _____cm**
Eyes Bilateral Schirmer's Tear Test (without anesthesia) in persons 9 years or older	Right Eye: mm of wetting	Left Eye: mm of wetting

Mouth



Mucosal change	No evidence of cGVHD		Mild		Moderate		Severe	
Erythema	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3
Lichenoid	None	0	Hyperkeratotic changes(<25%)	1	Hyperkeratotic changes(25-50%)	2	Hyperkeratotic changes (>50%)	3
Ulcers	None	0	None	0	Ulcers involving (≤20%)	3	Severe ulcerations (>20%)	6
Mucoceles*	None	0	1-5 mucoceles	1	6-10 scattered mucoceles	2	Over 10 mucoceles	3
			*Mucoceles scored for lower labial and soft palate only				**Total score for all mucosal changes**	

Blood Counts	Platelet Count K/uL	ULN K/uL	Total WBC K/uL	ULN K/uL	% Eosinophils %			
Liver Function Tests	Total serum bilirubin mg/dL	ULN mg/dL	ALT U/L	ULN U/L	Alkaline Phosphatase U/L	ULN U/L		

Gastrointestinal-Upper • 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-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-Lower = • 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 • Bronchiolitis Obliterans	Pulmonary Function Tests with Diffusing Capacity (attach report for person> 5 yrs old)	FEV-1 % Predicted	Single Breath DLCO (adjusted for hemoglobin) % Predicted
Health Care Provider Global Ratings: **In your opinion, do you think that this patient's chronic GVHD is mild, moderate or severe?** 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 past month 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

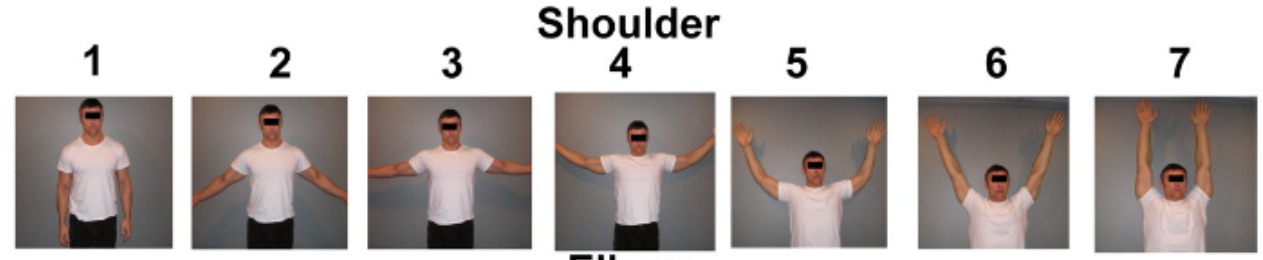
Functional Performance (in persons >4 years old) • Walk Time • Grip Strength	Total Distance Walked in 2 Minutes: Number of laps: _____ (x 50 feet) + final partial lap: _____ feet = _____ feet walked in 2 minutes	Grip Strength (Dominant Hand) Trial #1 psi	Trial #2 psi	Trial #3 psi	Range of Motion: o Not performed o Physical Therapy Report Attached

Score	Lansky Performance Status Scale Definitions (circle from 0-100) (persons < 16 years old)	Karnofsky Performance Status Scale Definitions (circle from 0-100) (persons 16 years or older)
100	Fully active, normal	Normal no complaints; no evidence of disease
90	Minor restrictions in physically strenuous activity	Able to carry on normal activity; minor signs or symptoms of disease
80	Active, but tires more quickly	Normal activity with effort; some signs or symptoms of disease
70	Both greater restriction of and less time spent in play activity	Cares for self; unable to carry on normal activity or to do active work
60	Up and around, but minimal active play; keeps busy with quieter activities	Requires occasional assistance but is able to care for most personal needs
50	Gets dressed but lies around much of the day, no active play but able to participate in all quiet play and activities	Requires considerable assistance and frequent medical care
40	Mostly in bed; participates in quiet activities	Disabled; requires special care and assistance
30	In bed; needs assistance even for quiet play	Severely disabled; hospital admission is indicated although death not imminent
20	Often sleeping; play entirely limited to very passive activities	Very sick; hospital admission necessary; active supportive treatment necessary
10	No play; does not get out of bed	Moribund; fatal processes progressing rapidly
0	Unresponsive	Dead

Source: http://asbmt.affiniscape.com/associations/11741/files/ResponseCriteriaAPPENDIXAFormA.pdf

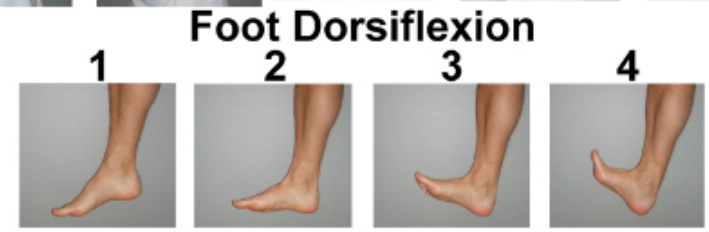
	Score 0	Score 1	Score 2	Score 3
JOINTS AND FACIA	□ No Symptoms	□ Mild tightness of arms or legs, normal or mild decreased range of motion(ROM) AND not affecting ADL	□ Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation 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):_____				
	Score 0	Score 1	Score 2	Score 3
EYES	□ No symptoms	□ Moderate dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	□ Moderate dry eye symptoms partially affecting ADL, (requiring eye drops > 3 x per day or punctual 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):_____				
	Score 0	Score 1	Score 2	Score 3
LUNGS	□ No symptoms	□ Mild symptoms (shortness of breath after climbing one flight of steps)	□ Moderate symptoms (shortness of breath after walking on flat surface)	□ Severe symptoms (shortness of breath at rest; requiring O_2)
□ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				

RANGE OF MOTION:



□ Not done

□ Not done



□ Not done

Appendix G. Chronic GVHD Activity Assessment – Patient Self Report

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?											
Your mouth dryness at its WORST?											
Your mouth sensitivity at its WORST?											

Eyes	**What is your main complaint with regard to your eyes?**	
	Please rate how severe is this eye symptom, between 0 (not at all severe) and 10 (most severe):	**0 1 2 3 4 5 6 7 8 9 10**
Vulvovaginal Symptoms (females only)	**Do you have any burning, pain or discomfort in the area of your vagina, vulva or labia?** **OR** **Do you have any discomfort or pain with sexual intercourse?**	o **Yes** o **No** o **Not applicable**

Patient Global Ratings:

1. Overall, do you think that your chronic graft versus host disease is mild, moderate or severe?
0= none
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 — Most severe cGVHD severe 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

Attach copies of:

Adults (persons 18 years or older):
- o Lee cGvHD Symptom Scale
- o Human Activity Profile
- o SF-36 v.2
- o FACT-BMT

Children/Adolescents (persons 17 years or younger):
- o Lee cGVHD Symptom Scale (persons 8-12 years old may complete with help of the health care professional)
- o ASK - Activities Scale for Kids
- o CHRIs - Generic and Disease Specific Inventory

Source: http://asbmt.affiniscape.com/associations/11741/files/ResponseCriteriaAPPENDIXBFormB.pdf

Appendix H. Response Criteria for Partial Response and Progression in cGVHD

Proposed calculations for partial response in chronic GVHD

Organ and Starting Score or Value	Partial Response Criterion*
Skin (percent of body surface)	
> 50	e/s ≤ 0.5 and e > 0
25 – 50	s – e ≥ 25 and e > 0
< 25	only CR; no PR possible
Eye (mm Schirmer's test)	
< 5 mm	e – s ≥ 5 mm and e < LLN
5 – 10 mm	only CR; no PR possible
Mouth (15-point Schubert scale)	
≥8	e/s ≤ 0.5 and e > 0
4 – 7	s – e ≥ 4 and e > 0
< 4	only CR; no PR possible
Platelet count	e – s ≥ 100,000/uL and e < LLN
Gastrointestinal (and other 0 – 3 scales)†	
3	e = 1 or 2
2	e = 1
1	only CR; no PR possible
Liver function tests (ALT, alkaline phosphatase and bilirubin) and eosinophil count	
≥ 3x ULN	e/s ≤0.5 and e > ULN
< 3 x ULN	only CR; no PR possible

* s, starting score or value; e, ending score or value; ULN, upper limit of normal; LLN, lower limit of normal

† The proposed response criterion could be appropriate for shorter-term phase II studies. For longer-term pivotal phase III studies, a 1-point change might not be sufficient for PR.

Examples :

1. Skin: start score = 85, end score = 30; e/s = 30/85 = 0.35 = PR
2. Skin: start score = 65, end score = 45; e/s = 45/65 = 0.75 = not PR
3. Skin: start score = 45, end score = 15; s – e = 30 = PR
4. Skin: start score = 30, end score = 15; s – e = 15 = not PR

Appendix H. Response Criteria for Partial Response and Progression in cGVHD (Cont'd)

Proposed calculations for progression in chronic GVHD

Organ and Starting Score or Value	Progression Criterion*
Skin (percent of body surface)	e – s ≥ 25
Eye	s – e ≥ 5 mm
Mouth (15-point Schubert scale)	e – s ≥ 3
Platelet count	s – e ≥ 50,000/uL and e < LLN
Gastrointestinal (and other 0 – 3 scales)	e – s ≥ 1
Liver (ALT, alkaline phosphatase and bilirubin), eosinophil count	
s ≥ 3x ULN	e – s ≥ 3 x ULN
s < 3x ULN	e – s ≥ 2 x ULN
Lungs (12-point Lung Function Scale)	e – s ≥ 3†

****Score changes from 0 to 1 are not considered progression.**

*s, starting score or value; e, ending score or value; ULN, upper limit of normal
† If the starting lung function score is ≥ 10, progression is defined as ≥ 5% decrease of FEV1 in two tests measured at least 2 weeks apart. This time interval was selected because these syndromes can progress rapidly.
http://asbmt.affiniscape.com/associations/11741/files/ResponseCriteriaAPPENDIXC_DCalculations.pdf

Appendix I. Guidelines for Chronic GVHD Activity Assessment – Clinician (FORM A)

Any measure that is normal and does not have cGVHD involvement at Day 1 = NE (not evaluable), remains NE unless criteria for PD is met.

Any measure that changes but is not felt to be related to cGVHD should be marked as NE. Organs with more than one component will have each component evaluated, and then an organ score will be assigned.

Overall cGVHD assessment: SD: no PR, no PD, no CR
PR: if no PD and ≥1 PR
PD: if ≥1 PD
CR: all CR

Measures	Individual Response*	Overall organ response
Skin (percent of body surface) Body surface area of erythematous rash		NE: no cGVHD SD: no PR, no PD, no CR PR: if no PD and ≥1 PR PD: if ≥1 PD CR: all CR
Skin Body surface area of moveable sclerosis		
Skin Body surface area of non-moveable sclerosis		
Eyes – Right eye Schirmer Tear Test (mm wetting)		NE: no cGVHD SD: no PR, no PD, no CR PR: if no PD and ≥1 PR PD: if ≥1 PD CR: all CR
Eyes – Left Eye Schirmer Tear Test (mm wetting)		
Mouth Mucosal change (Scores range from 0-15)		NE: no cGVHD SD: no PR, no PD, no CR PR PD CR
Blood Counts Platelet count and absolute eosinophil count		NE: no cGVHD SD: no PR, no PD, no CR PR: if no PD and ≥1 PR PD: if ≥1 PD CR: all CR
Liver Function Tests ALT, total serum bilirubin and alkaline phosphatase		NE: no cGVHD SD: no PR, no PD, no CR PR: if no PD and ≥1 PR PD: if ≥1 PD CR: all CR
GI – Upper		NE: no cGVHD SD: no PR, no PD, no CR PR: if no PD and ≥1 PR PD: if ≥1 PD CR: all CR
GI – Esophageal		
GI – Lower		
Lung response Pulmonary Function Tests with Diffusing Capacity, FEV1 and DLCO		NE: no cGVHD SD: no PD PD No possible PR or CR
Overall cGVHD Response		SD: no PR, no PD, no CR PR: if no PD and ≥1 PR PD: if ≥1 PD CR: all CR

*See Appendix H for individual response

Appendix J. Inhibitors and Inducers of CYP3A

Inhibitors and inducers 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 6.2.1 on instructions for concomitant use of CYP3A inhibitors and inducers with ibrutinib.

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

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

Appendix K. Child-Pugh Score

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

Source:

1. Child CG, Turcotte JG. "Surgery and portal hypertension". In Child CG. The liver and portal hypertension. Philadelphia:Saunders. 1964. pp. 50-64.
2. Pugh RN, Murray-Lyon IM, Dawson L, Pietroni MC, Williams R . "Transection of the oesophagus for bleeding oesophageal varices". The British journal of surgery, 1973;60: 646-9.