PROTOCOL

TITLE:	A Randomized, Double-Blind Phase 3 Study of Ibrutinib in Combination With Corticosteroids versus Placebo in Combination With Corticosteroids in Subjects with New Onset Chronic Graft Versus Host Disease (cGVHD)
PROTOCOL NUMBER:	**PCYC-1140-IM**
STUDY DRUG:	Ibrutinib (PCI-32765)
IND NUMBER:	102,688
EudraCT NUMBER:	**2016-003286-26**
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SPONSOR:	Pharmacyclics LLC 995 East Arques Avenue Sunnyvale, CA 94085-4521 United States of America
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Amendment 1 Date:	25 October 2016
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Amendment 3 Date:	06 February 2019

PROTOCOL APPROVAL PAGE

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Study Number: **PCYC-1140-IM**

Protocol Date: 11 August 2016

Amendment 1 Date: 25 October 2016

Amendment 2 Date: 03 October 2017

Amendment 3 Date: 6 February 2019

I have carefully read Protocol PCYC-1140-IM entitled "A Randomized, Double-Blind Phase 3 Study of Ibrutinib in Combination with Corticosteroids versus Placebo in Combination with Corticosteroids in Subjects with New Onset Chronic Graft Versus Host Disease (cGVHD)".

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:

[redacted] [redacted]

Date

Clinical Development, Pharmacyclics LLC

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SYNOPSIS

Study Title:	A Randomized, Double-Blind Phase 3 Study of Ibrutinib in Combination With Corticosteroids versus Placebo in Combination With Corticosteroids in Subjects with New Onset Chronic Graft Versus Host Disease (cGVHD)
Protocol Number:	PCYC-1140-IM
Study Phase:	3
Study Duration:	Estimated to be up to 7 years
Investigational Product and Reference Therapy:	**Ibrutinib (IMBRUVICA®)** will be supplied as 70 mg and 140 mg hard gelatin capsules for oral (PO) administration. Placebo will be supplied as hard gelatin capsules and will look identical to ibrutinib capsules.
Objectives:	**Primary Objective:** To evaluate the efficacy of ibrutinib in combination with prednisone (Arm A) versus placebo in combination with prednisone (Arm B) based on the response rate at 48 weeks (the proportion of responders [CR or PR]) as determined by NIH Consensus Development Project criteria in subjects with new onset moderate to severe cGVHD. **Secondary Objectives:** To compare the two treatment arms in terms of the following: ***Efficacy*** • Response rate at 24 weeks (the proportion of responders [CR or PR]) as defined by the NIH Consensus Development Project (2014) • Duration of response (DOR) • Proportion of subjects obtaining steroid dose level less than 0.15 mg/kg/d at 24 weeks • Time to withdrawal of all immunosuppressants (with the exception of ibrutinib/placebo) • Overall survival (OS) • Lee cGVHD symptom scale improvement ***Safety*** • Safety and tolerability • Differences in steroid-related morbidities (eg, hyperglycemia, hypertension)
Study Design:	This is a Phase 3, multicenter, international, randomized, double-blind study of oral ibrutinib in combination with prednisone versus placebo in combination with prednisone in subjects with new onset chronic GVHD. Approximately 186 subjects with newly diagnosed moderate or severe cGVHD, as defined by the NIH Consensus Development Project Criteria, will be randomized in a 1:1 ratio to receive either ibrutinib in combination with prednisone (Arm A) or placebo in combination with prednisone (Arm B). Treatment with ibrutinib/placebo will be administered continuously

	until unacceptable toxicity, progression of the underlying disease, death, or the start of a new systemic treatment for cGVHD. Ibrutinib/placebo can be discontinued after response in cGVHD disease symptoms and withdrawal of other systemic immunosuppressants (Section 5.3.1.6). Corticosteroid therapy will be tapered as per a standard taper regimen with the goal of reducing exposure to high-moderate dose corticosteroids as quickly as possible according to clinical severity of cGVHD. A standard steroid taper schedule is provided in the protocol as guidance for clinicians (Table 4). The primary endpoint is the response rate at 48 weeks. Response will be defined by the NIH Consensus Development Project Criteria (2014) and must occur: • In the absence of new therapy for cGVHD • In the absence of progression of the underlying disease that was the indication for transplant, or post-transplant lymphoproliferative disease (PTLD), or death Secondary endpoints will assess for additional clinical benefit including Week-24 response, DOR, corticosteroid dose reduction, time to withdrawal of all immunosuppressants, OS, and Lee cGVHD symptom scale. The randomization between arms will be stratified according to: • Age group (12 to <22 years old vs. ≥22 years old) • NIH Global Severity grade (moderate vs. severe) • Ongoing use of systemic immunosuppressants that were initiated for either treatment of or prophylaxis for acute GVHD (Yes vs. No)
Population:	• Subjects with new onset moderate or severe cGVHD as defined by the NIH Consensus Development Project Criteria (Jagasia 2015) • Subjects must be in need of systemic treatment for cGVHD with corticosteroids
Centers:	Multi-center, International
Inclusion Criteria:	Eligible subjects will meet all of the following criteria: 1. New onset moderate or severe cGVHD as defined by the NIH Consensus Development Project Criteria (2014, see Appendix M, Appendix N, Appendix O). 2. History of an allogeneic hematopoietic cell transplant. 3. Need for systemic treatment with corticosteroids for cGVHD. 4. No previous systemic treatment for cGVHD (including extracorporeal photopheresis [ECP]). 5. Participants may be receiving other immunosuppressants for the prophylaxis or treatment of acute GVHD but if the subject is receiving prednisone for prophylaxis or treatment of acute GVHD it must be at or below 0.5 mg/kg/d. 6. Participants may have received pre-transplant BTK inhibitors for other reasons besides cGVHD such as for the treatment of

	leukemia or lymphoma, but must not have received a BTK inhibitor since the time of transplant. 7. Age ≥12 years old. 8. Karnofsky or Lansky (subjects <16 years) performance score ≥60. 9. Adequate renal function defined as an estimated Creatinine Clearance ≥30 mL/min (Cockcroft-Gault formula) 10. Adequate hepatic function as defined by: • Total bilirubin of ≤ 1.5 x ULN (unless of non-hepatic origin or due to Gilbert's Syndrome) or • Total bilirubin of > 1.5 x ULN to 3.0 x ULN if due to GVHD 11. Adequate hematological function defined as: • Absolute neutrophil count ≥1.0 x 10^9/L and off growth factor support for 7 days • Platelets ≥30 x 10^9/L and no transfusion 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). When treated with warfarin or other vitamin K antagonist, then INR ≤3.0 (Section 6.2.3). *Ethical/Other* 13. Male and female subjects of reproductive potential who agree to use both a highly effective methods of birth control (eg, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence[1], or sterilized partner) and a barrier method (eg, condoms, cervical ring, sponge, etc.) during the period of therapy and for 90 days for both females and males after the last dose of study drug.
Exclusion Criteria:	Subjects are excluded if any of the following criteria are met: 1. Received any previous systemic treatment for cGVHD with the following exception: • Corticosteroids for cGVHD received within the 72 hours prior to signing the informed consent form. 2. Inability to begin a prednisone dose ≥0.5 mg/kg/d for the treatment of cGVHD. 3. Presence of single-organ, genito-urinary involvement with cGVHD as the only manifestation of cGVHD. 4. Received any investigational agent ≤28 days before randomization. 5. Received donor lymphocyte infusion (DLI) ≤56 days before randomization. 6. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart

[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

	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. 7. Any uncontrolled active systemic infection or active infection requiring systemic treatment that was ongoing ≤7 days before randomization. This does not include secondary prophylaxis of well controlled fungal infections, ongoing treatment of controlled viral reactivations (eg, CMV), or treatment or prophylaxis of controlled low-grade central line infections (eg, Staphylococcus epidermidis). 8. Progressive underlying malignant disease or active post-transplant lymphoproliferative disease. 9. 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 10. Subject has a concurrent illness which in the opinion of the investigator may interfere with the treatment and evaluation of the subject. 11. Known bleeding disorders (eg, von Willebrand's disease or hemophilia). 12. History of stroke or intracranial hemorrhage within 6 months prior to randomization. 13. Known history of human immunodeficiency virus (HIV). 14. Subject with chronic liver disease with hepatic impairment per Child-Pugh classification Class C (Appendix E). Please note that acute liver dysfunction due to cGVHD is not applicable to the evaluation of Child-Pugh classification. 15. Active hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody or hepatitis B surface antigen or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before randomization. Those who are PCR positive will be excluded. 16. Vaccinated with live, attenuated vaccines within 4 weeks of randomization. 17. Major surgery within 4 weeks of randomization. 18. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk. 19. 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. 20. Subjects requiring treatment with a strong CYP3A inducer are not eligible, unless a transition to an agent with less CYP3A induction is planned (Appendix D). 21. Female subject who is pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 3 months of last dose of study drug. Male subject who plans to father a child while enrolled in this study or within 3 months after the last dose of study drug. 22. Unwilling or unable to participate in all required study evaluations and procedures. 23. 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).
Study Treatment:	1:1 Randomization between Arm A and Arm B **Arm A:** Oral ibrutinib 420 mg daily (3 capsules) in combination with oral prednisone starting at 1 mg/kg/day until unacceptable toxicity, progression of underlying disease, death, or the need for a new systemic treatment for progressive cGVHD. **Arm B:** Oral matching placebo capsules daily (3 capsules) in combination with oral prednisone starting at 1 mg/kg/day until unacceptable toxicity, progression of underlying disease, death, or the need for a new systemic treatment for progressive cGVHD.
Concomitant Therapy:	Refer to Section 6 for information on concomitant therapy.
Safety Plan:	The safety of this study will be monitored by an independent data monitoring committee (DMC) as outlined in the DMC charter and in accordance with the Sponsor's Pharmacovigilance procedures.
Statistical Methods:	All efficacy analyses will be performed using the intent-to-treat (ITT) population. **Primary Efficacy Analysis:** The primary efficacy endpoint of this study is the response rate at 48 weeks (ie, the proportion of responders [CR or PR]). Response will be defined by the NIH Consensus Development Project Criteria (2014) and must occur: • In the absence of new systemic therapy for cGVHD • In the absence of progression of the underlying disease that was the indication for transplant, or death Response rates will be compared between the two treatment arms using the chi-square statistical test. **Secondary Efficacy Analysis:** • Response rate at 24 weeks (the proportion of responders [CR or PR]) as defined by the NIH Consensus Development Project

	(2014) • Duration of response (DOR) • Steroid dose reduction to a level of less than 0.15 mg/kg/d at 24 weeks: the proportion of subjects who have steroid dose reduced by 24 weeks will be compared between the two treatment arms • Time to withdrawal of all immunosuppressants (with the exception of ibrutinib/placebo) will be compared between the two treatment arms • Overall survival (OS): Overall survival will be compared between the two treatment arms using the log rank test • Improvement in Lee cGVHD symptom scale scores will be compared between the two treatment arms **Safety Analysis:** Safety data will be generated from the Safety Population (SP) which consists of all subjects randomized and receiving at least one dose of any study drug (ibrutinib or placebo). Detailed tabulations of safety data (adverse events, clinical laboratory tests and other safety endpoints) will be summarized by treatment arm for all subjects receiving study drug.
Interim Analysis:	An interim review for futility will be performed for the first 50 subjects who complete Week 25 visit or discontinue study drug before this time.
Sample Size Determination:	The null hypothesis is that the two treatment arms have the same response rate at 48 weeks and the alternative hypothesis is that the response rates of two arms are different. Assuming a response rate of 30% at 48 weeks for Arm B (placebo + prednisone), a sample size of 186 randomized subjects provides at least an 80% power to detect a 20% difference in the response rates at 48 weeks between the 2 treatment arms (Arm A – Arm B) at an alpha level of 5% (2-sided). The randomization between arms will be stratified according to: • Age group (12 to <22 years old vs. ≥22 years old) • NIH Global Severity grade (moderate vs. severe) • Ongoing use of systemic immunosuppressants that were initiated for either treatment of or prophylaxis for acute GVHD (Yes vs. No)

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASBMT	American Society for Blood and Marrow Transplantation
AST	aspartate aminotransferase
AUC	area under the curve
BAFF	B-cell activating factor
BCR	B-cell receptor
BTK	Bruton's tyrosine kinase
CFR	US Code of Federal Regulations
cGVHD	chronic graft versus host disease
CLL	chronic lymphocytic leukemia
CRF	case report form
CR	complete response
CTCAE v. 4.03	Common Terminology Criteria for Adverse Events version 4.03
CYP	cytochrome P450
DLI	donor lymphocyte infusion
DMC	data monitoring committee
DOR	Duration of response
ECG	Electrocardiogram
ECP	extracorporeal photopheresis
EDC	electronic data capture
EMR	electronic medical records
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
GCP	Good Clinical Practice
GI	gastrointestinal
GVHD	graft versus host disease
GVT	graft versus tumor
HCT	hematopoietic cell transplantation
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HPA	Hypothalamic-pituitary-adrenal
IB	Investigator's Brochure
IC_{50}	half maximal inhibitor concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IL	Interleukin
ILD	interstitial lung disease
INR	international normalized ratio
IRB	Institutional Review Board
ITK	IL-2 inducible T-cell kinase
ITT	intention-to-treat
IV	Intravenous
IWRS	Interactive Web Response System
KPS	Karnofsky Performance Status

MCL	mantle cell lymphoma
mITT	modified intention-to-treat
MZL	marginal zone lymphoma
SP	Safety population
MTD	maximum tolerated dose
NCI	National Cancer Institute
NIH	National Institutes of Health
NRM	non-relapse mortality
OS	overall survival
PCI-32765	ibrutinib or Imbruvica®
PCR	polymerase chain reaction
PCYC	Pharmacyclics LLC
PD	progressive disease
PK	pharmacokinetic
PO	oral
PR	partial response
PTLD	post-transplant lymphoproliferative disease
PT	prothrombin time
QD	daily
QOD	every other day
QTc	corrected QT interval
REB	Research Ethics Board
SAE	serious adverse event
SCARs	severe cutaneous adverse reactions
SD	stable disease
SF-36	36-Item Short Form Health Survey
SJS	Stevens - Johnson syndrome
$t_{1/2}$	half life
TEAE(s)	treatment-emergent adverse event(s)
TCR	T-cell receptor
TLS	tumor lysis syndrome
T_{max}	median time to maximum plasma concentration
ULN	upper limit of normal
USPI	United States Product Insert
VZIG	varicella zoster immune globulin
WM	Waldenström's macroglobulinemia

1. BACKGROUND

1.1. Disease/Histology

1.1.1. Disease Background

Since its first report in 1957, allogeneic hematopoietic cell transplant (HCT) has become a standard therapy for many hematologic malignancies and hematopoietic progenitor cell disorders (Thomas 1957). Hematopoietic cell transplant can cure patients with chemotherapy resistant malignancies through graft versus tumor (GVT) 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). In the U.S., approximately 8,000 allogeneic HCTs are now performed each year (Pasquini 2015). Roughly 35% of patients who have undergone HCT will develop cGVHD that requires systemic treatment (Flowers 2011). The prevalence of cGVHD is increasing due to both the increased use of allogeneic transplantation in older adults and the use of peripheral stem cells as a graft source. Chronic GVHD is a serious and life threatening impediment to the otherwise curative potential of HCT (Pidala 2011, Arai 2011, Baird 2006 and Lee 2003) and it is a leading cause of non-relapse mortality (NRM) (Lee 2008). Risk factors for developing cGVHD include prior acute GVHD, older age, use of peripheral blood stem cells, use of unrelated and mismatched donors, and lack of T-cell depletion (Lee 2008).

In the past, timing of manifestations of GVHD were used to classify GVHD into two subsets, acute GVHD classified as occurring within 100 days of HCT and chronic GVHD classified as manifestations beyond 100 days after HCT (Filipovich 2005). In 2005 the National Institutes of Health (NIH) sponsored a consensus development conference that proposed new criteria for diagnosis and classification of cGVHD for clinical trials (Filipovich 2005). The consensus met again in 2014 and proposed minor changes to the diagnostic criteria (Jagasia 2015). The published criteria for diagnosis emphasize the distinction between acute and chronic GVHD as different subsets of GVHD that can be distinguished by clinical manifestations and not time after transplant. The diagnosis of cGVHD is primarily clinical and requires at least one diagnostic sign in a target organ per NIH criteria (ie, a sign found only in cGVHD) or at least one distinctive sign (ie, a sign highly suggestive of cGVHD) in combination with some other laboratory, biopsy, or other test confirmation in the same or another organ. The diagnostic cGVHD findings include collagen-vascular changes involving the skin, mouth, genitalia, gastrointestinal tract, lung, muscle fascia, and joints (Jagasia 2015) (Appendix M). Pathologically, cGVHD is characterized by fibrosis and inflammation of affected organs (Shulman 2006).

Pathogenesis of Chronic Graft Versus Host Disease

The immunopathology underlying development of cGVHD can be quite variable and is not entirely characterized. Recent information implicates B cells as well as T cells in the generation of cGVHD (Sarantopoulos 2015, Allen 2014, Flynn 2014 and Johnston 2014). T cells have long

been 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 of underlying disease (Hale 2012, Perez-Simon 2002). Alloreactive T helper cells, including Th1, Th2, Th17, and T follicular helper cells, produce effector cytokines resulting in antibody deposition, tissue fibrosis, and autoimmunity.

More recently, alloreactive B cells have been implicated in the development of cGVHD (Sarantopoulos 2015, Allen 2014, Flynn 2014, Johnston 2014, Miklos 2005 and Miklos 2004). 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 (BAFF) of the tumor necrosis family, and donor-derived alloantibodies (Sarantopoulos 2009).

1.1.2. Current Treatment Options

Available therapy for cGVHD is primarily broad-spectrum immunosuppressants which increase the risk of infections and tumor relapse by inhibiting GVT immunity (Holler 2007). The initial and current standard of care treatment for cGVHD is corticosteroids. However, more than 50% of the patients eventually relapse or become refractory, requiring second-line treatment, for which there is no standard of care. Recently, ibrutinib received approval in the United States for the treatment of adult patients with cGVHD after failure of one or more lines of systemic therapy.

Treatment with immunosuppressants is typically needed for a median duration of 2 to 3 years, further contributing to morbidity (Syrjala 2012). During that time patients are likely to experience some or all of the side effects of corticosteroids which include more frequent infections, hypertension, hyperglycemia, decrease in bone density, avascular necrosis, adrenal insufficiency, cataracts and disturbed sleep patterns (Sullivan 1988, Rayos [Prednisone] USPI 2013). Because of the frequent morbidity associated with prolonged corticosteroid use, many other immunosuppressant agents have been investigated in cGVHD, both in the front line and second line setting. Several controlled, phase 3 studies where these agents have been added on to corticosteroid therapy were all unsuccessful in providing benefit despite showing efficacy in early phase studies (Gilman 2012, Martin 2009, Koc 2002, Arora 2001, Koc 2000, and Sullivan 1988). An analysis of clinical trial quality measures in 60 trials in cGVHD primarily conducted before the NIH standardized response criteria (Pavletic 2006) were developed,

revealed that poor study design (eg, lack of rigorous entry criteria, organ response criteria and overall response criteria) likely biased efficacy in the early phase trials (Martin 2011) thereby leading to later unsuccessful controlled studies with the same agents. Agents such as cyclosporine, tacrolimus, sirolimus, and/or mycophenolate mofetil are often added to corticosteroid therapy in both frontline and second line settings despite the lack of efficacy. There is a lack of standard of care and high unmet need for new therapeutic options to effectively suppress immune and fibrotic cascades while preserving GVT and immunity against infection.

While limited progress related to prevention or treatment of cGVHD has been made, the development of the NIH Consensus Criteria for grading and staging of cGVHD represents a significant advancement, providing a clinically useful disease burden measure for use in clinical trials (Jagasia 2015). In addition, the NIH Consensus Response Criteria have been shown to correlate with clinical outcomes (Olivieri 2013, Jacobsohn 2012).

1.2. 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 for the treatment of B-cell malignancies and cGVHD.

Ibrutinib has been approved in many regions, including the US and EU, for indications including treatment of patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy, patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), including CLL/SLL with a deletion of the short arm of chromosome 17 (del17p), patients with Waldenström's macroglobulinemia (WM), Marginal Zone Lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy, and cGVHD after failure of one or more lines of systemic therapy. For the most up to date and comprehensive nonclinical and clinical information regarding ibrutinib background, safety, efficacy, in vitro and in vivo preclinical activity, and toxicology of ibrutinib, always refer to the latest version of the ibrutinib Investigator's Brochure (IB) and/or the applicable regional labeling information.

1.2.1. Summary of Nonclinical Data

1.2.1.1. 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 (IC_{50} = 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 BCR and blocks primary B-cell activation (IC_{50} = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression (Herman 2011). In addition to BTK activity, ibrutinib inhibits ITK activity with a biochemical IC_{50} of 26.9 nM. Ibrutinib also blocks T cell receptor-induced IL-2 secretion

by a T cell line (Jurkat cells) with an EC_{50} of 200 nM. In CLL patients receiving ibrutinib, binding to ITK also has been demonstrated (Dubovsky 2013).

For more detailed and comprehensive information regarding nonclinical pharmacology and toxicology, please refer to the current IB.

1.2.1.2. Safety Pharmacology and Toxicology

No treatment-related effects were observed in the central nervous system 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 studies in pregnant rats and rabbits, ibrutinib administration was associated with malformations (teratogenicity) at ibrutinib doses that result in approximately 14 and 2 times the exposure (area under the concentration-time curve [AUC]) in patients administered the dose of 560 mg daily, respectively. Fetal loss and reduced fetal body weights were also seen in treated pregnant animals. Carcinogenicity studies have not been conducted with ibrutinib. In vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. No effects on fertility or reproductive capacities were observed in a study in male and female rats.

For the most comprehensive information regarding nonclinical safety pharmacology and toxicology, please refer to the current IB.

1.2.2. Summary of Clinical Data

For the most comprehensive clinical information regarding ibrutinib, please refer to the current version of the IB.

1.2.2.1. Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging from 420 to 840 mg/day, exposure to ibrutinib increased proportionally to doses increased with substantial intersubject variability. The mean half-life ($t_{1/2}$) of ibrutinib ranged from 4 to 13 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Taking into account the approximate doubling in mean systemic exposure when dosed with food and the favorable safety profile, ibrutinib can be dosed with or without food. Ibrutinib is extensively metabolized primarily by cytochrome P450 (CYP) 3A4 enzymes. The on-target effects of metabolite PCI-45227 are not considered clinically relevant. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of single dose exposure. Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not

altered in patients with creatinine clearance (CrCl) >30 mL/min. Patients with severe renal impairment or patients on dialysis have not been studied. 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. A higher proportion of Grade 3 or higher adverse reactions were reported in patients with B-cell malignancies (CLL, MCL and WM) with mild hepatic impairment based on NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction compared to patients with normal hepatic function. In the Phase 2 study in subjects with cGVHD, there were no differences in ibrutinib exposure between subjects with normal (n=29) and mild hepatic impairment based on baseline liver function test per NCI criteria (n=13).

For the most comprehensive information regarding pharmacokinetics (PK) and product metabolism, please refer to the current version of the IB.

1.2.3. Summary of Clinical Safety

A brief summary of safety data from monotherapy studies, combination therapy studies, and a cGVHD study is provided below.

1.2.3.1. Monotherapy Studies

Pooled safety data from a total of 1318 subjects treated with ibrutinib monotherapy in 13 studies that have completed primary analysis or final analysis as of the 31 May 2016 cutoff date for the current Investigator's Brochure update in B-cell malignancies are summarized below.

The most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N=1318):

Most frequently reported TEAEs ≥15% [a]	Most frequently reported Grade 3 or 4 TEAEs ≥3% [b]	Most frequently reported Serious TEAEs ≥2% [c]
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Febrile neutropenia
Cough	Anemia	Pyrexia
Pyrexia	Hypertension	
Anemia	Diarrhea	
Neutropenia	Atrial Fibrillation	
Upper respiratory tract infection		
Thrombocytopenia		
Oedema peripheral		

[a] Source is Table 6 of IB (v10), [b] Source is Table 8 of IB (v10), [c] Source is Table 9 of IB (v10).

1.2.3.2. Combination Studies

Pooled safety data from a total of 423 subjects treated with various therapies in combination with ibrutinib from 4 studies conducted in subjects with B-cell malignancies are briefly summarized below. Therapies used in combination with ibrutinib in these studies, included BR (bendamustine and rituximab), FCR (fludarabine, cyclophosphamide, and rituximab), ofatumumab, and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

The most frequently reported TEAEs in subjects receiving ibrutinib in combination therapy (N=423):

Most frequently reported TEAEs ≥20%[a]	Most frequently reported Grade 3 or 4 TEAEs ≥3%[b]	Most frequently reported Serious TEAEs ≥2%[c]
Neutropenia	Neutropenia	Pneumonia
Diarrhea	Thrombocytopenia	Febrile neutropenia
Nausea	Febrile neutropenia	Atrial fibrillation
Thrombocytopenia	Pneumonia	Pyrexia
Fatigue	Neutrophil count decreased	Cellulitis
Anemia	Anemia	
Pyrexia	Fatigue	
	Hypertension	
	Diarrhea	

[a] Source is Table 10 of IB (v10), [b] Source is Table 12 of IB (v10), [c] Source is Table 13 of IB (v10).

1.2.3.3. Chronic GVHD Study

Safety data from the 42 subjects enrolled in the PCYC-1129-CA study demonstrated that 100% of subjects have experienced a treatment-emergent adverse event (TEAE) with a total of 73.8% of subjects reported Grade 3 or higher AEs. Fifty-two percent (52.4%) of subjects reported serious adverse events (SAEs). The most frequent TEAEs and SAEs are summarized below.

Most frequently reported TEAEs in subjects receiving ibrutinib for cGVHD (N=42):

Most frequently reported TEAEs > 20%	Most frequently reported Grade 3 or 4 TEAEs > 10%	Serious TEAEs occurred in > 1 subject
Fatigue	Fatigue	Cellulitis
Diarrhea	Pneumonia	Headache
Muscle spasms		Pneumonia
Nausea		Pyrexia
Increased tendency to bruise		Septic shock

Thirty subjects (71.4%) were taking moderate or strong CYP3A inhibitors during the study with 9.5% of subjects taking posaconazole, 42.9% taking fluconazole, and 14.3% taking voriconazole.

Concomitant use of moderate and strong CYP3A inhibitors resulted in higher ibrutinib exposure but there was no association between concurrent CYP3A inhibitor use and dose reductions or discontinuations or with TEAEs leading to dose reductions or discontinuations.

1.2.4. Risks

1.2.4.1. Atrial Fibrillation

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Subjects who develop arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset dyspnea should be evaluated clinically, and if indicated, have an ECG performed. 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).

1.2.4.2. Bleeding-related Events

There have been reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, subdural 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 6.2.3 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. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen induced platelet aggregation were observed, refer to Section 6.2.3.

1.2.4.3. Cytopenias

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

1.2.4.4. 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).

1.2.4.5. Infections

Infections (including sepsis, bacterial, viral, aspergillus or other fungal infections) were observed in subjects treated with ibrutinib therapy. Some of these reported infections have been associated

with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections (see Section 6.1). Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in subjects treated with ibrutinib. Subjects should be monitored for symptoms (fever, chills, weakness, confusion) and appropriate therapy should be instituted as indicated.

1.2.4.6. Interstitial Lung Disease (ILD)

Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib. Monitor subjects for pulmonary symptoms indicative of ILD. Should symptoms develop follow the protocol dose modification guidelines (see Section 5.3.1.4).

1.2.4.7. Non-melanoma Skin Cancer

Non-melanoma skin cancers have occurred in subjects treated with ibrutinib. Monitor subjects for the appearance of non-melanoma skin cancer.

1.2.4.8. Rash

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

1.2.4.9. Hypertension

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

1.2.5. Summary of Clinical Data in Chronic GVHD

A Phase 1b/2 study (PCYC-1129-CA) to evaluate the safety and efficacy of ibrutinib treatment in subjects with cGVHD who had failed steroid therapy was initiated in June 2014. The NIH Consensus Panel Response Assessment 2005 was used to determine overall response. As of 01 September 2016, 42 subjects have been recruited and received at least one dose of study drug in the study. The median age is 56 years (19-74 years) with a median duration of GVHD of 13.6 months prior to study entry. The median number of prior therapeutic regimens is 2.0. Thirty-seven subjects have had a response assessment and 5 subjects discontinued prior to the first response assessment. Of the 42 subjects with response assessments or who discontinued

ibrutinib prior to response assessment, 28 subjects are responders (ORR=67%) based on NIH response criteria. Best responses include 9 CRs, 19 PRs, 7 stable disease (SD), 2 progressive disease (PD), and 5 unknown due to the early discontinuation of study drug without post baseline efficacy assessment. Twenty of the 28 responders (71%) achieved a sustained response for at least 20 weeks. Median corticosteroid dose in responding subjects was 0.29 mg/kg/d at baseline, 0.24 mg/kg/d at Week 12, 0.19 mg/kg/d at Week 24, 0.18 mg/kg/d at Week 36, and 0.13 mg/kg/d at Week 48. Five subjects were able to discontinue steroids. Overall response rate results were supported by exploratory analyses of patient-reported symptom bother which showed at least a 7-point decrease in Lee Symptom Scale overall summary score in 24% (10/42) of patients on at least 2 consecutive visits.

These efficacy results are consistent with a response rate and durability that is considered clinically compelling in this high-risk population and with an acceptable safety profile. Based on data from the PCYC-1129 study the US FDA approved ibrutinib for the treatment of adult patients with cGVHD after failure of one or more lines of systemic therapy.

1.3. Prednisone

Prednisone is a glucocorticoid. Glucocorticoids are adrenocortical steroids (corticosteroids), both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. The chemical name for prednisone is pregna-1,4-diene-3,11,20-trione monohydrate,17,21-dihydroxy. Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems. Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

1.3.1. Summary of Clinical Data

Prednisone is a corticosteroid indicated in the following conditions:

- As an anti-inflammatory or immunosuppressive agent for certain allergic, dermatologic, gastrointestinal, hematologic, ophthalmologic, nervous system, renal, respiratory, rheumatologic, specific infectious diseases or conditions and organ transplantation
- For the treatment of certain endocrine conditions
- For palliating of certain malignant conditions

1.3.2. Summary of Clinical Safety

Alterations in Endocrine Function

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia. Monitor patients for these conditions with chronic use.

Corticosteroids can produce reversible HPA axis suppression with the potential for corticosteroid insufficiency after withdrawal of treatment. Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. If the patient is receiving corticosteroids already, dosage may have to be increased.

Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently. Mineralocorticoid supplementation is of particular importance in infancy.

Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

Increased Risks Related to Infection

Corticosteroids may increase the risks related to infections with any pathogen, including viral, bacterial, fungal, protozoan, or helminthic infections. The degree to which the dose, route and duration of corticosteroid administration correlates with the specific risks of infection is not well characterized, however, with increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.

Corticosteroids may mask some signs of infection and may reduce resistance to new infections.

Corticosteroids may exacerbate infections and increase risk of disseminated infections.

The use of prednisone in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for management of the disease in conjunction with an appropriate anti-tuberculous regimen.

Chickenpox and measles can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In children or adults who have not had these diseases, particular care should be taken to avoid exposure. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

Corticosteroids should be used with great care in patients with known or suspected Strongyloides (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control drug reactions.

Corticosteroids may increase risk of reactivation or exacerbation of latent infection.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Corticosteroids may activate latent amebiasis. Therefore, it is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or any patient with unexplained diarrhea.

Corticosteroids should not be used in cerebral malaria.

Alterations in Cardiovascular/Renal Function

Corticosteroids can cause elevation of blood pressure, salt, and water retention, and increased excretion of potassium and calcium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. These agents should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.

Use in Patients with Gastrointestinal Disorders

There is an increased risk of gastrointestinal perforation in patients with certain GI disorders. Signs of GI perforation, such as peritoneal irritation may be masked in patients receiving corticosteroids.

Corticosteroids should be used with caution if there is a probability of impending perforation, abscess, or other pyogenic infections; diverticulitis; fresh intestinal anastomoses; and active or latent peptic ulcer.

Behavioral and Mood Disturbances

Corticosteroids use may be associated with central nervous system effects ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Decrease in Bone Density

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (ie, decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in children and adolescents and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (ie, postmenopausal women) before initiating corticosteroid therapy and bone density should be monitored in patients on long term corticosteroid therapy.

Ophthalmic Effects

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

The use of oral corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes.

Intraocular pressure may become elevated in some individuals. If corticosteroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation. Corticosteroids should not be used in active ocular herpes simplex.

Vaccination

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered; however, the response to such vaccines cannot be predicted. Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, eg, for Addison's disease.

While on corticosteroid therapy, patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high dose, because of possible hazards of neurological complications and a lack of antibody response.

Effect on Growth and Development

Long-term use of corticosteroids can have negative effects on growth and development in children.

Growth and development of pediatric patients on prolonged corticosteroid therapy should be carefully monitored.

Use in Pregnancy

Prednisone can cause fetal harm when administered to a pregnant woman. Human and animal studies suggest that use of corticosteroids during the first trimester of pregnancy is associated with an increased risk of orofacial clefts, intrauterine growth restriction, and decreased birth weight. If this drug is used during pregnancy, or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.

Neuromuscular Effects

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that they affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect.

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (eg, myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (eg, pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevation of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Kaposi's Sarcoma

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

1.3.3. Summary of Clinical Data in Chronic Graft versus Host Disease

Corticosteroids have been the backbone of treatment of cGVHD for more than 3 decades despite few formal trials to document its efficacy (Flowers 2015, Wolff 2011, Dignan 2012). While effective, prolonged administration of systemic corticosteroids results in substantial morbidity including hypertension, bone loss, weight gain, diabetes, cataracts, and myopathy as well as increasing the risk for underlying malignancy. The administration of alternate day steroids is often attempted to mitigate the risk of these toxicities. In addition, rapid corticosteroid taper and discontinuation is preferred in cGVHD.

1.4. Study Rationale

While corticosteroids are effective in some patients, until the approval of ibrutinib in August 2017 for adult patients with cGHVD after failure of one or more lines of systemic therapy, there

had been no approved therapies for cGVHD as no other immunosuppressant therapy has proven to be effective either in front-line or steroid refractory cGVHD patients. Pre-clinical results have demonstrated a substantial therapeutic benefit of ibrutinib treatment to reduce the prolonged allo-immune effects of cGVHD in animal models and supported investigation in clinical studies. Data supporting the approval of ibrutinib in cGVHD demonstrated that ibrutinib has robust clinical activity with high response rate by NIH criteria as well as an overall favorable safety profile. These data also support the continued clinical evaluation of ibrutinib in combination with prednisone as a treatment option for patients with new onset cGVHD.

2. STUDY OBJECTIVES

2.1. Primary Objective

To evaluate the efficacy of ibrutinib in combination with prednisone (Arm A) versus placebo in combination with prednisone (Arm B) based on the response rate at 48 weeks (the proportion of responders [CR or PR]) as determined by NIH Consensus Development Project Criteria in subjects with new onset moderate to severe cGVHD (Lee 2015, Jagasia 2015).

2.2. Secondary Objective(s)

- To compare the two treatment arms in terms of the following:

Efficacy

- Response rate at 24 weeks (the proportion of responders [CR or PR]) as defined by the NIH Consensus Development Project (2014)
- Duration of response (DOR)
- Proportion of subjects obtaining a steroid dose level less than 0.15 mg/kg/d at 24 weeks
- Time to withdrawal of all immunosuppressants (with the exception of ibrutinib/placebo)
- Overall survival (OS)
- Lee cGVHD symptom scale improvement

Safety

- Safety and tolerability
- Differences in steroid-related morbidities (eg, hyperglycemia, hypertension)

2.3. Exploratory Objective(s)

- Pharmacokinetics of ibrutinib when administered in combination with prednisone in subjects with cGVHD including adolescent subjects
- Pharmacodynamic characteristics of ibrutinib (including BTK and ITK occupancy) in subjects with cGVHD

- Evaluation of biomarkers relevant to disease biology and therapy with ibrutinib for cGVHD
- Improvement in SF-36 patients reported outcome

3. STUDY DESIGN

3.1. Overview of Study Design

This is a Phase 3, multicenter, international, randomized, double-blind study of oral ibrutinib in combination with prednisone versus placebo in combination with prednisone in subjects with new onset chronic GVHD.

Approximately 186 subjects with newly diagnosed moderate or severe cGVHD, as defined by the 2014 NIH Consensus Development Project Criteria, will be randomized in a 1:1 ratio to receive either ibrutinib in combination with prednisone (Arm A) or placebo in combination with prednisone (Arm B). It is expected that a minimum of 6 subjects in the adolescent group (≥12 and < 22 years of age) will be enrolled.

Treatment with ibrutinib/placebo will be administered continuously until unacceptable toxicity, progression of the underlying disease, death, or the start of a new systemic treatment for cGVHD. Progression of the underlying disease will be defined using standard consensus criteria for the individual malignancy.

Corticosteroid therapy will be tapered as per a standard taper regimen with the goal of reducing exposure to high-moderate dose corticosteroids as quickly as possible according to clinical severity of cGVHD. A standard corticosteroid taper schedule is provided in the protocol as guidance to clinicians (Table 4).

The primary endpoint is the response rate at 48 weeks. Response will be defined by the NIH Consensus Development Project Criteria (2014) and must occur:

- In the absence of new therapy for cGVHD
- In the absence of progression of the underlying disease that was the indication for transplant, or PTLD, or death

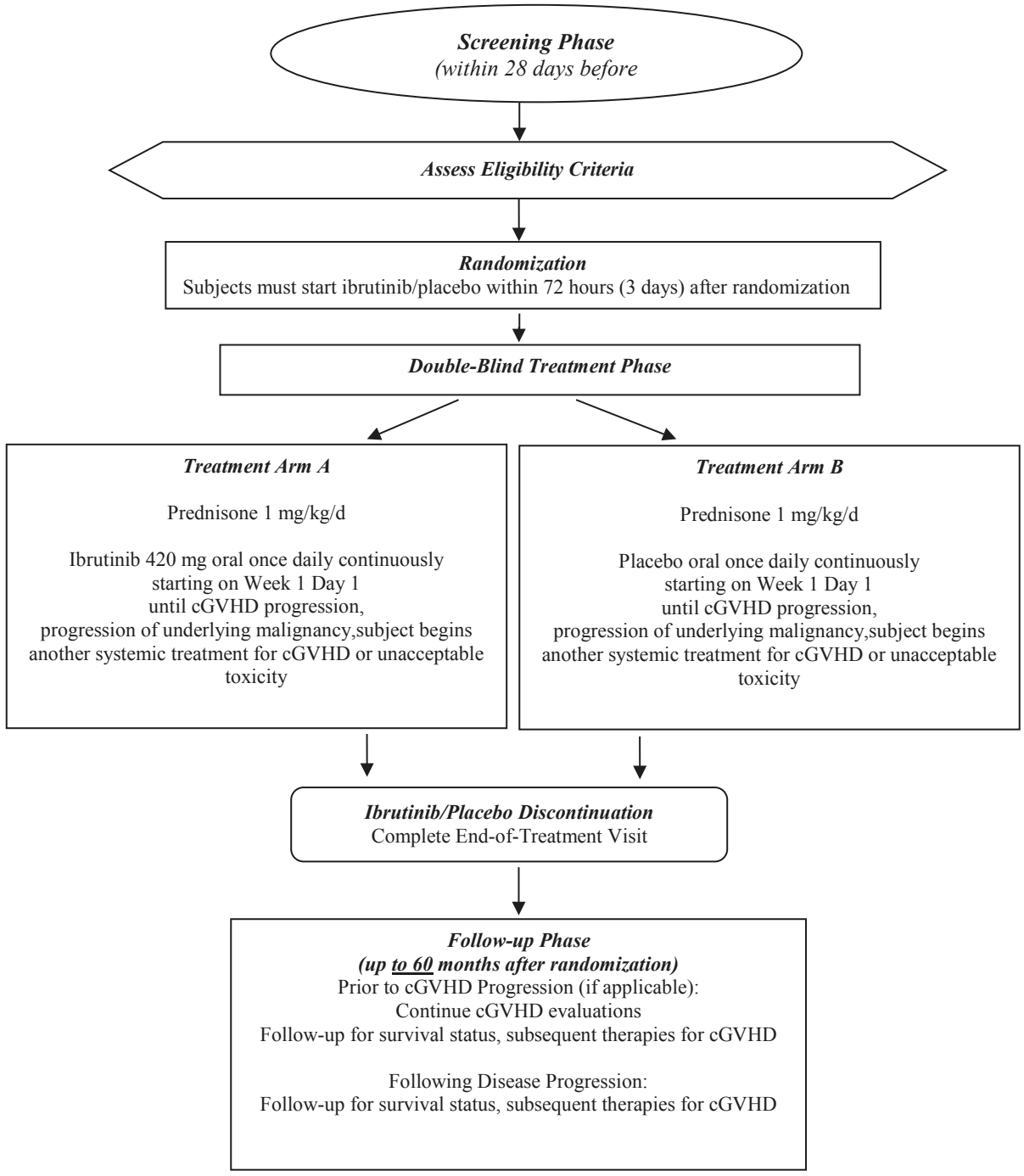
Secondary endpoints will assess for additional clinical benefit including Week-24 response, duration of response (DOR), corticosteroid dose reduction, time to withdrawal of all immunosuppressants, OS, and Lee cGVHD symptom scale. Corticosteroid reduction will be determined by a proportion of patients who are on < 0.15 mg/kg of prednisone at week 24, to allow for variations in corticosteroid taper that occur in practice, while at the same time reaching a dose that minimizes the toxicity associated with steroids.

The randomization between arms will be stratified according to:

- Age group (12 to <22 years old vs. ≥22 years old)
- NIH Global Severity grade (moderate vs. severe)
- Ongoing use of systemic immunosuppressants that were initiated for either treatment of or prophylaxis for acute GVHD (Yes vs. No)

The rationale for the study concept is provided in Section 1.4.

3.1.1. Study Schema



4. SUBJECT SELECTION

4.1. Inclusion Criteria

Prior to randomization, each potential subject must satisfy all of the following inclusion criteria.

Disease Related

1. New onset moderate or severe cGVHD as defined by the NIH Consensus Development Project Criteria (2014, see Appendix M, Appendix N, and Appendix O).
2. History of an allogeneic hematopoietic cell transplant.
3. Need for systemic treatment with corticosteroids for cGVHD.
4. No previous systemic treatment for cGVHD (including extracorporeal photopheresis [ECP]).
5. Participants may be receiving other immunosuppressants for the prophylaxis or treatment of acute GVHD but if the subject is receiving prednisone for prophylaxis or treatment of acute GVHD it must be at or below 0.5 mg/kg/d.
6. Participants may have received pre-transplant BTK inhibitors for other reasons besides cGVHD such as for the treatment of leukemia or lymphoma, but must not have received a BTK inhibitor since the time of transplant.

Demographic

7. Age ≥12 years old.
8. Karnofsky or Lansky (subjects <16 years) performance status ≥60.

Laboratory

9. Adequate renal function defined as estimated Creatinine Clearance ≥30 mL/min (Cockcroft-Gault formula)
10. Adequate hepatic function as defined by:
    - Total bilirubin of ≤ 1.5 x ULN (unless of non-hepatic origin or due to Gilbert's Syndrome) or
    - Total bilirubin of > 1.5 x ULN to 3.0 x ULN if due to GVHD
11. Adequate hematological function defined as:
    - Absolute neutrophil count ≥1.0 x 10^9/L and off growth factor support for 7 days
    - Platelets ≥30 x 10^9/L and no transfusion 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). When treated with warfarin or other vitamin K antagonist, then INR ≤3.0 (Section 6.2.3).

Ethical/Other

13. Male and female subjects of reproductive potential who agree to use both a highly effective methods of birth control (eg, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence[2], or sterilized partner) and a barrier method (eg, condoms, cervical ring, sponge, etc.) during the period of therapy and for 90 days for both females and males after the last dose of study drug.

4.2. Exclusion Criteria

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

Disease-Related

1. Received any previous systemic treatment for cGVHD with the following exception:
   - Corticosteroids for cGVHD received within the 72 hours prior to signing the informed consent form.
2. Inability to begin a prednisone dose ≥0.5 mg/kg/d for the treatment of cGVHD.
3. Presence of single-organ, genito-urinary involvement with cGVHD as the only manifestation of cGVHD.

Concurrent Conditions

4. Received any investigational agent ≤28 days before randomization.
5. Received donor lymphocyte infusion (DLI) ≤56 days before randomization.
6. 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.
7. Any uncontrolled active systemic infection or active infection requiring systemic treatment that was ongoing ≤7 days before randomization. This does not include secondary prophylaxis of well controlled fungal infections, ongoing treatment of controlled viral reactivations (eg, CMV), or treatment or prophylaxis of controlled low-grade central line infections (eg, Staphylococcus epidermidis).
8. Progressive underlying malignant disease or active post-transplant lymphoproliferative disease.
9. History of other malignancy (not including the underlying malignancy that was the indication for transplant), with the following exceptions:

[2] 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

10. Subject has a concurrent illness which in the opinion of the investigator may interfere with the treatment and evaluation of the subject.
11. Known bleeding disorders (eg, von Willebrand's disease or hemophilia).
12. History of stroke or intracranial hemorrhage within 6 months prior to randomization.
13. Known history of human immunodeficiency virus (HIV).
14. Subjects with chronic liver disease with hepatic impairment per Child-Pugh classification Class C (Appendix E). Please note that acute liver dysfunction due to cGVHD is not applicable to the evaluation of Child-Pugh classification.
15. Active hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody or hepatitis B surface antigen or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before randomization. Those who are PCR positive will be excluded.
16. Vaccinated with live, attenuated vaccines within 4 weeks of randomization.
17. Major surgery within 4 weeks of randomization.
18. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.
19. 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.
20. Subjects requiring treatment with a strong CYP3A inducer are not eligible, unless a transition to an agent with less CYP3A induction is planned (Appendix D).
21. Female subject who is pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 3 months of last dose of study drug. Male subject who plans to father a child while enrolled in this study or within 3 months after the last dose of study drug.
22. Unwilling or unable to participate in all required study evaluations and procedures.
23. 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

5.1.1. Randomized Double-blind Phase

After the subject provides informed consent on study, site personnel will register the subject in Interactive Web Response System (IWRS) to assign a screening number. After the subject has completed all screening procedures and has met all requirements of the inclusion/exclusion criteria, the site personnel will update IWRS and answer key questions to randomize the subject, and have drug assigned. The first dose of ibrutinib/placebo must be administered after randomization, which should be no more than 72 hours (3 days) after the subject has been randomized by IWRS.

Approximately 186 subjects will be randomized in a 1:1 ratio to each of the 2 treatment arms.

Treatment Arm A: ibrutinib in combination with prednisone

Treatment Arm B: placebo in combination with prednisone

The randomization between arms will be stratified according to:

- Age group (12 to <22 years old vs. ≥22 years old)
- NIH Global Severity grade (moderate vs. severe)
- Ongoing use of systemic immunosuppressants that were initiated for either treatment of or prophylaxis for acute GVHD (yes vs. no)

5.1.1.1. Blinding

This is a double-blind study; therefore, the subjects, the investigators, and the Sponsor's study team members will be blinded to the treatment assignment. The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject if necessary to appropriately manage or treat the subject. Data that may potentially unblind the treatment assignment (ie, study drug plasma concentrations) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized.

The investigator should contact the Sponsor or its designee to discuss the particular situation before breaking the blind whenever possible. Telephone contact with the Sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the Sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented in IWRS in the appropriate section of the eCRF and in the source document. The IWRS confirmation indicating the code break must be retained with the subject's source documents in a secure manner. A subject whose treatment assignment has been unblinded may continue the study treatment if the subject is expected to continue receiving clinical benefit. The

subject should continue to return for scheduled study visits. The single-blind (ie, subject remains blinded to treatment assignment) should be maintained provided the subject's safety is not compromised.

At the time of the futility analyses, the randomization codes and, if required, the translation of randomization codes into treatment and control groups will be disclosed to those authorized and only for those subjects included in the interim analyses.

5.2. Study Treatment

Ibrutinib (420 mg) or placebo will be given orally once daily continuously starting on Week 1 Day 1 until cGVHD progression, progression of underlying malignancy, subject begins another systemic treatment for cGVHD or unacceptable toxicity.

Prednisone 1 mg/kg/d will be given orally once daily continuously starting on Week 1 Day 1 until unacceptable toxicity or until subject is successfully tapered from the prednisone (see Section 5.3.2.2.1). Starting prednisone dose may be as low as 0.5 mg/kg/d if a subject cannot tolerate higher doses.

During Screening, prednisone to treat cGVHD may be started prior to randomization if the clinical condition of the subject necessitates it. If a subject is started on high dose prednisone for treatment of cGVHD prior to randomization, the patient must be randomized within 7 days of starting high dose prednisone.

5.3. Study Medication

5.3.1. Ibrutinib/Placebo

5.3.1.1. Formulation/Packaging/Storage

Ibrutinib capsules are provided as a hard gelatin capsule containing 70 mg and 140 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib IB for a list of excipients. 70 mg capsules will only be used for subjects who have dose reductions that require a dose of 70 mg and will not be used to constitute a dose larger than 70 mg (eg, 2 x 70 mg capsules to give 140 mg).

The ibrutinib (or placebo) 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 study drug will be dispensed in child-resistant packaging.

Refer to the Pharmacy Manual/site investigational product manual for additional guidance on study drug storage, preparation and handling.

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

5.3.1.2. Dose and Administration

Ibrutinib or placebo is administered orally once daily. It is expected that many subjects commencing therapy with high dose prednisone will require anti-fungal prophylaxis. Please see Section 6.2.1 for dose modification guidelines with concomitant use of CYP3A inhibitors or inducers.

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 subjects should not attempt to open capsules or dissolve them in water. 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 subject 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 at each visit. Unused ibrutinib dispensed during previous visits 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 420 mg is considered to be an overdose. Signs and symptoms of an overdose that meet any SAE criterion must be reported as a SAE 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 maximum tolerated dose (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

The dose of ibrutinib/placebo must be modified according to the dose modification guidance in Table 1 and Table 2 if any of the following toxicities occur:

- Grade 4 neutropenia (ANC <500/µL) for more than 7 days. See Section 6.1 for instructions regarding the use of growth factor support
- Grade 3 thrombocytopenia (platelets <50,000/µL) in the presence of clinically significant bleeding events
- Grade 4 thrombocytopenia (platelets <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

Adverse events that are considered related to concomitant high dose corticosteroids (eg, hyperglycemia, insomnia) do not require dose modification or holding of ibrutinib.

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 6.2.3).

For other AEs not listed above, including Grade 2 AEs that are deemed per the investigator potentially manageable by dose reduction, these can be managed with a one dose level reduction.

In the event that the investigator feels deviation from the recommendations above is required, please consult the medical monitor to discuss for approval.

If the dose of ibrutinib/placebo is reduced for an adverse event, at the investigator's discretion, the dose of ibrutinib may be re-escalated after 4 weeks of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction. Dose changes must be recorded in the Dose Administration eCRF.

Table 1. Ibrutinib/Placebo Dose Modifications

Occurrence	Action to be Taken
First	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at original dose level
Second	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (eg, 280 mg/day for 420 mg/day dose)
Third	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (eg, 140 mg/day for 420 mg/day dose)
Fourth	Discontinue study drug

Table 2. Ibrutinib/Placebo Dose Reduction Levels

Starting Dose Level	420 mg	280 mg	140 mg
Dose Reduction Level 1	280 mg	140 mg	70 mg
Dose Reduction Level 2	140 mg	70 mg	Discontinue
Dose Reduction Level 3	Discontinue	Discontinue	--

For required dose modification for hepatic impairment refer to Section 5.3.1.5 and for concomitant treatment with CYP3A inhibitors refer to Section 6.2.1.

5.3.1.5. Dose Modification for Subjects with Hepatic Impairment

Dose modifications for hepatic impairment will depend on baseline total bilirubin level and subsequent changes in bilirubin levels per Table 3 below. If the elevation of bilirubin is due to a non-hepatic cause or Gilbert's Syndrome, then no dose modifications are necessary.

Table 3. Ibrutinib/Placebo Dose Modifications for Subjects with Hepatic Impairment

Starting Dose Level by Bilirubin Levels	**Bili** ≤1.5 x ULN at baseline: **420 mg**	**Bili** >1.5-3 x ULN at baseline: **140 mg**
On-study bilirubin level ≤1.5 x ULN	Continue 420 mg	Increase to 420 mg
On-study bilirubin level >1.5-3 x ULN	Reduce to 140 mg	Continue 140 mg
On-study bilirubin level >3 x ULN	• Hold* until bili level >1.5-3 x ULN restart at 140mg • When bili level ≤1.5 x ULN restart at 420mg	• Hold* until bili level >1.5-3 x ULN restart at 140mg • When bili level ≤1.5 x ULN restart at 420mg

Bili = bilirubin

* In cases where the investigator wishes to restart ibrutinib/placebo after ibrutinib/placebo has been held for more than 28 days for hepatic impairment, please contact the medical monitor for approval.

In the event a patient has had a dose reduction due to a non-hepatic toxicity and then develops elevated bilirubin level (or vice versa) that requires a dose reduction, the lower of the two dose reductions should be used. The medical monitor should be consulted for any questions involving dose reductions.

5.3.1.6. Ibrutinib/Placebo Hold after Withdrawal of All Immunosuppressants

At the physician's discretion, ibrutinib/placebo may be held if ALL of the following conditions are met:

- All systemic immunosuppressants used for the treatment of cGVHD have been discontinued. (The continued use of very low doses of corticosteroids used only for physiologic adrenal replacement is allowed)
- cGVHD response has been maintained for 12 weeks after complete withdrawal of all immunosuppressants (not including ibrutinib/placebo)
- The subject has received a minimum of 48 weeks of ibrutinib/placebo

If cGVHD returns/worsens after ibrutinib/placebo has been held for the above criteria, ibrutinib/placebo may be re-started after consulting with the medical monitor.

5.3.2. Prednisone

5.3.2.1. Formulation/Packaging/Storage

Prednisone tablets for oral administration are available in multiple strengths. Commercially available prednisone will be supplied by the Sponsor where applicable. The commercial material will be relabeled for clinical trial use.

For situations where a subject who must receive an IV or alternate formulation of corticosteroid (eg, hospitalization for AE), the dose should be equivalent to the subject's prednisone dose using the prednisone equivalency table (Appendix K) unless the subjects clinical condition warrants a different dose (eg, stress doses of steroids for sepsis). All doses of corticosteroids must be entered into the eCRF.

Refer to the Pharmacy Manual for additional guidance on prednisone storage, preparation and handling.

5.3.2.2. Dose and Administration

Prednisone will be given orally at 1.0 mg/kg/d with rounding to multiples of 5 mg (eg, 15, 20, 25, etc.).

If a prednisone dose of 1.0 mg/kg/d is contraindicated (eg, poorly controlled diabetes, major mood disturbances) then the starting dose of prednisone may be reduced to 0.5-1.0 mg/kg/d. Subjects unable to receive a starting dose of prednisone of at least 0.5 mg/kg/d are ineligible for the study.

If, during Screening, the clinical condition of the subject requires immediate initiation of treatment with prednisone, prednisone may be started prior to randomization. If the subject begins prednisone during Screening and prior to randomization the eligible subject must be randomized within 7 days of starting prednisone.

If a subject has started corticosteroids within the 72 hours prior to consent, then the subject is eligible and can continue corticosteroids after signing consent but must be randomized within 7 days of signing consent.

5.3.2.2.1. Prednisone Taper

Prednisone taper should be attempted by the schedule outlined in Table 4:

Table 4. Prednisone Taper Schedule

Study Week #	Dose (mg/kg, body weight)
0	1.0 qd
2	0.75 qd
4	0.65 qd
6	0.50 qd
8	0.70 qod*
10	0.55 qod
12	0.45 qod
14	0.35 qod
16	0.25 qod
18	0.20 qod
20	0.15 qod
22	0.10 qod
24	0.0

*qod=every other day. #Timing of steroid taper is defined by when the first dose of prednisone is given.

The prednisone taper should commence by week 2, but it is understood that considerable variation in prednisone taper will occur depending on the subjects' response and other intercurrent illnesses. More rapid tapering of prednisone doses is allowed if clinically appropriate. Rounding of corticosteroid doses is acceptable. Decisions about the use of qod or alternative dosing schedules (eg, Mon/Wed/Fri) may follow institutional practice. Prednisone taper should be completed prior to tapering of other immunosuppressants unless the clinical condition of the subject dictates tapering/discontinuing other medications sooner (eg, toxicity associated with the use of the medication).

5.3.2.2.2. Flares in cGVHD

Exacerbation of cGVHD symptoms may occur during prednisone taper or with intercurrent illnesses. Temporary re-escalation of prednisone dose is allowed at the physician's discretion. Tapering of increased prednisone dose for a flare should begin within 4 weeks.

5.3.2.3. Overdose

The effects of accidental ingestion of large quantities of prednisone over a very short period of time have not been reported, but prolonged use of the drug can produce mental symptoms, moon face, abnormal fat deposits, fluid retention, excessive appetite, weight gain, hypertrichosis, acne, striae, ecchymosis, increased sweating, pigmentation, dry scaly skin, thinning scalp hair, increased blood pressure, tachycardia, thrombophlebitis, decreased resistance to infection, negative nitrogen balance with delayed bone and wound healing, headache, weakness, menstrual disorders, accentuated menopausal symptoms, neuropathy, fractures, osteoporosis, peptic ulcer,

decreased glucose tolerance, hypokalemia, and adrenal insufficiency. Hepatomegaly and abdominal distention have been observed in children.

Treatment of acute overdosage is by immediate gastric lavage or emesis followed by supportive and symptomatic therapy. For chronic overdosage in the face of severe disease requiring continuous steroid therapy the dosage of prednisone may be reduced only temporarily, or alternate day treatment may be introduced.

5.3.2.4. Dose Modification for Adverse Reactions

Prednisone will be tapered by study design according to clinical response in cGVHD (Table 4). Prednisone suppresses the hypothalamic-pituitary-adrenal (HPA) axis and, therefore, doses must be tapered slowly after long-term use. The occurrence of unmanageable adverse reactions from prednisone (eg, poorly controlled hypertension) may require a more rapid reduction in prednisone dosing, but may not necessitate a change in dose of study drug (ibrutinib/placebo). Dose modifications will be at the discretion of the physician and should reflect a balance of appropriately treating cGVHD and minimizing adverse effects.

5.4. Criteria for Permanent Discontinuation of Ibrutinib/Placebo

Investigators are encouraged to keep a subject who is experiencing clinical benefit in the study unless significant toxicity puts the subject at risk or routine noncompliance puts the study outcomes at risk. For a complete list of criteria for permanent discontinuation of ibrutinib/placebo, refer to Section 9.2.

An End-of-Treatment visit (Section 8.2.3) is required for all subjects except for those subjects who have withdrawn full consent.

6. CONCOMITANT MEDICATIONS/PROCEDURES

Concomitant therapies must be recorded from 30 days prior to signing of the ICF through 30 days after the last dose of study treatment (ibrutinib/placebo or corticosteroids), start of another therapy for cGVHD, or start of a new therapy for progression for the underlying malignancy.

6.1. Permitted Concomitant Medications

6.1.1. Ancillary Therapy and Supportive Care

Ancillary therapy and supportive care for cGVHD is permitted as outlined in the NIH Consensus Development Project 2014 Ancillary Therapy and Supportive Care Working Group Report (Carpenter 2015, Appendix L). In particular, the use of regimen to specifically treat or prevent bronchiolitis obliterans are allowed (eg, inhaled steroids/azithromycin/montelukast) and will not be considered systemic treatment for cGVHD.

Other supportive medications in accordance with standard clinical 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. Transfusions may be given in accordance with institutional policy. Anti-fungal prophylaxis should be given as outlined in Appendix L.

After consultation with the medical monitor the following may be considered; localized hormonal or bone sparing treatment for malignancies, and localized radiotherapy for medical conditions other than the underlying disease.

6.1.2. Systemic Immunosuppressant Therapy

During the Screening period, the physician will have the discretion to start prednisone while eligibility for the study is being confirmed, however, the subject must be randomized within 7 days of initiating treatment with prednisone.

Addition of any other new systemic immunosuppressant therapy (including ECP) to treat cGVHD is prohibited during Screening and subsequent enrollment into the study. Addition of a new systemic immunosuppressant for cGVHD will be considered a treatment failure and ibrutinib/placebo will be discontinued.

At enrollment, subjects may be receiving other immunosuppressants for the prophylaxis or treatment of acute GVHD. Tapering of these other immunosuppressants upon start of ibrutinib/placebo or prednisone is permitted (see Section 5.3.2.2.1).

Use of immunosuppressants for reasons other than treatment for cGVHD should be discussed with the medical monitor.

6.2. Medications to be Used with Caution

6.2.1. CYP3A Enzyme Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A4. The dose of ibrutinib/placebo should be adjusted for concomitant use of CYP3A inhibitors per Table 5 below:

Table 5. Ibrutinib/Placebo Dose Modifications for Concomitant Use of CYP3A Inhibitors

CYP inhibitor class	Dose modification instructions
• Mild CYP3A inhibitors	420 mg once daily. No dose adjustment required.
• Moderate CYP3A inhibitors	420 mg once daily. No dose adjustment required.
• **Voriconazole** at any dose or • **Posaconazole** at doses less than or equal to suspension 200 mg BID or delayed-release tablet 300 mg QD	280 mg once daily
• **Strong CYP3A inhibitors** or • **Posaconazole** at higher doses	140 mg once daily or consider alternative with less CYP3A inhibitory potential

Avoid concomitant use of strong CYP3A inducers (Appendix D). Consider alternative agents with less CYP3A induction and transition to a new agent within 4 weeks of randomization.

A list of common CYP3A inhibitors and inducers is provided in Appendix D. For further information, please refer to the current version of the ibrutinib IB and examples of inhibitors, inducers, and substrates can be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

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. 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/placebo.

6.2.3. Antiplatelet Agents and Anticoagulants

Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib/placebo with caution in subjects requiring anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. For guidance on ibrutinib/placebo and the use of anticoagulants during procedures/surgeries see Section 6.4.

Subjects requiring the use of therapeutic anticoagulation therapy (eg, atrial fibrillation), consider the risks and benefits of continuing ibrutinib treatment. Subjects treated with warfarin (or other

vitamin K antagonists) should maintain an INR ≤ 3.0 and if unable to maintain this level another anticoagulant agent should be considered. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib/placebo should be held while anticoagulation is being initiated and not be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

6.3. Other Systemic Immunosuppressant Therapy for cGVHD

Addition of any other ***new*** systemic immunosuppressant therapy (including ECP) to treat cGVHD is prohibited during Screening and subsequent enrollment into the study. The addition of other systemic immunosuppressant therapy to treat cGHVD will not allow for the appropriate assessment of response attributable to ibrutinib/placebo. 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/placebo in the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib/placebo.

6.4.1. Minor Surgical Procedures

For minor procedures (such as a central line placement, skin or needle biopsy, lumbar puncture [other than shunt reservoir access], thoracentesis, or paracentesis) ibrutinib/placebo 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/placebo, it is not necessary to hold ibrutinib/placebo.

6.4.2. Major Surgical Procedures

For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib/placebo should be held at least 7 days prior to the intervention (except for emergency procedures) 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.

7. STUDY EVALUATIONS

7.1. Description of Procedures

7.1.1. Assessments

7.1.1.1. Informed Consent Form (ICF)

Adult subjects must read, understand, and sign the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) approved ICF confirming his or her willingness to participate in this study before any study-specific screening procedures are performed. Consent of minors consists of signed parental permission form and minor's assent. 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.

7.1.1.2. 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 prior to first dose on Day 1 (Section 4). Details of establishing diagnosis of moderate or severe cGVHD are listed in Appendix M, Appendix N, and Appendix O. Please refer to NIH Staging and Response Assessment Manual for further details.

All subjects with prior malignancy as the indication for transplantation must be assessed prior to randomization to rule out progression of underlying malignancy. Assessments are to be performed and collected as deemed appropriate for the follow-up and management for routine standard of care of the underlying malignancy. The results of these assessments do not have to be known prior to randomization.

An enrollment eligibility form must be completed prior to enrollment into the trial.

7.1.1.3. Medical History and Demographics

The subject's relevant medical history through review of medical records and by interview will be collected and recorded. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of initial diagnosis will be recorded. For subjects <22 years of age at the time of enrollment, medical history will include surveillance for potential late effects (Appendix P).

7.1.1.4. Prior and Concomitant Medications

All medications from 30 days prior to signing of ICF through 30 days after the last dose of ibrutinib/placebo or prednisone, start of another therapy for cGVHD, or start of a new therapy for progression of underlying malignancy will be documented.

7.1.1.5. Adverse Events

The accepted regulatory definition for an AE is provided in Section 11.1. The occurrence of an AE from 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 of ibrutinib/placebo or prednisone until 30 days after the last dose of ibrutinib/placebo or prednisone, start of new medication for cGVHD or start of a new therapy for progression of the underlying malignancy that meet the AE definition must be recorded as AEs in the eCRF. If the subject rolls over into a follow-up study, AE collection will stop after the last dose is given as part of that study. Laboratory abnormalities designated clinically significant by the investigator will also be documented as AEs. Assessment for corticosteroid-related AEs, in particular (Appendix Q), should be performed. Additional important requirements for AE and SAE reporting are explained in Section 11.4.

7.1.1.6. Physical Examination

The physical examination will include height (at Screening for adults, and at Screening and annually for subjects <22 years at the time of enrollment), weight, and examination per clinical practice.

7.1.1.7. Karnofsky/Lansky Performance Scale

The Karnofsky/Lansky Performance Scale is provided in Appendix C. The Lansky scale is to be used for all subjects less than 16 years of age.

7.1.1.8. Vital Signs

Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature.

7.1.2. Laboratory

7.1.2.1. Hematology

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

7.1.2.2. Chemistry (Serum)

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

7.1.2.3. Infection Surveillance

Subjects should be monitored closely for signs or symptoms of aspergillus infection and other opportunistic infections. Screening for infectious agents, including fungal (eg, aspergillus) and viral (eg, CMV) infections as appropriate for the subjects' clinical course and medical history, should be performed.

7.1.2.4. Coagulation Studies

Measurement of PT/INR and aPTT will be performed at Screening using a local laboratory.

7.1.2.5. Hepatitis Serologies

Hepatitis serologies will be evaluated by a local laboratory and include hepatitis C antibody, hepatitis B surface antigen, and hepatitis B core antibody. If hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody is positive, then PCR to quantitate hepatitis B DNA or hepatitis C RNA must be performed and must be negative prior to randomization. Hepatitis serologies and/or PCR obtained as part of standard of care within 28 days prior to randomization are acceptable for use in establishing eligibility.

7.1.2.6. Serum Immunoglobulins

Serum immunoglobulins will be evaluated by a central laboratory and include IgA, IgG and IgM levels.

7.1.2.7. Pregnancy Test

Serum pregnancy test will be required at Screening by local laboratory 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.

7.1.3. Diagnostics/Procedures

7.1.3.1. Electrocardiograms (ECG)

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

During visits in which both ECGs and blood draws are performed, ECGs should be performed first.

At Screening, a 12-lead ECG is required.

Abnormalities noted at Screening should be included in the medical history. Subjects <22 years of age at enrollment will have a second ECG on Week 2 Day 1 during PK testing. This ECG should be done 2-4 hours after ibrutinib/placebo has been taken.

7.1.3.2. Forced Expiratory Volume in 1 Second (FEV1)

Forced expiratory volume in 1 second (FEV1) should be measured using spirometry and FEV1 measurement should be obtained prior to randomization. FEV1 values obtained as standard of care within 56 days prior to randomization can be used to fulfill the requirement for a baseline FEV1 measurement. If FEV1 results are abnormal at baseline, then subsequent FEV1 measurements should be obtained every 12 weeks. If the FEV1 result is normal at baseline, then subsequent FEV1 measurements should be obtained every 24 weeks. The NIH Lung score should be ascertained with every cGVHD activity assessment regardless of whether a FEV1 is performed.

7.1.4. Pharmacokinetics/Biomarkers

7.1.4.1. Pharmacokinetics

Plasma concentrations of ibrutinib and metabolite PCI-45227 after repeated dosing will be determined using a validated analytical method. Other potential metabolites of ibrutinib may be explored. Refer to Appendix B for PK sample collection schedule.

If ibrutinib/placebo is on hold or missed at the Week 2 or Week 25 PK evaluation, PK testing should be obtained on the next scheduled visit after ibrutinib dose has been stable for a minimum of 7 days.

7.1.4.2. Biomarkers and Pharmacodynamic Studies

Biological specimens collected at specified timepoints during the study may be used for pharmacodynamic and biomarker assessments as indicated as well as sequencing expression analysis, immunophenotyping and secreted protein analyses. Refer to Appendix B for pharmacodynamic, biomarker and T/B/NK sample collection schedule.

Samples collected in this study may be stored at a biorepository for up to 10 years (or according to local regulations) for additional research as new assays are developed for ibrutinib and cGVHD. Samples will be used to better understand the effects of ibrutinib, cGVHD, sensitivity and/or resistance to the investigational treatment regimen in this study. The research may begin at any time during the study or the post-study storage period. Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers.

Specific analysis and platforms may include, but are not limited to, soluble protein isolation including chemokine and cytokine, protein identification and quantification, viable cell manipulation, stimulation and co-culture, kinase drug occupancy studies, flow cytometric or

CyTOF based cell identification, and phospho-protein analyses. New analysis platforms and assays directed at protein specific outputs may be considered as technologies develop and improve or as new relevant disease or therapy markers are recognized.

7.1.4.3. Biomarker DNA and RNA Sequencing

T-cell and B-cell genetic functional diversity will be determined using a combination of TCR and BCR sequencing platform data alongside functional and immunophenotyping assays. The goal of these studies will be to establish study drug related changes to the systemic immune environment of the subjects.

RNA and DNA species analysis and or RNA/DNA sequencing may be performed on cells obtained from biomarkers specimens in an effort to quantify the expression or mutation of specific genes implicated in cGVHD disease pathogenesis and or therapy response.

7.2. Sample Collection and Handling

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

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

7.3. Efficacy Evaluations

7.3.1. NIH Consensus Panel Response Criteria

Response will be defined using the NIH Consensus Panel Chronic GVHD Activity Assessment (Appendix H and Appendix I).

Overall Response:

Skin, mouth, liver, upper and lower GI, esophagus, lung, eye, and joint/fascia are the organs or sites considered in evaluating overall response.

- Complete Response (CR) is defined as resolution of all manifestations in each organ or site.
- Partial Response (PR) is defined as improvement in at least 1 organ or site without progression in any other organ or site.
- Disease Progression is defined as clinically meaningful worsening in one or more organs regardless of improvement in other organs. Note that mixed response (ie, improvement in at least 1 organ accompanied by progression in another organ) is considered disease progression.

- Stable disease (SD): response that does not meet the criteria for CR, PR, or disease progression.

Please refer to NIH Staging and Response Assessment Manual and Appendix I for further details.

7.3.2. Lee cGVHD Symptom Scale and SF-36 Questionnaire

All subjects in the study will complete the Lee cGVHD Symptom Scale (Appendix F) and SF-36 questionnaire (Appendix G) at all cGVHD activity assessment visits. These questionnaires should be administered before other study procedures.

7.3.3. Late effects surveillance for adolescents (<22 years at randomization)

Late effects surveillance for adolescents will consist of the collection of data on growth and development (height, weight, and Tanner Stage) and medical records review for late effects of transplantation. This assessment will be performed at Screening and annually up to 5 years post randomization (Appendix P).

8. STUDY PROCEDURES

8.1. Screening Phase

8.1.1. Screening/Consenting Visit

The following procedures will be performed at the Screening Visit within 28 days prior to randomization unless otherwise noted:

- Obtain signed, written informed consent and if applicable, child assent, and parental permission
- Medical history including demographic information
- Record history related to late effect surveillance for subjects <22 years of age at the time of enrollment using the Late-Effects surveillance form (Appendix P)
- Collection of transplant history, including indication
- cGVHD Diagnosis and staging (NIH) (Appendix M, Appendix N, and Appendix O)
- Assessment for relapse/progressive disease for subjects receiving transplant for malignant disorders
- Infection surveillance
- Evaluation of Karnofsky/Lansky performance status (Appendix C)
- Physical examination including, height and weight. Document Tanner stage for subjects <22 years of age (subjects ≥22 years may use prior height measurement if available in source documents) (Appendix P)
- Record AEs since signing the ICF

- Record concomitant medication history including corticosteroids requirement, over-the-counter drugs, vitamins and herbs since 30 days prior to signing ICF
- cGVHD activity assessment (eg, NIH assessments [Appendix H and Appendix J]). For subjects who begin prednisone prior to randomization, cGVHD activity assessment should be completed prior to start of prednisone. If prednisone is started at the time that ibrutinib/placebo is started (Day 1) then activity assessment can be completed any time during Screening up until the day of first dose of ibrutinib/placebo (Day 1).
- Lee cGVHD Symptom Scale (Appendix F)/SF-36 questionnaire (Appendix G). Perform at the same time as cGVHD assessment.
- FEV1 (see Section 7.1.3.2)
- Obtain vital signs (including blood pressure, heart rate, respiratory rate, and body temperature) after the subject has rested in the sitting position for ≥3 minutes
- Obtain blood specimens for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Coagulation studies: PT/INR, aPTT
  - Hepatitis serologies/PCR
- T/B/NK sampling (Appendix B)
- Biomarker sampling (Appendix B)
- Obtain 12-lead ECG after the subject has been in a supine position and resting for at least 10 minutes
- Obtain serum pregnancy test for women of childbearing potential only
- Complete eligibility form prior to randomization in Treatment Phase
- Obtain subject number in the IWRS system

At any time from consent throughout the treatment period, the subject may be called to discuss potential prednisone dosing changes. The phone call will be documented in the source documentation and will be entered in the CRF.

8.2. Treatment Phase

8.2.1. Treatment Visits

8.2.1.1. Week 1 Day 1

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

Predose

- Physical examination
- Vital signs
- Performance status (KPS/Lansky) (Appendix C)
- cGVHD activity assessment per NIH (Appendix H and Appendix J). Only perform if not performed previously during Screening (see Section 8.1.1 above).
- Lee cGVHD Symptom Scale (Appendix F)/SF-36 Questionnaire (Appendix G). Only perform if not performed previously during Screening (see Section 8.1.1 above).
- FEV1. Only perform if not performed previously during Screening (see Section 7.1.3.2)
- Hematology
- Serum chemistry
- Urine pregnancy test for women of childbearing potential
- Quantitative serum immunoglobulins (IgA, IgM, IgG)
- Review of baseline AEs and concomitant medications (including corticosteroid requirements)
- Review of inclusion and exclusion criteria to re-confirm subject eligibility prior to first dosing
- Pharmacodynamic sampling (Appendix B)
- T/B/NK sampling (Appendix B)
- Biomarker sampling (Appendix B)

Postdose

- Administer ibrutinib/placebo at specified dose level, and then dispense remaining amount to subject for at-home dosing
- Provide drug diary and dosing instructions to subject
- Review AEs

8.2.1.2. Week 2

Predose

- Physical examination
- Hematology
- Serum chemistry
- Vital signs
- Review AEs and concomitant medications (including corticosteroid requirements)
- Pharmacokinetic sampling (Appendix B)

Postdose

- Administer ibrutinib/placebo at specified dose level
- Pharmacokinetic sampling at 1, 2, 4, and 6 hours postdose (Appendix B)
- For subjects <22 years of age at enrollment: Obtain 12-lead ECG approximately 2-4 hours post ibrutinib/placebo dose, after the subject has been in a supine position and resting for at least 10 minutes

8.2.1.3. Week 5, 9, 13, 17, 21, 25

Predose

- Physical examination
- Vital signs
- Performance status (KPS/Lansky) (Appendix C)
- Hematology
- Serum chemistry
- cGVHD activity assessment per NIH (Appendix H and Appendix J) (Weeks 5, 13 and 25 only)
- cGVHD response assessment (Appendix I) (Weeks 5, 13 and 25 only)
- Lee cGVHD Symptom Scale (Appendix F)/SF-36 Questionnaire (Appendix G) (Weeks 5, 13 and 25 only)
- FEV1 (Week 13 if abnormal at Screening, Week 25 for all subjects, see Section 7.1.3.2)
- Quantitative serum immunoglobulins (IgA, IgG, and IgM) (Weeks 13 and 25 only)
- Pharmacokinetic sampling (Appendix B) (Week 25 only)
- Pharmacodynamic sampling (Appendix B)
- T/B/NK sampling (Appendix B)
- Biomarker sampling
- Review returned subject dosing diary
- Drug accountability
- Review AEs and concomitant medications (including corticosteroid requirements)

Postdose

- Administer ibrutinib/placebo at specified dose level, and then dispense remaining amount to subject
- Pharmacokinetic sampling at 1, 2, 4, and 6 hours postdose (Week 25 only)

8.2.1.4. Week 37, 49, and every 12 weeks thereafter (± 7 days)

Predose

- Physical examination
- Vital signs
- Performance status (KPS/Lansky) (Appendix C)
- Hematology
- Serum chemistry
- cGVHD activity assessment per NIH (Appendix H and Appendix J)
- cGVHD response assessment (Appendix I)
- Lee cGVHD Symptom Scale (Appendix F)/SF-36 Questionnaire (Appendix G)
- FEV1 every 12 weeks if prior FEV1 was abnormal, every 24 weeks if prior FEV1 was normal (see Section 7.1.3.2)
- Quantitative serum immunoglobulins (IgA, IgG, and IgM)
- Pharmacodynamic sampling (Appendix B) (Weeks 49, 73, and 97 only)
- T/B/NK sampling (Appendix B) (Weeks 37, 49, 73 and 97 only)
- Biomarker sampling (Appendix B) (Weeks 37, 49, 73 and 97 only)
- Review returned subject dosing diary
- Drug accountability
- Review AEs and concomitant medications (including corticosteroid requirements)

Postdose

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

8.2.2. 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. If possible, the visit should be performed within 72 hours after the subject's previous dose.

- Physical examination
- Vital signs
- Performance status (KPS/Lansky) (Appendix C)
- Hematology
- Serum chemistry
- cGVHD activity assessment per NIH (Appendix H and Appendix J)
- cGVHD response assessment (Appendix I)
- Lee cGVHD Symptom Scale (Appendix F)/SF-36 Questionnaire (Appendix G)

- FEV1 (if not obtained within the previous 12 weeks, see Section 7.1.3.2)
- Quantitative serum immunoglobulins (IgA, IgG, and IgM)
- Review AEs and concomitant medications (including corticosteroid requirements)
- Review returned subject dosing diary
- Final drug accountability
- Pharmacodynamic sampling (Appendix B)
- T/B/NK sampling (Appendix B)
- Biomarker sampling (Appendix B)

8.2.3. 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. If ibrutinib/placebo is held after Week 48 due to response (see Section 5.3.1.6), the End-of-Treatment visit should occur 30 days after ibrutinib/placebo was put on hold.

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

- Physical examination
- Vital signs
- Performance status (KPS/Lansky) (Appendix C)
- Hematology
- Serum chemistry
- cGVHD activity assessment per NIH (Appendix H and Appendix J) (if not performed within previous 30 days)
- cGVHD response assessment (Appendix I) (if not performed within previous 30 days)
- Lee cGVHD Symptom Scale (Appendix F)/SF-36 Questionnaire (Appendix G) (if not performed within previous 30 days)
- FEV1 (if not obtained within previous 12 weeks)
- Quantitative serum immunoglobulins (IgA, IgG, and IgM)
- Review AEs and concomitant medications (including corticosteroid requirements and any new cGVHD treatment if applicable)
- Review returned subject dosing diary
- Final drug accountability

8.3. Follow-up Phase

Once a subject has completed the End-of-Treatment visit they will enter the Follow-up Phase. Subjects that withdraw from treatment for reasons other than progressive cGVHD or progression of their underlying malignancy will participate in ongoing response follow-up.

8.3.1. Response Follow-up

Subjects who discontinue ibrutinib/placebo for reasons other than progressive cGVHD or progression of underlying malignancy will be followed at pre-specified response assessment time points (Weeks 5, 13, 25 and every 12 weeks thereafter) by clinic visit until progressive disease or progression of underlying malignancy. During this period, the following procedures will be performed:

- Physical examination
- Vital signs
- Performance status (KPS/Lansky) (Appendix C)
- Hematology
- Serum chemistry
- cGVHD activity assessment per NIH (Appendix H and Appendix J)
- cGVHD response assessment (Appendix I)
- Lee cGVHD Symptom Scale (Appendix F)/SF-36 Questionnaire (Appendix G)
- FEV1 every 12 weeks if prior FEV1 abnormal, every 24 weeks if prior FEV1 normal
- Review corticosteroid requirements and any new cGVHD treatment if applicable

8.3.2. Long-Term Follow-up

Once subjects have cGVHD progression, or have progression of their underlying malignancy (for subjects who have not withdrawn consent), they will be contacted approximately every 12 weeks (±14 days) by clinic visit or telephone to assess survival and the use of alternative cGVHD therapy. In addition, subjects who have progressive cGVHD will continue to have the Lee Symptom Scale and SF-36 assessments until the week 60 visit. Subjects will be contacted until death, subject withdrawal, lost to follow-up, or study termination by the Sponsor, whichever occurs first.

8.3.3. Expected length of participation on study

The Sponsor will continue to follow adult subjects up to approximately 3 years after the first subject was randomized. Adolescents (<22 years of age at the time of randomization) will be followed for up to 5 years after randomization; however, the study may close after the last patient below 18 years of age has exited the study if all other participating subjects have completed a minimum of 1 year of follow-up. Subjects may be rolled over to a long-term extension study for long-term follow-up.

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. Discontinuation from Ibrutinib/Placebo

Ibrutinib/placebo will be discontinued in the event of any of the following events:

- Subject begins treatment with another systemic therapy (including ECP) for cGVHD
- cGVHD progression
- Progression or relapse of the malignancy that was the indication for transplantation or development of PTLD
- Unacceptable toxicity: an intercurrent illness or AE that prevents further ibrutinib/placebo administration despite dose adjustment
- 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
- Unblinding at primary efficacy analysis
- Study termination by Sponsor
- Subject becomes pregnant
- Death

All subjects, regardless of reason for discontinuation of ibrutinib/placebo will undergo an End-of-Treatment visit and be followed as outlined under Section 8.3.

The investigator should notify the Sponsor within 24 hours if a subject discontinues ibrutinib/placebo treatment due to cGVHD progression and should provide documentation of cGVHD progression for review by the Sponsor's medical monitor.

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 completion / termination
- 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 full consent (ie, withdraws consent to treatment and all further contact) or partial consent (ie, withdraws consent to treatment but agrees to participate in follow-up visits); and/or, withdraws consent from future biomarker research.

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.

10.1. Analysis Sets

10.1.1. Intention-to-Treat Population (ITT)

The ITT Population is defined as all subjects who are randomized in the study. The ITT population will be used for all efficacy analyses.

The mITT Population is defined as all subjects who are randomized in the study (ITT) and who do not have evidence of progression of underlying malignancy from measurements made at or before the time of randomization. If indicated, the mITT population may be used for additional efficacy analyses.

10.1.2. Safety Population (SP)

The Safety Population will consist of all randomized subjects who received at least one dose of any study drug.

10.2. Sample Size Determination

The null hypothesis is that the two treatment arms have the same response rate at 48 weeks and the alternative hypothesis is that the response rates of two arms are different.

Assuming a response rate of 30% at 48 weeks for Arm B (placebo + prednisone), a sample size of 186 randomized subjects provides at least 80% power to detect a 20% difference in the response rates at 48 weeks between the 2 treatment arms (Arm A – Arm B) at an alpha level of 5% (2-sided).

No replacement of subjects will be implemented.

10.3. Subject Information

The distribution of subjects by treatment arm for each of the analysis populations will be provided. The number of subjects randomized, dosed, and discontinued will be summarized. Treatment discontinuation will be summarized according to the reasons for discontinuation and by treatment arm.

Demographic and baseline variables and baseline disease characteristics will be summarized by treatment arm.

10.4. Efficacy Analyses

10.4.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the response rate at 48 weeks (ie, the proportion of responders [CR or PR]). Response will be defined by the NIH Consensus Development Project Criteria (2014).

A subject will not be considered as a responder at 48 weeks if the response was not CR or PR, or if he/she meets any of following criteria:

- Starts a second-line systemic therapy for cGVHD at or prior to the response assessment at 48 weeks
- Has evidence of progression of the underlying malignancy that was the indication for transplant at or prior to response assessment at 48 weeks

Subjects who withdraw from the study prior to, or are missing the response at, 48 weeks will not be considered responders.

The primary efficacy analysis will be performed using the ITT population. The chi-square test will be used to compare the proportions between the two treatment arms.

10.4.2. Secondary Endpoints for Efficacy

The secondary efficacy endpoints are:

- Response rate at 24 weeks (the proportion of responders [CR or PR]) as defined by the NIH Consensus Development Project (2014)
- Duration of response (DOR) will be defined from the time of initial partial or complete response until progression of cGVHD
- Proportion of subjects with steroid dose reduction to a level of less than 0.15 mg/kg/d at 24 weeks
- Time to withdrawal of all immunosuppressants (with the exception of ibrutinib/placebo)

- Overall survival (OS) is defined as the time from randomization until death due to any cause
- Improvement in Lee cGVHD Symptom Scale scores will be compared between the two treatment arms

Proportion of subjects with improvement in overall score on the Lee cGVHD Symptom Scale and the proportion of subjects with steroid dose reduction will be analyzed using the same method for the primary efficacy endpoint. The Kaplan Meier methodology will be used to estimate the distribution of OS for each treatment group. The log-rank test will be used to compare the OS between the 2 treatment arms. Time to withdrawal of all immunosuppressants will be analyzed using the same method used for OS.

Duration of response is defined as the interval between the date of initial documentation of a response (PR or better), and the date of first documented evidence of progressive cGVHD or death for responders only. Responders will include subjects who achieve response (PR or better) based on NIH 2014 cGVHD criteria. Non-responders will be excluded from the analysis for DOR. Median duration of response will be estimated using Kaplan Meier methodology.

10.4.3. Exploratory Endpoints

- Pharmacokinetics (PK) parameters of ibrutinib when administered in combination with prednisone in subjects with cGVHD including adolescent subjects
- Pharmacodynamic characteristics (including BTK and ITK occupancy) of ibrutinib in subjects with cGVHD
- Biomarkers relevant to disease biology and therapy with ibrutinib for cGVHD
- Summary scales of SF-36 patient reported outcome

Pharmacokinetic

Ibrutinib and PCI-45227 bioanalytical data will be used in non-compartmental PK analysis. Plasma concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the PK report.

Descriptive statistics will be used to summarize ibrutinib and PCI-45227 concentrations at each sampling time point and PK parameters of ibrutinib and PCI-45227 (including, but not limited to: C_{max}, t_{max}, AUC_{last}, and $t_{1/2}$).

Individual and mean plasma ibrutinib and PCI-45227 concentration time profiles will be plotted.

Ibrutinib data from this study may also 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.

Biomarker and Pharmacodynamics

The following biomarker assessments will be undertaken:

1. Sequence-directed Immune Function Assessment
2. Cytokine, Chemokine, and Soluble Biomarker Assessment
3. Co-culture Immunologic Function Tests
4. CyTOF-based Phospho-immunophenotyping

PK/PD and biomarkers will be evaluated separately and will not be covered in the statistical analysis plan (SAP).

Patient Reported Outcomes

SF-36 summary scores will be evaluated; detailed analyses will be covered in the statistical analysis plan (SAP).

10.5. Safety Analysis

Analysis of safety data will be conducted on the safety population, which includes randomized subjects who receive at least 1 dose of ibrutinib/placebo. The baseline value is defined as the last value collected on or prior to the first dose date of ibrutinib/placebo, whichever comes first.

The safety variables to be summarized include exposure to ibrutinib/placebo and prednisone, AEs, clinical laboratory test results (hematology and chemistry), Karnofsky/Lansky performance status, and vital sign measurements. In general, safety data will be tabulated or listed. No formal statistical testing is planned.

Growth and development and late effects will be summarized in adolescent subjects.

Adverse Events

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

Treatment-emergent period is defined as the period of time from the first dose of study treatment, until the earlier of:

- Thirty days following the last dose of ibrutinib/placebo or prednisone whichever occurs later
  OR

- The start date of a new therapy for cGVHD or for the progression of the underlying malignancy.

The TEAEs are those events that:

- Are not present prior to the treatment-emergent period and occur during the treatment-emergent period,
- Are considered related to study drug by the investigator regardless of the start dates of the events, or
- Are present prior to the treatment-emergent period but worsen in severity during the treatment-emergent period or are subsequently considered related to study drug by the investigator.

All treatment-emergent AEs will be summarized. For each AE, the number and percentage of subjects who experience at least one occurrence of the given event will be summarized. The number and percent of subjects with TEAEs will be summarized according to intensity (CTCAE, v4.03) and drug relationship, as well as categorized by system organ class and preferred term. Summaries and listings may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe or a SAE.

Clinical Laboratory Tests

Laboratory tests will be summarized separately for hematology and serum chemistry. All laboratory values will be graded using the NCI CTCAE v4.03. The worst toxicity grade during the study will be tabulated.

Steroid-related Toxicities

Treatment-emergent steroid-related AEs will be summarized by the two study arms (Appendix Q). The number and percent of subjects with steroids related TEAEs will be summarized according to intensity (CTCAE, v4.03) and will be categorized by system organ class and preferred term.

10.6. Interim Futility Review

An interim analysis (for futility only) will be performed for the first 50 subjects who complete the Week 25 visit or discontinue study drug before this time. The independent DMC will review the interim futility analysis results and make a recommendation accordingly. Details regarding the interim futility review will be described in the DMC charter.

10.7. Data Monitoring Committee (DMC)

An independent DMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study and to meet efficacy objectives. The committee will meet periodically to review interim data. After the review, the DMC will make

recommendations regarding the continuation of the study. The DMC will also oversee the interim futility review. This review will be performed for the first 50 subjects who complete the Week 25 visit or discontinue study drug before this time. Available pharmacokinetics data will be provided to the DMC for the interim futility review.

The DMC will consist of at least one medical expert in the relevant therapeutic area and at least one statistician. The DMC responsibilities, authorities, and procedures will be documented in a separate charter.

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 AE 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 subject and/or observed by the investigator or study staff including laboratory abnormalities of clinical significance.
- Any AEs experienced by the subject through the completion of final study procedures.
- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with the underlying disease 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 ICF 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 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 SAE based on International Conference on Harmonisation (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 subject 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 subject'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 subject or subject 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 4.03 (CTCAE v4.03) will be used for grading the severity (intensity) of AEs. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE v4.03, 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 subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, 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 subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject 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 IB/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 IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be “unexpected” (by virtue of greater specificity) if the IB/package insert listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the IB 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 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 AE, it should be recorded on the AEs eCRF. If the AE is considered serious, it should be recorded on the AEs eCRF as serious and should be reported on the Serious Adverse Event Report Form. The Serious Adverse Event 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 AEs and SAEs at all subject evaluation timepoints during the study. All AEs and SAEs 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 AEs CRF and, when applicable, on the Serious Adverse Event Report Form.

Each recorded AE or SAE 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 from the time signed and dated ICF is obtained until 30 days following the last dose of study drug (ibrutinib/placebo or prednisone) or the start date of a new therapy for cGVHD. 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 of study drug until 30 days after the last dose of study drug that meet the AE definition must be recorded as AEs in the eCRF. SAEs will be reported to the Sponsor Drug Safety via an SAE reporting form and will be recorded in the eCRF from the time of ICF signing. 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.

Progression of cGVHD should NOT be reported as an event term, but instead symptoms/clinical signs of disease progression may be reported (see Section 11.1.1).

All AEs, 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 AE to study therapy. All measures required for AE 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. Autopsy and postmortem reports must be forwarded to the Sponsor, or designee, as outlined above, if allowed per local regulatory guidelines.

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

11.4.3. Expediting Reporting Requirements for Serious Adverse Events

All SAEs (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 SAEs 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. 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 or female partner of a male subject must immediately inform the investigator if she becomes pregnant from the time of consent to 90 days after the last dose of study drug (s). 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 AE, the outcome will need to be documented. Any pregnancy occurring in a female subject or female partner of a male subject must be reported from the time of first dose up until 90 days after the last dose of study drug (s). 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 SAE.

11.4.5. Other Malignancies

All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for OS. If observed, enter data in the corresponding eCRF. Relapse of underlying malignancy will not be considered a new malignancy.

11.4.6. Eye-Related Adverse Events

New or worsening eye-related symptoms that are Grade 2 or higher, or a symptom that was Grade 2 or higher at baseline worsens, should be evaluated by an ophthalmologist whose findings should be reported on the ophthalmologic eCRF.

11.4.7. Adverse Events of Special Interest (AESI)

Specific AEs, or groups of AEs, 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.

11.4.7.1. 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 11.4.7 above.

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 ICF 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. Parental permission will be obtained for subjects who are below the age of legal consent and assent procedures for minors will follow country specific national regulations. 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 the Food and Drug Administration (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 7.1.1.1), 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 who have consented to enroll 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 case report forms (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

The case report forms 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 exists 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 and any comparator used 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 ibrutinib 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-1140-IM)
2. Subject identification number
3. Lot number(s) of ibrutinib or placebo 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.

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. If access to the EMR cannot be granted to the monitor, the site must ensure that all certified copies of documents are available during monitoring visits for all screened and enrolled subjects. 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 sub-investigator (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.

The ICF will include a description of treatment in the event of a study related injury and handling of the costs associated therewith, 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.

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14. APPENDICES

Appendix A. Schedule of Assessments

	Screening Phase	Treatment Phase							Post-Treatment/ Follow-up Phase		Late effects surveillance (adolescents only)
Study Weeks		**1**	**2**	**5**	**9, 13, 17, 21, 25 q4 weeks**	**37, 49 q12 weeks**	**Progressive Disease Visit**	**End-of-Treatment Visit (30 days from last dose of study drug)**	**Response Follow-up Visits (Until progressive disease) q12 weeks[m]**	**Survival Follow-up q12 weeks**	**Month 12, 24, 36, 48, and 60**
Study Day of Study Week		**1**	**1**	**1**	**1**	**1**					
Study Windows	*-28 days*	*On time*		*±3 days*		*± 7 days*	*anytime*	*± 7 days*		*± 14 days*	*± 30 days*
Administrative Procedures											
Informed consent/Child Assent/Parental permission	x										
Confirm eligibility	x	x[b]									
Randomization		x[b]									
cGVHD diagnosis & staging (NIH)	x										
Medical history and demographics	x										
Malignancy relapse evaluation	x										
Infection surveillance	x										
GVHD/Transplant history	x										
Physical exam	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]		
KPS/Lansky status	x	x		x	x	x	x	x	x		
Vital signs	x	x	x	x	x	x	x	x	x		
Survival										x	
ECG [c]	x		x[c]		If clinically indicated (eg, subjects with palpitations, lightheadedness)						

	Screening Phase	Treatment Phase							Post-Treatment/ Follow-up Phase		Late effects surveillance (adolescents only)
Study Weeks		**1**	**2**	**5**	**9, 13, 17, 21, 25 q4 weeks**	**37, 49 q12 weeks**	**Progressive Disease Visit**	**End-of-Treatment Visit (30 days from last dose of study drug)**	**Response Follow-up Visits (Until progressive disease) q12 weeks[m]**	**Survival Follow-up q12 weeks**	**Month 12, 24, 36, 48, and 60**
Study Day of Study Week		**1**	**1**	**1**	**1**	**1**					
Study Windows	*-28 days*	*On time*		*±3 days*		*± 7 days*	*anytime*	*± 7 days*		*± 14 days*	*± 30 days*
Documentation of height, weight, and Tanner Stage	x[j]										x[j]
Surveillance for late effects (adolescents only)	x[j]										x[j]
Clinical Laboratory Assessments											
Hematology	x	x[g]	x	x	x	x	x	x	x		
Serum chemistry	x	x[g]	x	x	x	x	x	x	x		
Coagulation (PT, INR, and aPTT)	x										
Pregnancy test[d]	x	x									
Hepatitis serologies and/or PCR	x										
Quantitative serum immunoglobulins (IgA, IgG and IgM)		x			Weeks 13, 25	x	x	x			
PK/PD, T/B/NK cell counts, biomarkers[f]	Please see Appendix B for sample requirements and timing for these assays										
Efficacy Assessments											
cGVHD activity assessment (NIH Form)	x[k]			x	Weeks 13, 25[h]	x[h]	x	x[l]	x		
cGVHD response assessment				x	Weeks 13, 25[h]	x[h]	x	x[l]	x		

	Screening Phase	Treatment Phase							Post-Treatment/ Follow-up Phase		Late effects surveillance (adolescents only)
Study Weeks		**1**	**2**	**5**	**9, 13, 17, 21, 25 q4 weeks**	**37, 49 q12 weeks**	**Progressive Disease Visit**	**End-of-Treatment Visit (30 days from last dose of study drug)**	**Response Follow-up Visits (Until progressive disease) q12 weeks[m]**	**Survival Follow-up q12 weeks**	**Month 12, 24, 36, 48, and 60**
Study Day of Study Week		**1**	**1**	**1**	**1**	**1**					
Study Windows	*-28 days*	*On time*		*±3 days*		*± 7 days*	*anytime*	*± 7 days*		*± 14 days*	*± 30 days*
Lee cGVHD Symptom Scale/ SF-36 [e]	x[k]			x	Weeks 13, 25[h]	x[h]	x	x[l]	x	(x)	x
FEV1 by spirometry[h]	x				Weeks 13, 25[h]	x[h]	x	x	x		
Corticosteroid requirements	x	x	x	x	x	x	x	x	x		
Ongoing Subject Assessments											
Concomitant medications	x	30 days prior to Informed Consent to 30 days after last dose of ibrutinib/placebo or prednisone									
Prednisone dosing changes – phone contacts	x	Continuous from Informed Consent to 30 days after last dose of ibrutinib/placebo or prednisone									
Adverse events	x	Continuous from Informed Consent to 30 days after last dose of ibrutinib/placebo or prednisone									
Study Drug Administration and Dispensation											
Prednisone 1 mg/kg/day		Continuous daily dosing Dispensed on Week 1 D1, Week 5 and every on treatment visit thereafter									
Ibrutinib/Placebo 420 mg PO		Continuous daily dosing Dispensed on Week 1 D1, Week 5 and every on treatment visit thereafter									
Drug diary dispensing, review, and drug accountability		Continuous throughout study					x[i]	x[i]			

Abbreviations: AEs = adverse events; aPTT = activated partial thromboplastin time; ECG = electrocardiogram; KPS = Karnofsky Performance Status; EOT = end-of-treatment; INR = international normalized ratio; PD = pharmacodynamic; PK = pharmacokinetics; PO = orally; PT = prothrombin time; q4 weeks = every 4 weeks; q8 weeks = every 8 weeks; q12 weeks =every 12 weeks

Footnote:

[a] The physical examination will include, height (at Screening for adults, and at Screening and annually for subjects <22 years of age at the time of enrollment), weight, and examination per clinical practice.
[b] Confirm eligibility and randomize within 3 days prior to first dose.
[c] ECG's may be performed at the investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset of dyspnea. At Week 2 12-lead ECG (subject in supine position and resting for at least 10 min prior to ibrutinib dose) performed on subjects <22 years of age at enrollment.
[d] 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.
[e] Lee cGVHD Symptom Scale and SF-36 should be completed prior to any assessments, and before being clinically evaluated by the study nurse or physician.
[f] Pharmacokinetic (PK) samples will be drawn for all subjects according to the schedule in Appendix B predose specimen is required. Pharmacodynamic (PD), T/B/NK and Biomarker sampling will be performed on selected days. Refer to Appendix B for more details.
[g] Hematology and Serum Chemistry may be done within 3 days of Day 1.
[h] The cGVHD Response assessment, Lee cGVHD Symptom Scale, SF-36, and FEV1 may be done from 7 days prior to Week 25/49 to 21 days after Week 25/49. If FEV1 results are abnormal at Screening FEV1 should be obtained every 12 weeks, and if normal at Screening repeat every 24 weeks. Lung score should be obtained with every cGVHD assessment.
[i] Drug diary review and drug accountability only. Must be done at End of Treatment Visit if not already done at Progressive Disease visit.
[j] Tanner stage and late effects are needed annually up to 60 months post enrollment only for subjects <22yrs of age at enrollment. Adolescents (<22 years of age at the time of enrollment) will be followed for up to 5 years after enrollment and may be rolled-over to a long-term extension study during late-effects follow-up.
[k] cGVHD should be evaluated prior to start of prednisone (if initiated during Screening) or prior to Week1 Day 1 start of prednisone and ibrutinib/placebo.
[l] cGVHD response assessments and PRO measures at EOT visit need not be repeated if performed within the previous 30 days.
[m] Subjects in Response follow-up should be evaluated at all pre-specified response assessment time points, including week 5, week 13, week 25, and every 12 weeks afterward.

Appendix B. Schedule of Assessments for Pharmacokinetics, Pharmacodynamics, Biomarker and T/B/NK

Day 1, Week	Time	Pharmacokinetics	Pharmacodynamics	Biomarkers	T/B/NK
Screening				X €, α	X
1	Predose		X	X €, α, N	X
2	Predose[a] (trough value)	X			
	1h post dose[b] (± 15 min)	X			
	2 h post dose[b] (± 15 min)	X			
	4 h post dose[b] (± 30 min)	X			
	6 h post dose[b] (± 1 h)	X			
5	Predose		X	X €, α	X
9	Predose		X	X €, α, N	X
13	Predose		X	X €, α	X
17	Predose		X	X €, α, N	X
21	Predose		X	X €, α	X
25	Predose[a] (trough value)	X	X	X €, α, N	X
	1h post dose[b] (± 15 min)	X			
	2 h post dose[b] (± 15 min)	X			
	4 h post dose[b] (± 30 min)	X			
	6 h post dose[b] (± 1 h)	X			
37	Predose			X €	X
49	Predose		X	X €, α, N	X
73	Predose		X	X €	X
97	Predose		X	X €, α	X
Progressive Disease Visit			X	X €, α	X
Sample Collection Tube Type		NaHep (2mL)	ACD (8.5 mL)	€=EDTA (10 mL), α=ACD (8.5 mL) N=NaHep (10 mL)	EDTA (10 ml)

[a] Sample collected 24 hours (± 2 hours) after last intake and prior to dosing on that PK day (applies only on days when PK is collected).

[b] Record actual time of sample collection (applies only on days when PK is collected).

The same timepoints as Week 2 and Week 25 PK sample collection will be followed. If ibrutinib/placebo is on hold during scheduled Week 2 and 25 Week PK evaluation, PK testing should be obtained on the next scheduled visit after ibrutinib dose has been stable for 7 days.

Appendix C. Karnofsky/Lansky Performance Status

Karnofsky Scale (recipient age ≥16 years)		**Lansky Scale (recipient age <16 years)**	
Able to carry on normal activity; no special care is needed		**Able to carry on normal activity; no special care is needed**	
100	Normal, no complaints, no evidence of disease	**100**	Fully active
90	Able to carry on normal activity	**90**	Minor restriction in physically strenuous play
80	Normal activity with effort	**80**	Restricted in strenuous play, tires more easily, otherwise active
Unable to work, able to live at home, cares for most personal needs, a varying amount of assistance is needed		**Mild to moderate restriction**	
70	Cares for self, unable to carry on normal activity or to do active work	**70**	Both greater restrictions of, and less time spent in active play
60	Requires occasional assistance but is able to care for most needs	**60**	Ambulatory up to 50% of time, limited active play with assistance/supervision
50	Requires considerable assistance and frequent medical care	**50**	Considerable assistance required for any active play, fully able to engage in quiet play
Unable to care for self, requires equivalent of institutional or hospital care, disease may be progressing rapidly		**Moderate to severe restriction**	
40	Disabled, requires special care and assistance	**40**	Able to initiate quiet activities
30	Severely disabled, hospitalization indicated, although death not imminent	**30**	Needs considerable assistance for quiet activity
20	Very sick, hospitalization necessary	**20**	Limited to very passive activity initiated by others (eg, TV)
10	Moribund, fatal process progressing rapidly	**10**	Completely disabled, not even passive play

Appendix D. Inhibitors and Inducers of CYP3A

Inhibitors and inducers of CYP3A enzymes are defined as follows. Refer to Section 6.2.1 on instructions for concomitant use of CYP3A inhibitors and inducers with ibrutinib. Further information can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/main-table/.

Inhibitors of CYP3A	Inducers of CYP3A
Strong inhibitors:	carbamaze
indinavir	nevirapine
nelfinavir	barbiturates
ritonavir	glucocorticoids
clarithromycin	modafinil
Itraconazole	oxcarbazepine
Ketoconazole	pioglitazone
nefazodone	troglitazone
saquinavir	pioglitazone
suboxone	**Strong CYP3A inducers**
telithromycin	avasimibe
cobicistat	carbamazepine
boceprevir	phenobarbital
mibefradil	phenytoin
telaprevir	rifabutine
troleandomycin	rifampin
posaconazole	St. John's Wort
voriconazole	
Moderate inhibitors:	
aprepitant	
amprenavir	
amiodarone	
atazanavir	
ciprofloxacin	
isavuconazole	
crizotinib	
darunavir	
dronedarone	
erythromycin	
diltiazem	
fluconazole	
fosamprenavir	
grapefruit juice	
Seville orange juice	
verapamil	
imatinib	
Weak inhibitors:	
cimetidine	
fluvoxamine	
All other inhibitors:	
chloramphenicol	
delavirdine	
gestodene	
mifepristone	
norfloxacin	
star fruit	

[a] Itraconazole and ketoconazole will be replaced with voriconazole for study subjects

Appendix E. Child-Pugh Score for Subjects with Chronic Liver Impairment

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

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

Appendix F. 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 G. SF-36 Questionnaire

Your Health and Well-Being

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Thank you for completing these questions!

Appendix H. Chronic GVHD Activity Assessment – Clinician

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

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN

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

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

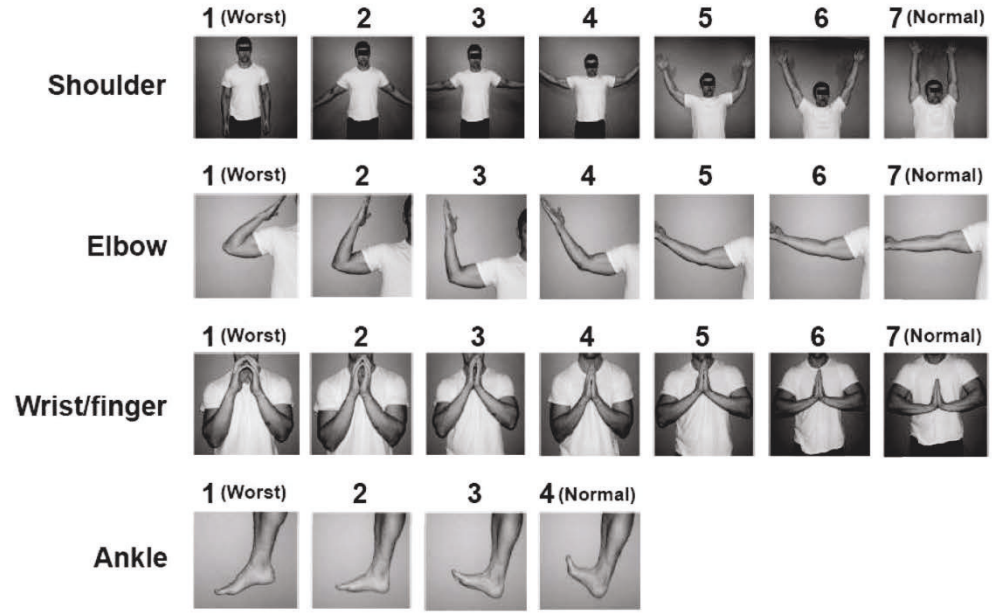
Gastrointestinal-Esophageal • Dysphagia OR Odynophagia	*0= no esophageal symptoms* *1=Occasional dysphagia or odynophagia with solid food or pills during the past week* *2=Intermittent dysphagia or odynophagia with solid foods or pills, but not for liquids or soft foods, during the past week* *3=Dysphagia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

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

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN (FORM A)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
SKIN	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
GVHD features to be scored by BSA: **Check all that apply**: ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like				
☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				
SKIN FEATURES SCORE	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
If skin features score = 3, BSA% of non-moveable sclerosis/fasciitis _____ How would you rate the severity of this patient's skin and/or joint tightening on the following scale, where 0 is not at all severe and 10 is the most severe symptoms possible: 0 1 2 3 4 5 6 7 8 9 10 Symptoms not at all severe … Most severe symptoms possible				
EYES	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops >3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyewear 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 ground)	Severe symptoms (shortness of breath at rest; requiring 0_2)
Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				
JOINTS AND FASCIA	No symptoms	Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL	Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self, etc.)
Abnormality present but explained entirely by non-GVHD documented cause (specify):_____				



❑ Not done

❑ Not done

❑ Not done

❑ Not done

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

Reference:

Lee SJ, Wolff D, Kitko C, 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. The 2014 Response CriteriaWorking Group Report. Biol Blood Marrow Transplant. 2015;21:984-999.

Appendix I. Response Determination for Chronic GVHD Clinical Trials based on Clinician Assessments

Organ	Complete Response	Partial Response	Progression
Skin	NIH Skin Score 0 after previous involvement	Decrease in NIH Skin Score by 1 or more points	Increase in NIH Skin Score by 1 or more points, except 0 to 1
Eyes	NIH Eye Score 0 after previous involvement	Decrease in NIH Eye Score by 1 or more points	Increase in NIH Eye Score by 1 or more points, except 0 to 1
Mouth	NIH Modified OMRS 0 after previous involvement	Decrease in NIH Modified OMRS of 2 or more points	Increase in NIH Modified OMRS of 2 or more points
Esophagus	NIH Esophagus Score 0 after previous involvement	Decrease in NIH Esophagus Score by 1 or more points	Increase in NIH Esophagus Score by 1 or more points, except 0 to 1
Upper GI	NIH Upper GI Score 0 after previous involvement	Decrease in NIH Upper GI Score by 1 or more points	Increase in NIH Upper GI Score by 1 or more points, except 0 to 1
Lower GI	NIH Lower GI Score 0 after previous involvement	Decrease in NIH Lower GI Score by 1 or more points	Increase in NIH Lower GI Score by 1 or more points, except from 0 to 1
Liver	Normal ALT, alkaline phosphatase, and Total bilirubin after previous elevation of 1 or more	Decrease by 50%	Increase by 2 × ULN
Lungs	- Normal %FEV1 after previous involvement - If PFTs not available, NIH Lung Symptom Score 0 after previous involvement	- Increase by 10% predicted absolute value of %FEV1 - If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points	- Decrease by 10% predicted absolute value of %FEV1 - If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1
Joints and fascia	Both NIH Joint and Fascia Score 0 and P-ROM score 25 after previous involvement by at least 1 measure	Decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 point for any site	Increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 point for any site
Global	Clinician overall severity score 0	Clinician overall severity score decreases by 2 or more points on a 0-10 scale	Clinician overall severity score increases by 2 or more points on a 0-10 scale

ULN indicates upper limit of normal.

Overall Response:

Skin, mouth, liver, upper and lower GI, esophagus, lung, eye, and joint/fascia are the organs or sites considered in evaluating overall response.

- Complete Response (CR) is defined as resolution of all manifestations in each organ or site
- Partial Response (PR) is defined as improvement in at least 1 organ or site without progression in any other organ or site.
- Disease Progression is defined as clinically meaningful worsening in one or more organs regardless of improvement in other organs. Mixed Response: CR or PR in at least 1 organ accompanied by progression in another organ is considered disease progression.
- Stable disease (SD): response that does not meet the criteria for CR, PR, or disease progression.

If a patient shows overall cGVHD improvement while organ responses indicate progression in one or more organs, cGVHD assessment should be repeated at a different time point, to confirm progression, before discontinuing study drug. Response assessments coinciding with chronic GVHD flares (transient worsening of organs that were previously involved) will be inevaluable and should be repeated as soon as the flare resolves or at the next assessment time point. If progression is confirmed, time to progression will be calculated using first date of disease progression. Lack of Response includes categories of disease progression or stable disease.

Lee SJ, Wolff D, Kitko C, 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. The 2014 Response Criteria Working Group Report. Biol Blood Marrow Transplant. 2015;21:984-999.

Appendix J. 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 You Present Imagine** 0	1	2	3	4	5	6	7	8	9	**As Bad As Can** 10
Your **skin itching** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **skin and/or joint tightening** at their WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **mouth sensitivity** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **genital discomfort** at its WORST? (Women – vagina, vulva, or labia) (Men – penis)	O	O	O	O	O	O	O	O	O	O	O

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

Patient Global Ratings:

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

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

0 1 2 3 4 5 6 7 8 9 10

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

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

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

Reference:

Lee SJ, Wolff D, Kitko C, 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. The 2014 Response Criteria Working Group Report. Biol Blood Marrow Transplant. 2015;21:984-999.

Appendix K. Prednisone Equivalents Table

Corticosteroid Doses Equivalent to 20 mg Prednisone

Corticosteroid	**Equivalent dose (mg)**
Prednisone	20
Cortisone	100
Cortisol	80
Hydrocortisone	80
Prednisolone	20
Methylprednisolone	16
Triamcinolone	16
Betamethasone	3
Dexamethasone	3

Source:

Brunton LL, Chabner BA, Knollmann BC (Eds). The Pharmacological Basis of Therapeutics, 12th ed. McGraw Hill, New York 2011. p.1216.

Appendix L. Summary of Ancillary Therapy and Supportive Care Interventions

Organ System	Organ-Specific Intervention*	
	Prevention	**Treatment**
Skin and appendages	Photoprotection -sun avoidance and physical sunblocks (eg, protective clothing, UVA, and UVB sunscreens). Avoidance of photosensitizing agents (eg, voriconazole). Surveillance for malignancy [Inamoto 2015, Majhail 2012].	For intact skin topical emollients including urea containing products, corticosteroids, antipruritic agents, and others (eg, PUVA or narrow band UVB, calcineurin inhibitors). For erosions/ulcerations e microbiologic cultures, topical antimicrobials, protective films or other dressings, debridement, hyperbaric oxygen, wound care specialist consultation.
Mouth and oral cavity	Maintain good oral/dental hygiene. Routine dental cleaning and radiographs. Surveillance for infection and malignancy. Nutritional counseling, if needed.	Topical high and ultra-high potency corticosteroids and topical calcineurin inhibitors. Topical analgesics. Therapy for oral dryness (eg, salivary stimulants, sialogogues) and for prevention of related complications (ie, dental decay).
Eyes	Photoprotection. Surveillance for infection, cataract formation, and increased intraocular pressure.	Artificial tears, ocular ointments, topical corticosteroids or cyclosporine, punctal occlusion, humidified environment, occlusive eye wear, moisture chamber eyeglasses, cevimeline, pilocarpine, gas-permeable scleral contact lens, autologous serum, microbiologic cultures, topical antimicrobials, doxycycline.
Vulva and vagina	Surveillance for estrogen deficiency, infection (HSV, HPV, yeast, bacteria) and malignancy [Majhail 2012].	Water-based or silicone lubricants, topical estrogens, topical corticosteroids or calcineurin inhibitors, dilators or vibrators, surgery for extensive synechiae or obliteration, early gynecology consultation. Avoid glycerin, paraben, fragrance, and other additive products.
Gastrointestinal tract and liver	Surveillance for infection (viral, bacterial, fungal, parasites)	Rule out other potential etiologies. Dietary modification, enzyme supplementation for pancreatic insufficiency, bile salt resins, gastroesophageal reflux management, esophageal dilatation, ursodeoxycholic acid, topical glucocorticoids, limitation of ethanol intake, avoidance of hepatotoxins.

Organ System	Organ-Specific Intervention*	
	Prevention	**Treatment**
Lungs	Surveillance for infection (Pneumocystis jiroveci, viral, fungal, bacterial).	Rule out other potential etiologies (eg, infection, gastroesophageal reflux). Inhaled corticosteroids, bronchodilators, supplementary oxygen, pulmonary rehabilitation. Consideration of lung transplantation in appropriate candidates.
Hematopoietic	Surveillance for infection (CMV, parvovirus)	Rule out other potential etiologies (eg, drug toxicity, infection). Hematopoietic growth factors, immunoglobulin for immune cytopenias
Neurologic	Calcineurin drug level monitoring. Seizure prophylaxis as indicated, including blood pressure control, electrolyte replacement, anticonvulsants. EMG monitoring and staging in symptomatic patients taking medications known to cause neuropathy. Close monitoring of distal extremities for wounds in insensate patients.	Occupational and physical therapy to prevent falls and improve function, treatment of neuropathic syndromes with tricyclic antidepressants, SSRI, or anticonvulsants [Smith 2013]. Orthotics and assistive devices (canes and walkers). Bracing, splinting or surgical release for entrapment neuropathies.
Immunologic and infectious diseases	Immunizations and prophylaxis against Pneumocystis jirovecii, VZV, and encapsulated bacteria based on CDC guidelines. Consider immunoglobulin replacement based on levels and recurrent infections. Surveillance for infection (viral, bacterial, fungal, atypical).	Organism-specific antimicrobial agents. Empiric parenteral broad-spectrum antibacterial coverage for fever.
Musculoskeletal	Surveillance for decreased ROM, bone densitometry, calcium levels and 25-OH vitamin D. Physical therapy, calcium, vitamin D, and bisphosphonates. Flexion-extension x-rays to look for instability.	Physical therapy, bisphosphonates for osteopenia, and osteoporosis. Spinal orthosis for instability and/or intractable pain. Walking program, resistance training, core strengthening.

SSRI indicates selective serotonin reuptake inhibitors; CDC, Centers for Disease Control.

*In general, close serial monitoring of all organ systems is recommended to promote early detection and intervention directed toward reversing or preventing progression of chronic GVHD manifestations and treatment-associated toxicities. Ancillary and supportive care therapies are commonly employed in addition to systemic GVHD treatment, although in some cases their use may circumvent the need for systemic treatment or allow doses of systemic agents to be reduced.

Carpenter PA, Kitko CL, Elad S. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: V. The 2014 Ancillary Therapy and Supportive Care Working Group Report. Biol Blood Marrow Transplant. 2015;21:1167–87.

Inamoto Y, Savani BN, Shaw BE, et al. Secondary solid cancer screening following hematopoietic cell transplantation. Bone Marrow Transplant. 2015.[Epub ahead of print].

Majhail NS, Rizzo JD, Lee SJ, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2012;18:348–71.

Smith EM, Pang H, Cirrincione C, et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA. 2013;309:1359–67.

Appendix M. Diagnosis of cGVHD – Signs and Symptoms of cGVHD

ORGAN OR SITE	DIAGNOSTIC (Sufficient to establish the diagnosis of chronic GVHD)	DISTINCTIVE[a] (Seen in chronic GVHD, but insufficient alone to establish a diagnosis)	OTHER FEATURES OR UNCLASSIFIED ENTITIES[b]	COMMON[c] (Seen with both acute and chronic GVHD)
Skin	• Poikiloderma • Lichen planus-like features • Sclerotic features • Morphea-like features • Lichen sclerosus-like features	• Depigmentation • Papulosquamous lesions	• Sweat impairment • Ichthyosis • Keratosis pilaris • Hypopigmentation • Hyperpigmentation	• Erythema • Maculopapular rash • Pruritus
Nails		• Dystrophy • Longitudinal ridging, splitting or brittle features • Onycholysis • Pterygium unguis • Nail loss (usually symmetric, affects most nails)		
Scalp and body hair		• New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) • Loss of body hair • Scaling	• Thinning scalp hair, typically patchy, coarse or dull (not explained by endocrine or other causes) • Premature gray hair	
Mouth	• Lichen planus-like changes	• Xerostomia • Mucoceles • Mucosal atrophy • Ulcers • Pseudomembranes		• 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)	

ORGAN OR SITE	**DIAGNOSTIC** (Sufficient to establish the diagnosis of chronic GVHD)	**DISTINCTIVE**[a] (Seen in chronic GVHD, but insufficient alone to establish a diagnosis)	**OTHER FEATURES OR UNCLASSIFIED ENTITIES**[b]	**COMMON**[c] (Seen with both acute and chronic GVHD)
Genitalia *Females* *Males*	• Lichen planus-like features • Lichen sclerosus-like features • Vaginal scarring or clitoral/labial agglutination • Phimosis or urethral/meatus 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 x upper limit of normal • ALT >2 x upper limit of normal
Lung	• Bronchiolitis obliterans diagnosed with lung biopsy • Bronchiolitis obliterans syndrome (BOS)[d]	• Air trapping and bronchiectasis on chest CT	• Cryptogenic organizing pneumonia (COP)[e] • Restrictive lung disease[e]	

ORGAN OR SITE	DIAGNOSTIC (Sufficient to establish the diagnosis of chronic GVHD)	DISTINCTIVE[a] (Seen in chronic GVHD, but insufficient alone to establish a diagnosis)	OTHER FEATURES OR UNCLASSIFIED ENTITIES[b]	COMMON[c] (Seen with both acute and chronic GVHD)
Muscles, fascia, joints	• Fasciitis • Joint stiffness or contractures secondary to fasciitis or sclerosis	• Myositis or polymyositis[f]	• Edema • Muscle cramps • Arthralgia or arthritis	
Hematopoietic and Immune			• Thrombocytopenia • Eosinophilia • Lymphopenia • Hypo- or hyper-gammaglobulinemia • Autoantibodies (AIHA, ITP) • Raynaud's phenomenon	
Other			• Pericardial or pleural effusions • Ascites • Peripheral neuropathy • Nephrotic syndrome • Myasthenia gravis • Cardiac conduction abnormality or cardiomyopathy	

Abbreviations: ALT indicates alanine aminotransferase; AIHA, autoimmune hemolytic anemia; ITP, idiopathic thrombocytopenic purpura.

[a] In all cases, infection, drug effect, malignancy, or other causes must be excluded.

[b] Can be acknowledged as part of the chronic GVHD manifestations if diagnosis is confirmed.

[c] Common refers to shared features by both acute and chronic GVHD.

[d] BOS can be diagnostic for lung chronic GVHD only if distinctive sign or symptom present in another organ (see text).

[e] Pulmonary entities under investigation or unclassified.

[f] Diagnosis of chronic GVHD requires biopsy.

Jagasia HM, Greinix HT, Arora M, et al. Biol Blood Marrow Transplant.2015;21:389–401.

Appendix N. Staging of cGVHD

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

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

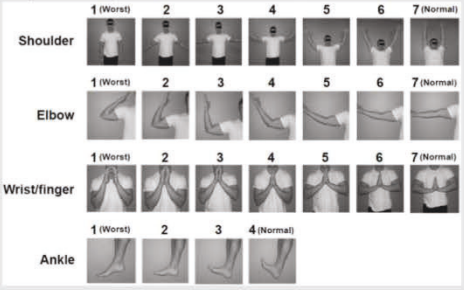
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	No symptoms	Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	Tightness of arms or legs **OR**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

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

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

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

Photographic Range of Motion (P-ROM)



† Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring.

* Weight loss within 3 months.

**Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

Abbreviations: ECOG (Eastern Cooperative Oncology Group), KPS (Karnofsky Performance Status), LPS (Lansky Performance Status); BSA (body surface area); ADL (activities of daily living); LFTs (liver function tests); AP (alkaline phosphatase); ALT (alanine aminotransferase); ULN (normal upper limit).

‡ To be completed by specialist or trained medical providers (see Supplemental Figure).

Source:

Jagasia HM, Greinix HT, Arora M, et al. Biol Blood Marrow Transplant.2015;21:389–401.

Appendix O. NIH Global Severity/Staging of cGVHD

Mild chronic GVHD

1 or 2 Organs involved with no more than score 1

plus

Lung score 0

Moderate chronic GVHD

3 or More organs involved with no more than score 1

OR

At least 1 organ (not lung) with a score of 2

OR

Lung score 1

Severe chronic GVHD

At least 1 organ with a score of 3

OR

Lung score of 2 or 3

Key points:

- In skin: higher of the 2 scores to be used for calculating global severity.
- In lung: FEV1 is used instead of clinical score for calculating global severity.
- If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.
- If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

Reference:

Jagasia HM, Greinix HT, Arora M, et al. Biol Blood Marrow Transplant.2015;21:389–401.

Appendix P. Late Effects Surveillance for Adolescents

In addition to procedures listed in Appendix A and Appendix B, adolescents (≥12 to <22 years of age at the time of randomization) will be monitored for growth and development, immune reconstitution, and late effects up to 5 years post randomization.

	Screening	**Week 49±7 days**	**At month 24, 36, 48, 60 ±30 days**
Additional measurements			
Height and Weight	X	X	X
Tanner Stage	X	X	X
Immune Reconstitution[a] Tests		X	X
History of Late Effects (chart review)	X	X	X[b]

[a] Immune reconstitution studies will include the following studies obtained as part of standard of care:

- T and B cell enumeration
- Quantitative Immunoglobulins
- Post-vaccination titers

[b] Are obtained annually. Post vaccination studies may not be performed annually

Medical Record Review for Transplant-Related Late Effects

Symptom	No	yes		
		Date of Diagnosis	Was therapy Given?	Was therapy still given at the time this assessment
Diabetes/hyperglycemia requiring chronic treatment				
Hyperlipidemia requiring therapy				
Hypothyroidism requiring hormone replacement				
Gonadal dysfunction requiring hormone replacement (testosterone or estrogen/progesterone)				
Growth hormone deficiency/short stature				
Avascular necrosis				
Osteoporosis				
Osteoporotic fracture				
Depression or anxiety requiring therapy				
Post-traumatic stress disorder requiring therapy				
Cataracts				
Other impairment or disease				
B-cell immune deficiency				
vaccines received over the last year		If vaccines administered complete immunization CRF		

Tanner Stage

Boys – Development of external genitalia

Stage 1: Prepubertal

Stage 2: Enlargement of scrotum and testes; scrotum skin reddens and changes in texture

Stage 3: Enlargement of penis (length at first); further growth of testes

Stage 4: Increased size of penis with growth in breadth and development of glans; testes and scrotum larger, scrotum skin darker

Stage 5: Adult genitalia

Girls – Breast development

Stage 1: Prepubertal

Stage 2: Breast bud stage with elevation of breast and papilla; enlargement of areola

Stage 3: Further enlargement of breast and areola; no separation of their contour

Stage 4: Areola and papilla form a secondary mound above level of breast

Stage 5: Mature stage: projection of papilla only, related to recession of areola

Boys and Girls – Pubic hair

Stage 1: Prepubertal (can see velus hair similar to abdominal wall)

Stage 2: Sparse growth of long, slightly pigmented hair, straight or curled, at base of penis or along labia

Stage 3: Darker, coarser and more curled hair, spreading sparsely over junction of pubes

Stage 4: Hair adult in type, but covering smaller area than in adult; no spread to medial surface of thighs

Stage 5: Adult in type and quantity, with horizontal distribution (“feminine”)

Appendix Q. Corticosteroid-related toxicities and CTCAE preferred terms

Corticosteroid symptom	CTCAE graded AE
Glucose intolerance related to steroid use	Glucose intolerance
Elevated lipids related to steroid use	Hypertriglyceridemia, Cholesterol high
Hypertension	Hypertension
Steroid myopathy	Generalized muscle weakness
Steroid skin toxicity (eg, striae, thinning of skin, etc.)	Skin atrophy
Neuropsychiatric symptoms including insomnia	Insomnia, Agitation, Psychosis, or other psychiatric symptoms
Oral/vaginal candidiasis or uncomplicated zoster infection	Mucosal infection (e.g. oral/vaginal candidiasis)
Any other infection	Infections
Diabetic nephropathy-related to steroid use	Proteinuria
Posterior reversible encephalopathy	Encephalopathy, Reversible posterior leukoencephalopathy syndrome
Abnormal bone density (>than - 2 Z score)	Osteoporosis (Osteopenia with a t-score -1 to -2.5)
Insufficiency (pathologic) bone fractures	Fracture
Adrenal insufficiency	Adrenal insufficiency
Gastrointestinal perforation	Gastric perforation, Esophageal perforation, Duodenal perforation, Colonic perforation, Ileal perforation
Peptic ulcer disease	Duodenal ulcer
Osteonecrosis of bones (avascular necrosis)	Periodontal disease, Avascular necrosis
Tendon rupture	Musculosceletal and connective disorders, other
Retinopathy (diabetic or central serous (choroidal) retinopathy)	Retinopathy
Intraocular pressure elevation	Glaucoma, papilledema or eye disorder, other
Posterior subcapsular cataract	Cataract