Janssen Pharmaceutical K.K.*

Clinical Protocol

A Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib in Subjects with Steroid Dependent/Refractory Chronic Graft Versus Host Disease (cGVHD)

Protocol 54179060GVH3001; Phase 3
AMENDMENT 1

JNJ-54179060 (Ibrutinib)

*This study is being conducted by Janssen Pharmaceutical K.K. in Japan. The term "sponsor" is used throughout the protocol to represent Janssen Pharmaceutical K.K.

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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TABLES

PROTOCOL AMENDMENTS

Protocol Version	Date
Original Protocol	28 Dec 2017
Amendment 1	24 Jul 2018

Amendments below are listed beginning with the most recent amendment.

Amendment 1 (24 Jul 2018)

The overall reason for the amendment: To modify a definition of steroid-dependent in inclusion criteria 1 so that the definition further fit the clinical practices. And to add explanation to cGVHD response criteria of Complete Response in Liver (Attachment 5).

Applicable Section(s)	Description of Change(s)
Rationale: To modify a definition of steroid dependent in inclusion criteria 1 so that the definition further fit the clinical practices.	
4.1. Inclusion Criteria 1	Following description was added to definition of steroid-dependent cGVHD: In case of inability to taper the dose to ≤0.25 mg/kg/day or ≤0.5 mg/kg every other day (prednisolone doses) due to recurrence or progression of cGVHD manifestations, it is considered as steroid-dependent disease if the lowest tapering dose of the second occasion is equal or higher than the lowest tapering dose of the first occasion.
Rationale: To add explanation to cGVHD response criteria of Complete Response in Liver (Attachment 5).	
Attachment 5	Definition of liver score in Diagnosis and Staging Working Group Report by NIH cGVHD Consensus Development Project (2014) was added as an annotation.
Rationale: The background safety information for ibrutinib was updated to align with the current ibrutinib Investigator's Brochure.	
1.4.3. Risks	Description of infections was updated.
Rationale: To correct errors.	
3.1. Overview of Study Design	"Approximately 20 subjects will be enrolled to have 17 response evaluable subjects." was deleted.
Table 6: Ibrutinib Dose Modifications for Subjects with Hepatic Impairment	The case of bilirubin >1.5-3 x ULN at baseline was deleted.
9.1.3. Treatment Phase	Deleted that ibrutinib will dispensed at each visit.
11.1. Subject Information	Regarding response evaluable population, "this population will be used for the primary efficacy analysis." was deleted.
Rationale: To clarify the procedure, some descriptions were modified.	
4.1. Inclusion Criteria 8	Descriptions around criteria for transfusion or growth factor support were modified.
4.2. Exclusion Criteria 24	To be consistent with inclusion criteria 15, length of time that subjects should avoid planning to father a child after the last dose of ibrutinib was corrected from 1 month to 3 months.

Applicable Section(s)	Description of Change(s)
9.1.1. Overview	Procedure of after cGVHD progression in The Posttreatment Follow-up Phase was added. "Other measurements may be done earlier than specified timepoints if needed." was deleted because there were no applicable measurements.
9.1.2. Screening Phase	Procedure of cGVHD assessment at the day of informed consent was clarified.
9.5. Safety Evaluations	Added a procedure of the case if donor/host chimerism cannot be performed due to any specific reason such as no donor information.
TIME AND EVENTS SCHEDULE, 9.5. Safety Evaluations	Clarified timepoints of FEV1. Added that FEV1 evaluation other than mandatory timepoints is encouraged in cGVHD activity assessment for a subject who has cGVHD features in lung whenever possible.
Rationale: Dose modification criteria was changed to align with Study PCYC-1129-CA.	
6.1.1. Dose Modification for Adverse Reactions	Dose modification criteria regarding reescalation of ibrutinib after dose reduction for a toxicity was changed as below: If the dose of ibrutinib is reduced for a toxicity, at the investigator's discretion, the dose of ibrutinib may be reescalated after 8 weeks of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction.
Rationale: To clarify the procedure of study enrollment.	
9.1.2. Screening Phase	Added that a subject will be enrolled in this study within 3 days before the planned first dose of ibrutinib.
Rationale: To simplify evaluations of Week 1 Day 1.	
TIME AND EVENTS SCHEDULE, 9.1.3. Treatment Phase	Specified that clinical laboratory tests and spirometry of Week 1 Day 1 do not need to repeat if the screening tests were performed within 3 days of the first dose of ibrutinib.
Rationale: To correct minor errors and to unify description.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made. To unify description, several words were changed.

SYNOPSIS

A Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib in Subjects with Steroid Dependent/Refractory Chronic Graft Versus Host Disease (cGVHD)

Ibrutinib (PCI-32765; JNJ-54179060) is a potent, orally administered covalently-binding inhibitor of Bruton's tyrosine kinase (BTK), which is also an irreversible inhibitor of interleukin-2-inducible T cell kinase (ITK). It is being codeveloped by Janssen Research & Development LLC and Pharmacyclics LLC for the treatment of B-cell malignancies. Investigations in other indications including chronic graft versus host disease (cGVHD) have also been initiated. Ibrutinib is approved in the United States (US) for the treatment of adult patients with cGVHD after failure of one or more lines of systemic therapy.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives	Endpoints
Primary	
• Evaluate efficacy of ibrutinib in Japanese subjects with steroid dependent/refractory cGVHD by measuring overall cGVHD response (Complete Response [CR] and partial response [PR] defined by National Institutes of Health (NIH) Consensus Development Project Criteria [2014])	• The overall response rate (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 therapy for cGVHD – In the absence of progression of the underlying disease, or death
Secondary	
• Evaluate efficacy by measuring: – Rate of sustained response for at least 20 weeks – Duration of response (DOR) – cGVHD response rate at each timepoint of efficacy evaluation – Corticosteroid requirement changes over time – Change in symptom burden measured by the Lee cGVHD Symptom Scale	• Rate of sustained response for at least 20 weeks is defined as rate of NIH-defined CR or PR that was sustained for at least 20 weeks • DOR is defined as the duration from the date of initial response (CR or PR) to the date of progressive cGVHD or death, whichever occurs first • cGVHD response rate at each timepoint of efficacy evaluation is defined as rate of NIH-defined CR or PR at each timepoint • Corticosteroid requirement changes over time: Corticosteroid requirement will be monitored cross the study. • Change in symptom burden measured by the Lee cGVHD Symptom Scale: A change in ≥7 points on the Lee cGVHD Symptom Scale will be considered significant and relates to improvement in quality of life (QoL).
• Evaluate the safety of ibrutinib in Japanese subjects with steroid dependent/refractory cGVHD	• Safety parameters of ibrutinib, including adverse events (AE) and clinical laboratory assessments
• Evaluate the pharmacokinetics (PK) of ibrutinib in Japanese subjects with cGVHD	• Pharmacokinetic parameters of ibrutinib and the metabolite PCI-45227 (if possible and

Objectives	Endpoints
	judged relevant)
Exploratory	
• Evaluate efficacy of ibrutinib by measuring: – Failure free survival (FFS) – Overall survival (OS) – Number and proportion of subjects with all immunosuppressants withdrawn	• FFS is defined as the duration from the date of initial dose to the date of relapse of malignancy, initiation of new immunosuppressive therapy for GVHD or death, whichever occurs first. • OS is defined as the duration from the date of initial dose to the date of the subject's death. • Number and proportion of subjects with all immunosuppressants withdrawn
• Evaluate the BTK and ITK binding site occupancy as a pharmacodynamic (PD) parameters	• Proportion of BTK and ITK binding site occupancy in subjects with cGVHD

Hypothesis: Ibrutinib is an effective agent as measured by an overall cGVHD response rate (the lower bound of 95% confidence interval >25%) in Japanese subjects with steroid dependent/refractory cGVHD.

OVERVIEW OF STUDY DESIGN

This is an open-label, single arm, multicenter Phase 3 study to evaluate the efficacy, safety, and PK of single-agent ibrutinib 420 mg in Japanese subjects 12 years of age or older with steroid dependent/refractory cGVHD. Subject participation will include a Screening Phase, a Treatment Phase, and a Posttreatment Follow-up Phase. The Screening Phase assessments will be performed within 42 days prior to study treatment initiation. The Treatment Phase will extend from first dose of study treatment until treatment discontinuation. During the Treatment Phase, efficacy and safety evaluations, sampling of PK and PD will be performed. The Posttreatment Follow-up Phase will begin once a subject discontinues ibrutinib treatment. Subjects who discontinue for reasons other than cGVHD progression will complete an End-of-treatment Visit and will be followed for the cGVHD evaluations until cGVHD progression, death, loss to follow-up, consent withdrawal, or study end, whichever occurs first. Subjects who discontinue due to cGVHD progression will complete an End-of-treatment Visit and be followed for survival status and the use of subsequent cGVHD treatment.

SUBJECT POPULATION

Key eligibility criteria include: Male or female subjects ≥12 years of age. Subjects with steroid dependent/refractory cGVHD defined at any time post-hematopoietic cell transplant (HCT). Subjects receiving baseline systemic glucocorticoid therapy for cGVHD at study entry with no more than 3 previous systemic treatments for cGVHD.

DOSAGE AND ADMINISTRATION

Ibrutinib 420 mg (3×140 mg capsules) will be administered orally once daily. It is expected that many subjects enrolled in the trial will require antifungal prophylaxis. Dose adjustments will be required for concomitant use of moderate or strong CYP3A inhibitors.

STUDY EVALUATIONS

Efficacy evaluations: Response will be defined using the NIH Consensus Panel cGVHD Activity Assessment (2014). Skin, mouth, liver, upper and lower gastrointestinal tract (GI), esophagus, lung, eye,

and joint/fascia are the organs or sites considered in evaluating overall response. All subjects in the study will complete the Lee cGVHD Symptom Scale at all response assessment visits.

Pharmacokinetic/Pharmacodynamic evaluations: Venous blood samples will be collected to determine plasma concentration of ibrutinib and the metabolite PCI-45227 at the timepoints specified in TIME AND EVENTS SCHEDULE. The plasma concentration data of ibrutinib and PCI-45227 will be used to determine PK parameters by noncompartmental method, including: AUC_{last}, AUC_{24h}, C_{max}, T_{max}, and $t_{1/2}$. Venous blood samples for PD evaluation (BTK and ITK binding site occupancy) will be collected at the timepoints specified in the TIME AND EVENTS SCHEDULE.

Safety evaluations: This includes AEs, physical examination, Karnofsky/Lansky Performance Scale, vital signs, electrocardiogram (ECG), forced expiratory volume in 1 second (FEV1), and laboratory tests as described in TIME AND EVENTS SCHEDULE. All AEs will be reported from the time a signed and dated informed consent form is obtained until 30 days following the last dose of ibrutinib or the time of starting a subsequent systemic treatment for cGVHD, if earlier.

STATISTICAL METHODS

With a sample size of 17 subjects and assuming an expected overall cGVHD response rate of approximately 60%, it is expected to have at least 80% power to show the efficacious treatment effect (the lower bound of 95% confidence interval of the response rate >25%). The primary efficacy endpoint is overall cGVHD response rate (CR+PR). Its 95% confidence interval will be calculated with the exact test for binomial distribution in the all treated population (defined as all enrolled subjects who will receive at least 1 dose of study drug). The study will be considered to be positive if the lower limit of the exact 2-sided 95% confidence interval based on binominal distribution exceeds the threshold value (0.25). The primary analysis for all efficacy and safety endpoints will be conducted at the time when the last subject has completed the efficacy assessment at Week 37 or has discontinued treatment before Week 37. Final analysis will be conducted at the study end.

TIME AND EVENTS SCHEDULE

Phase 3	**Screening Phase**	**Treatment Phase**								**Posttreatment Follow-up Phase**	
Study weeks		**1**	**1**	**2**	**5**	**9, 13, 17, 21, 25 q4 weeks**	**37 and every 12 weeks thereafter**	**Progressive cGVHD Visit**	**End-of-Treatment Visit (30 days from last dose of study drug)**	**Response Follow-up Visits (Until progressive cGVHD) q12 weeks**	**Survival Follow-up q12 weeks**
Study Day of study week		1	2	1	1	1					
Study Windows	-42 days	*On time*			*±3 days*		*±7 days*	*anytime*	*+7 days*	*±7 days*	*±7 days*
Screening/Administrative											
Informed consent/Child assent/Parental consent[a]	X										
Demographics	X										
Review medical history requirements	X										
Inclusion/exclusion criteria	X	X									
GVHD/Transplant History	X										
Study Treatment Administration											
Ibrutinib administration		*Continuous daily dosing*									
Efficacy Evaluations											
cGVHD Assessment (NIH Form)	X	X			X	Weeks 13, 25	X	X	X	X	
Lee cGVHD Symptom Scale[b]	X	X			X	Weeks 13, 25	X	X	X	X	
Corticosteroid Requirements	X	X		X	X	X	X	X	X	X	
Safety Evaluations											
Physical examination (height at screening)[c]	X	X		X	X	X	X	X	X		
Karnofsky/Lansky Performance Scale	X	X			X	X	X	X	X		
Vital signs	X	X		X	X	X	X	X	X		
FEV1 by spirometry[d]	X	X[1]			X	Weeks 13, 25	X	X	X	X	
12-lead ECG[e]	X										
Survival											X

Phase 3	**Screening Phase**	**Treatment Phase**								**Posttreatment Follow-up Phase**	
Study weeks		**1**	**1**	**2**	**5**	**9, 13, 17, 21, 25 q4 weeks**	**37 and every 12 weeks thereafter**	**Progressive cGVHD Visit**	**End-of-Treatment Visit (30 days from last dose of study drug)**	**Response Follow-up Visits (Until progressive cGVHD) q12 weeks**	**Survival Follow-up q12 weeks**
Study Day of study week		1	2	1	1	1					
Study Windows	-42 days	*On time*			*±3 days*		*±7 days*	*anytime*	*+7 days*	*±7 days*	*±7 days*
Clinical Laboratory Tests											
Hematology	X	X[i]		X	X	X	X	X	X		
Serum Chemistry	X	X[i]		X	X	X	X	X	X		
Coagulation (PT, INR, and aPTT)	X										
Pregnancy test[f]	X	X									
Serology	X										
Donor/host chimerism	X					Weeks 13, 25	X	X	X		
Quantitative serum immunoglobulins (IgA, IgG and IgM)	X					Weeks 13, 25	X	X	X		
Pharmacokinetics											
PK[g]		X	X	X							
Pharmacodynamics											
BTK and ITK binding site occupancy[h]		X	X	X		Week 13					
Ongoing Participant Review											
Concomitant therapy	X	Continuous from Informed Consent to 30 days after last dose of study drug									
Adverse events	X	Continuous from Informed Consent to 30 days after last dose of study drug									

Key: aPTT: activated partial thromboplastin time; BTK: Bruton's Tyrosine Kinase; cGVHD: chronic graft versus host disease; ECG: electrocardiogram; FEV1: forced expiratory volume in 1 second; IgA: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M; INR: International normalized ratio; ITK: interleukin-2-inducible T cell kinase; NIH: National Institutes of Health; PD: pharmacodynamics; PK: pharmacokinetics; PT: prothrombin time.

Footnotes:

a. Must be signed before first study-related activity. Subjects less than 20 years old must have parental consent and must sign an assent. Consent of guardian (legally-acceptable representative) is accepted instead of parental consent.

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

c. The physical examination will include, height (at screening), weight, and examination per clinical practice. Review of symptoms should include inquiry of ocular symptoms; subjects should be referred to an ophthalmologist for a formal examination if any Grade ≥2 symptoms are reported.

d. Forced expiratory volume in 1 second (FEV1) required for all subjects at screening and Week 1 Day 1. After Week 1 Day 1, if prior FEV1 result is abnormal FEV1 should be obtained every 12 weeks. If prior FEV1 result is normal FEV1 should be obtained every 24 weeks. If a subject has cGVHD features in lung, FEV1 evaluation other than these mandatory timepoints is encouraged in cGVHD activity assessment whenever possible.
e. At screening, ECG is mandatory to confirm eligibility. Other ECGs will be performed at the investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset of dyspnea.
f. 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.
g. Pharmacokinetic (PK) sampling will be performed for all subjects according to Section 9.3 and the schedule in BLOOD SAMPLING SCHEDULE FOR PK AND PD
h. Pharmacodynamic (PD) sampling will be performed for all subjects according to Section 9.4 and the schedule in BLOOD SAMPLING SCHEDULE FOR PK AND PD
i. For Week 1 Day 1 only, clinical laboratory tests and spirometry do not need to be repeated if the screening tests were performed within 3 days of the first dose of ibrutinib.

BLOOD SAMPLING SCHEDULE FOR PK AND PD

PK Sampling Schedule

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

[a] Sample collected 24 hours (±2 hours) after dosing on the previous day and prior to dosing on the study day. Record exact times of both drug administrations.

PD (BTK and ITK Occupancy) Sampling Schedule

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

[a] Sample collected 24 hours (±2 hours) after dosing on the previous day and prior to dosing on the study day.

ABBREVIATIONS

allo-HCT	allogeneic hematopoietic cell transplant
aPTT	activated partial thromboplastin time
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
BAFF	B cell-activating factor
β-hCG	beta-human chorionic gonadotropin
BTK	Bruton's tyrosine kinase
cGVHD	chronic graft versus host disease
CI	calcineurin inhibitor
CLL	chronic lymphocytic leukemia
CR	complete response
CRF	case report form(s) (paper or electronic as appropriate for this study)
CYP	cytochrome P450
DOR	duration of response
ECG	electrocardiogram
eDC	electronic data capture
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
ECP	extracorporeal photopheresis
ERK	extracellular signal-regulated kinase
FFS	failure free survival
GCP	Good Clinical Practice
GI	gastrointestinal
GVT	graft versus tumor
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
HBsAb	hepatitis B surface antibody
HBV	hepatitis B virus
IB	investigator's brochure
IC_{50}	minimum concentration of drug required to inhibit activity by 50%
ICF	informed consent form
ICH	International Conference on Harmonisation
Ig	immunoglobulin
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
ITK	interleukin-2-inducible T cell kinase
LAR	legally acceptable representative
MCL	mantle cell lymphoma

MMF	mycophenolate mofetil
NIH	National Institutes of Health
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NRM	nonrelapse mortality
OS	overall survival
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PQC	product quality complaint
PR	partial response
PRO	patient reported outcome(s)
PTLD	posttransplant lymphoproliferative disease
PTT	partial thromboplastin time
QoL	quality of life
SD	standard deviation
SAE	serious adverse event
SLL	small lymphocytic lymphoma
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
Th	T helper
ULN	upper limit of normal
US	United States
WM	Waldenström's macroglobulinemia

1. INTRODUCTION

JNJ-54179060 (PCI-32765; ibrutinib) is an orally administered covalently-binding small molecule inhibitor of Bruton's tyrosine kinase (BTK), which is also an irreversible inhibitor of interleukin-2 inducible T cell kinase (ITK). Codeveloped by Janssen Research & Development LLC and Pharmacyclics LLC as an anticancer agent, ibrutinib is the focus of an extensive clinical development program in the treatment of B cell malignancies. Investigations in other indications including chronic graft-versus-host disease (cGVHD) have also been initiated.

Ibrutinib has been approved in the United States (US) for the treatment of adult patients with cGVHD after failure of one or more lines of systemic therapy and other indications. Ibrutinib is currently under investigation in various indications as a single agent and in treatment combinations.

For the most comprehensive nonclinical and clinical information regarding ibrutinib, refer to the latest version of the Investigator's Brochure (IB).[21] The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Chronic Graft Versus Host Disease

Since the first report in 1957, allogeneic hematopoietic cell transplant (allo-HCT) has become a standard therapy for many hematologic malignancies and hematopoietic progenitor cell disorders.[55] Hematopoietic cell transplant can cure patients with chemotherapy resistant malignancies through graft versus tumor (GVT) effects generated by the donor immune system against the recipient's tumor.[3] However, just as the donor 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). According to retrospective analysis of patients received allo-HCT by the Japan Society of Hematopoietic Cell Transplantation (JSHCT) in 2009, the incidence of cGVHD at 2 years after HCT was 37% in 4,818 patients.[25] Risk factors for developing cGVHD include older patient age, use of peripheral blood stem cells versus bone marrow, and lack of T cell depletion.[27] 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,[4,6,30,41] and is a leading cause of nonrelapse mortality (NRM).[27] Chronic GVHD is an important cause of late morbidity and mortality after allo-HCT.[29,49] Chronic GVHD is also associated with decreased quality of life (QoL) and the continued need for immunosuppressive medications.[15,28,30,51]

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.[12] 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.[12] The consensus met again in 2014 and proposed

minor changes to the diagnostic criteria.[23] 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.[23]

1.2. Pathogenesis of Chronic Graft Versus Host Disease

The immunopathology underlying development of cGVHD may be quite variable and is not entirely characterized. Recent information implicates B cells as well as T cells in the generation of cGVHD.[1,14,24,45] 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.[2] In vivo T cell depletion with antithymocyte 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.[17,40] Alloreactive T helper (Th) 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.[1,14,24,35,36,45] 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.[44] Following activation via the B cell receptor 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.[47] 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.[46]

1.3. Current Treatment Options for cGVHD

Therapy for cGVHD is primarily broad-spectrum immunosuppressants that increase the risk of infections and tumor relapse by inhibiting GVT immunity.[18] Available therapies for cGVHD in Japan are only corticosteroids and calcineurin inhibitor (CI), such as cyclosporine and tacrolimus. After allo-HCT, a CI is commonly used as preventive treatment of GVHD.[53] The initial and current standard of care treatment for cGVHD is corticosteroids. Approximately 50% to 60% of the cGVHD subjects become dependent on or refractory to steroids, requiring second-line treatment within 2 years.[13] There is no standard of care treatment for these patients.

Corticosteroids are the primary therapy for cGVHD. An early double-blind, randomized trial compared prednisone and placebo with prednisone and azathioprine as initial treatment for standard risk cGVHD.[50] The NRM was significantly lower (21% versus 40%, p=0.003) and overall survival significantly higher (61% versus 47%, p=0.03) in the prednisone and placebo arm with a minimum follow-up of 42 months after study entry, establishing prednisone as the primary therapy for cGVHD. During corticosteroid treatment, patients may experience the side effects of corticosteroids: more frequent infections, avascular necrosis, adrenal insufficiency, cataracts, altered mental states, and disturbed sleep patterns.[50] Koc tested the addition of cyclosporine to prednisone as a steroid-sparing agent and observed fewer complications such as

avascular necrosis.[26] However, the relapse rate was increased resulting in no overall survival benefit compared to the prednisone only arm.

Second line therapy for cGVHD patients who fail corticosteroids is not well established. Second-line treatment is chosen from same agents as are used for initial treatment, because there are no other available therapies in Japan. In the Japanese guideline for GVHD, mycophenolate mofetil (MMF), sirolimus, hydroxychloroquine, extracorporeal photopheresis (ECP), rituximab, pentostatin and steroid pulse therapy are mentioned as cGVHD treatments that are used in the US and Europe.[53] However, these treatments are not approved for cGVHD in Japan. Until the approval of ibrutinib in the US 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 in these countries.

Treatment with immunosuppressants is typically needed for a median duration of 2 to 3 years, further contributing to morbidity.[52] 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.[5,16,26,34,50] An analysis of clinical study quality measures in 60 studies of cGVHD primarily conducted before the NIH standardized response criteria[39] 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[33] thereby leading to later unsuccessful controlled studies with the same agents. Agents such as cyclosporine, tacrolimus, sirolimus, or MMF are often added to corticosteroid therapy in both frontline and second line settings despite the lack of efficacy. There is a lack of a 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.

1.4. Background

1.4.1. Nonclinical Studies

Pharmacologic Profile

Ibrutinib was designed as a selective and covalent inhibitor of the BTK.[38] In vitro, ibrutinib is a potent inhibitor of BTK activity (minimum concentration of drug required to inhibit activity by 50% [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. A cellular signal transduction assay conducted to investigate ibrutinib inhibition of B-cell receptor signaling showed concentration-dependent inhibition of autophosphorylation of BTK by ibrutinib, phosphorylation of the physiological substrate of BTK, phospholipase-Cγ, and phosphorylation of a further downstream kinase, extracellular signal-regulated kinase (ERK).[19] 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 chronic

lymphocytic leukemia (CLL) patients receiving ibrutinib, binding to ITK also has been demonstrated.[10]

For more detailed and comprehensive information regarding nonclinical pharmacology and toxicology, please refer to the current IB.[21]

1.4.2. Clinical Studies

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

Human Pharmacokinetics

Following oral administration of ibrutinib at doses ranging from 420 to 840 mg/day, exposure to ibrutinib increased proportionally to doses. 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. Ibrutinib is extensively metabolized primarily by cytochrome P450 (CYP) 3A4 enzymes. Following single dose administration, the area under plasma concentration versus time curve (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, mantle cell lymphoma [MCL] and Waldenström's macroglobulinemia [WM]) with mild hepatic impairment based on National Cancer Institute-organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction compared to patients with normal hepatic function. In a Phase 1b/2 study (PCYC-1129-CA) 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).

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 (37 subjects) or who discontinued ibrutinib prior to response assessment (5 subjects), 28 subjects were responders (ORR=67%) based on NIH response criteria. Best responses include 9 complete responses (CRs), 19 partial responses (PRs), 7 stable disease, 2 progressive disease, 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/day at baseline, 0.24 mg/kg/day at Week 12, 0.19 mg/kg/day at Week 24, 0.18 mg/kg/day at Week 36, and 0.13 mg/kg/day at Week 48. Five

subjects discontinued 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 Food and Drug Administration (FDA) approved ibrutinib for the treatment of adult patients with cGVHD after failure of one or more lines of systemic therapy.

Safety

Monotherapy studies

Integrated safety data for 1,523 subjects with B cell malignancies treated with ibrutinib monotherapy in 17 studies that have completed primary analysis or final analysis included in the CSR***s*** as of the 31 July 2017 cutoff date for this IB (09 November 2017) are summarized in Table 1.

The most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N=1,523) are summarized in Table 1:

Table 1: Most Frequently Reported Treatment-emergent Adverse Events With Ibrutinib Monotherapy (Pooled Data from 1,523 Subjects)

Most frequently reported TEAEs >15%[a]	Most frequently reported Grade 3 or 4 TEAEs >5%[a]	Most frequently reported Serious TEAEs >2%[b]
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Pyrexia
Cough	Anemia	Febrile neutropenia
Pyrexia		
Anemia		
Upper respiratory tract infection		
Neutropenia		
Oedema peripheral		
Thrombocytopenia		
Muscle spasms		

[a] Source is Table 5 of IB,[21]
[b] Source is Table 6 of IB,[21]

Combination Studies

Pooled safety data from a total of 422 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 bendamustine and rituximab (BR); fludarabine, cyclophosphamide, and rituximab (FCR); ofatumumab; and rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP).

The most frequently reported TEAEs in subjects receiving ibrutinib in combination therapy (N=422) are summarized in Table 2:

Table 2: Most Frequently Reported TEAEs in Subjects Receiving Ibrutinib in Combination Therapy (Pooled Data From 422 Subjects)

Most frequently reported TEAEs >10%[a]	Most frequently reported Grade 3 or 4 TEAEs >2%[a]	Most frequently reported Serious TEAEs >1%[b]
Neutropenia	Neutropenia	Febrile neutropenia
Diarrhoea	Thrombocytopenia	Pneumonia
Nausea	Febrile neutropenia	Atrial fibrillation
Thrombocytopenia	Pneumonia	Pyrexia
Fatigue	Neutrophil count decreased	Cellulitis
Anaemia	Anemia	Sepsis
Pyrexia	Fatigue	Neutropenia
Infusion related reaction	Hypertension	Tumor lysis syndrome
Upper Respiratory tract infection	Diarrhea	Urinary tract infection
Constipation	Pyrexia	
Vomiting	Cellulitis	
Rash	Leukopenia	
Headache	Tumor lysis syndrome	
Cough	Atrial fibrillation	
Muscle spasms	Hyperuricaemia	
Pneumonia	Urinary tract infection	
Oedema peripheral	White blood cell count decreased	
Arthralgia		
Decreased appetite		
Contusion		
Insomnia		
Chills		
Peripheral sensory neuropathy		
Stomatitis		
Febrile neutropenia		
Abdominal pain		
Back pain		
Bronchitis		

[a] Source is Table 7 of IB,[21]
[b] Source is Table 8 of IB,[21]

Summary of Clinical Data in Chronic GVHD

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

Table 3: Most frequently reported TEAEs in subjects receiving ibrutinib for cGVHD

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 of the 42 subjects (71.4%) were taking moderate or strong CYP3A inhibitors during the study with 42.9% taking fluconazole, 14.3% taking voriconazole and 9.5% of subjects taking posaconazole. 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.

1.4.3. Risks

Cardiac Arrhythmias

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

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 (GI) bleeding, subdural intracranial hemorrhage, and hematuria. Use of ibrutinib in subjects requiring anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen induced platelet aggregation were observed.

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.

Diarrhea

Diarrhea is the most frequently reported nonhematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported GI events include nausea, vomiting, and constipation. These events are rarely severe. Should symptoms be severe or prolonged, ibrutinib should be considered to follow dose modification guidelines (see Section 6.1.1).

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 8.1). Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) and hepatitis B reactivation have occurred in subjects treated with ibrutinib. Subjects should be monitored for symptoms (fever, chills, weakness, confusion, vomiting and jaundice) and appropriate therapy should be instituted as indicated.

Interstitial Lung Disease

Cases of interstitial lung disease have been reported in subjects treated with ibrutinib. Monitor subjects for pulmonary symptoms indicative of interstitial lung disease.

Nonmelanoma Skin Cancer

Nonmelanoma skin cancers have occurred in subjects treated with ibrutinib. Monitor subjects for the appearance of nonmelanoma skin cancer.

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 including Stevens-Johnson syndrome have been reported in subjects treated with ibrutinib. Subjects should be closely monitored for signs and symptoms suggestive of severe cutaneous adverse reaction including Stevens-Johnson syndrome. 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.

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 antihypertensive medications and/or initiate antihypertensive treatment as appropriate.

1.5. Overall Rationale for the Study

Available therapies for cGVHD in Japan are only corticosteroids and CI, such as cyclosporine and tacrolimus. After allo-HCT, a CI is commonly used as preventive treatment of GVHD. The initial and current standard treatment for cGVHD is corticosteroid. However, approximately 50-60% of the cGVHD subjects become dependent on or refractory to steroids, requiring second-line treatment within 2 years.[13] There is no standard of care for these patients. Second-line treatment is chosen from the same agents that are used for initial treatment, because there are no other available therapies in Japan. In addition, treatment of cGVHD including corticosteroids is needed for a median duration of 2 to 3 years. Long treatment period of high dose systemic corticosteroids will lead to the occurrence of side effects of steroids including hypertension, bone loss, weight gain, diabetes, cataracts, and adrenal disorder as well as increasing the risk of infection.[50,52] These issues highlight the need for well-tolerated and effective treatment options in Japan.

Ibrutinib is a potent inhibitor of BTK, and inhibits ITK. Through this novel mechanism, ibrutinib has shown the potential to affect B and T cells that are critical in the pathogenesis of cGVHD.[11] Preclinical 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. In addition, the results of ibrutinib administration in the

Phase 1b/2 PCYC-1129-CA study in subjects with active cGVHD who have failed first line corticosteroid therapy demonstrate that ibrutinib has beneficial clinical activity with high response rate by NIH criteria as well as an overall favorable safety profile. Ibrutinib was approved for the treatment of subjects with cGVHD by the FDA on the basis of this promising early data in June 2016. These findings suggest that ibrutinib may also demonstrate clinical benefit for Japanese cGVHD subjects.

Appropriateness of enrolling adolescent (12 - 17 years old) subjects

Not only in adult patients but also in pediatric patients, cGVHD is a leading cause of mortality, side effects, and loss of QoL after allo-HCT. Treatment algorithm for pediatric cGVHD is same as adult and treatment option is also very limited. Because of this treatment situation and the expectation of long-term survival for pediatric subjects, novel, well-tolerated and effective treatment option is strongly required for pediatric cGVHD.

So far, there is no clinical data of ibrutinib in cGVHD subjects 17 years of age or younger, but it is considered that the PK profile of ibrutinib in adolescents (12 to 17 years of age) is similar to adults. Cytochrome P450 (CYP3A4), which predominantly metabolizes ibrutinib, reaches adult expression levels before 1 year of age[9] and ibrutinib is not a substrate of major transporters. In addition, physiological characteristics (eg, body size, liver weight, and blood flow) have reached adult proportions in adolescents (median body weight in Japanese adolescent at 12 years of age: 40.74 kg [male] and 41.51 kg [female])[54] and population PK analysis including 1,202 adult subjects with B cell malignancy did not suggest significant effect of body weight on the exposure of ibrutinib (median 77.2 kg; range 38.5 to 152 kg). In addition, preliminary PK data in pediatric population is available from a clinical study for ibrutinib in pediatric patients with B cell malignancy (study PCI-32765LYM3003) where body surface area-based dose (329 mg/m^2, corresponds to 560 mg in adults) was adopted. In the 12- to 17-year age group (N=7; body weight range 33 to 103 kg; actual dose range 350 to 560 mg per body), in general, exposures fell within the target exposure range in adults at 560 mg dose.[42] Overall, it is considered appropriate to enroll adolescent subjects in this study.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• Evaluate efficacy of ibrutinib in Japanese subjects with steroid dependent/refractory cGVHD by measuring overall cGVHD response (Complete Response [CR] and partial response [PR] defined by NIH Consensus Development Project Criteria [2014])	• The overall response rate (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 therapy for cGVHD – In the absence of progression of the underlying disease that was the indication for transplant (or posttransplant lymphoproliferative disease [PTLD]), or

Objectives	Endpoints
	death
Secondary	
• Evaluate efficacy of ibrutinib in Japanese subjects with steroid dependent/refractory cGVHD by measuring: – Rate of sustained response for at least 20 weeks – Duration of response (DOR) – cGVHD response rate at each timepoint of efficacy evaluation – Corticosteroid requirement changes over time – Change in symptom burden measured by the Lee cGVHD Symptom Scale	• Rate of sustained response for at least 20 weeks is defined as rate of NIH-defined CR or PR that was sustained for at least 20 weeks • DOR is defined as the duration from the date of initial response (CR or PR) to the date of progressive cGVHD or death, whichever occurs first • cGVHD response rate at each timepoint of efficacy evaluation is defined as rate of NIH-defined CR or PR at each timepoint • Corticosteroid requirement changes over time: Corticosteroid requirement will be monitored cross the study • Change in symptom burden measured by the Lee cGVHD Symptom Scale: A change in ≥7 points on the Lee cGVHD Symptom Scale will be considered significant and relates to improvement in QoL
• Evaluate the safety of ibrutinib in Japanese subjects with steroid dependent/refractory cGVHD	• Safety parameters of ibrutinib, including AEs and clinical laboratory assessments
• Evaluate the pharmacokinetics (PK) of ibrutinib in Japanese subjects with cGVHD	• Pharmacokinetic parameters of ibrutinib and the metabolite PCI-45227 (if possible and judged relevant)
Exploratory	
• Evaluate efficacy of ibrutinib by measuring: – Failure free survival (FFS) – Overall survival (OS) – Number and proportion of subjects with all immunosuppressants withdrawn	• FFS is defined as the duration from the date of initial dose to the date of relapse of malignancy, initiation of new immunosuppressive therapy for GVHD or death, whichever occurs first • OS is defined as the duration from the date of initial dose to the date of the subject's death • Number and proportion of subjects with all immunosuppressants withdrawn
• Evaluate the BTK and ITK binding site occupancy as a pharmacodynamic (PD) parameters	• Proportion of BTK and ITK binding site occupancy in subjects with cGVHD

2.2. Hypothesis

The primary hypothesis of this study is that ibrutinib is an effective agent as measured by an overall cGVHD response rate (the lower bound of 95% confidence interval is greater than 25%) in Japanese subjects with steroid dependent/refractory cGVHD.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is an open-label, single arm, multicenter Phase 3 study to evaluate the efficacy, safety, and PK of single-agent ibrutinib 420 mg in Japanese subjects 12 years of age or older with steroid dependent/refractory cGVHD. At least 1 adolescent subject (12-17 years of age) will be enrolled in this study.

Subject participation will include a Screening Phase, a Treatment Phase, and a Posttreatment Follow-up Phase.

The Screening Phase assessments will be performed within 42 days prior to study treatment initiation. Eligible subjects will have clinically determined cGVHD and are dependent on or refractory to steroids. Subjects may have had no more than 3 previous therapies for cGVHD.

Clinical assessment of cGVHD must be clinically stable or worsening for a minimum of 14 days between screening and first dose of ibrutinib. If cGVHD assessment shows clinical improvement during this period, subject may be reassessed. Reassessment should be performed at least 14 days later from the last assessment. If cGVHD assessment is stable or worsening between the last 2 assessments then the subject may receive first dose of ibrutinib.

The Treatment Phase will extend from first dose of study treatment until treatment discontinuation. Subjects will receive 420 mg of oral ibrutinib once daily unless they have intervening unacceptable toxicity or meet other criteria for subject discontinuation. Dose modification of ibrutinib should be taken for the defined toxicities in Section 6.1.1 and Section 6.1.2. During the Treatment Phase, efficacy and safety evaluations, sampling of PK and PD will be performed according to the TIME AND EVENTS SCHEDULE. All subjects will be evaluated for response according to NIH Consensus Development Project Criteria (2014).

The Posttreatment Follow-up Phase will begin once a subject discontinues ibrutinib treatment. Subjects who discontinue for reasons other than cGVHD progression (ie, for an AE or Investigator decision) will complete an End-of-treatment Visit (30+7 days from the last dose of ibrutinib) and will be followed for the disease evaluation until death, lost to follow-up, consent withdrawal, or study end, whichever occurs first. Subjects who discontinue due to cGVHD progression will complete an End-of-treatment Visit and be followed for survival status and the use of subsequent cGVHD treatment (clinic visits or telephone contacts). A clinical data cut off is planned at the time when the last subject has completed the efficacy assessment at Week 37 or has discontinued treatment before Week 37. Subjects will continue to be followed until the study completion or withdrawal from the study. The study is considered completed with the last visit

scheduled study assessment shown in the TIME AND EVENTS SCHEDULE for the last subject participating in the study.

3.2. Study Design Rationale

This is an open label study and no randomization will occur. The results of ibrutinib administration in the Phase 1b/2 PCYC-1129-CA study in subjects with active cGVHD who have failed first line corticosteroid therapy demonstrate that ibrutinib has beneficial clinical activity with high response rate by NIH criteria as well as an overall favorable safety profile. This study is conducted to confirm the evidence of reproducibility of PCYC-1129-CA study in Japanese steroid dependent/refractory cGVHD.

Study population

For patients with steroid dependent/refractory cGVHD, there are currently no standard treatment options. Efficacy and safety of ibrutinib for steroid dependent/refractory cGVHD were shown in PCYC-1129-CA study and ibrutinib may also demonstrate clinical benefit for Japanese steroid dependent/refractory cGVHD subjects. The study population (patients with 1-3 previous systemic treatments for cGVHD) is considered to be appropriate because this is the same criterion as PCYC-1129-CA study and responses in patients with 3 previous treatments for cGVHD were shown in PCYC-1129-CA study. Refer to Section 1.5. for appropriateness of enrolling adolescent (12 to 17 years old) subjects in this study.

Study Treatments

The 420 mg daily dose of ibrutinib in this study was selected as the recommended dose for cGVHD and it was determined based on clinical studies for B cell malignancy and PCYC-1129-CA. In Japan, approved doses of ibrutinib are 420 mg/day for CLL/small lymphocytic lymphoma (SLL) and 560 mg/day for MCL. Common AEs reported in clinical trials of ibrutinib for B cell malignancies were GI upset (diarrhea, nausea, vomiting), fatigue, respiratory infections, and rash. Because these AEs may overlap with cGVHD manifestations, a conservative dose of 420 mg will be used as the starting does for this trial. At 420 mg daily dose, 40% to 80% ITK occupancy was reported.[10] The tolerability of 420 mg/day was confirmed in the phase 1 part of PCYC-1129-CA study and favorable efficacy at the dose was confirmed in total subjects in the study.

Endpoints

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.[23] In addition, the NIH Consensus Response Criteria have been shown to correlate with clinical outcomes.[22,37] Per the NIH Clinical Trial Design Response Criteria Working Group Report, use of response assessment is recommended as a primary endpoint in clinical trials.[31] Response evaluation must occur in the absence of new therapy for cGVHD, and in the absence of relapse of the underlying disease that was the indication for transplant, or death. These

additional restrictions on ascertaining response have been added as they support the finding that cGVHD was adequately controlled because no new systemic treatment was added.

The assessment of PK is important in understanding both safety and efficacy of ibrutinib in Japanese cGVHD patients. In addition, it is expected that substantial number of patients are expected to receive a prophylactic antifungal (which is a CYP3A inhibitor) as a concomitant medication. Since ibrutinib is metabolized primarily by CYP3A, assessment of ibrutinib PK with a concomitant CYP3A inhibitor in Japanese cGVHD patients in this study will provide valuable information.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 42 days before administration of the study intervention.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Steroid dependent/refractory cGVHD defined as modified NIH criteria (2014) below at any time post-HCT:

    a. Dependent disease - defined when glucocorticoid (prednisolone doses ≥0.25 mg/kg/day or ≥0.5 mg/kg every other day) are needed to prevent recurrence or progression of manifestations as demonstrated by unsuccessful attempts to taper the dose to lower levels on at least 2 occasions, separated by at least 8 weeks.

    In case of inability to taper the dose to ≤0.25 mg/kg/day or ≤0.5 mg/kg every other day (prednisolone doses) due to recurrence or progression of cGVHD manifestations, it is considered as steroid-dependent disease if the lowest tapering dose of the second occasion is equal or higher than the lowest tapering dose of the first occasion.

    b. Refractory disease - defined when cGVHD manifestations progress despite the use of a regimen containing glucocorticoid (prednisolone at ≥1 mg/kg/day for at least 1 week) or persist without improvement despite continued treatment with glucocorticoid (prednisolone at ≥0.5 mg/kg/day or 1 mg/kg every other day) for at least 4 weeks.

2. Subjects must be receiving baseline systemic glucocorticoid therapy for cGVHD at study entry. The dose of steroids must be stable for 14 days prior to starting ibrutinib.

3. At the time of trial enrollment, participants may be receiving other immunosuppressive therapies in addition to glucocorticoids. Immunosuppressant doses must be stable for

14 days prior to starting ibrutinib.

4. Clinically stable or worsening cGVHD for a minimum of 14 days between screening and Day 1 cGVHD response assessment.

5. Male or female ≥12 years of age.

6. Karnofsky or Lansky (subjects <16 years) performance status ≥60 (see Attachment 2).

7. Adequate hepatic and renal function as defined as:

    a. Aspartate aminotransferase (AST), alanine aminotransferase (ALT) ≤3×upper limit of normal (ULN), (unless of nonhepatic origin). If AST/ALT increase is associated with cGVHD then ≤5×ULN is acceptable

    b. Total bilirubin ≤1.5×ULN (neither nonhepatic origin nor due to Gilbert's syndrome)

    c. Estimated Creatinine Clearance ≥30 mL/min (Cockcroft-Gault formula)

8. Adequate hematological function defined as:

    a. Absolute neutrophil count (ANC) ≥1,000/μL and off growth factor support in 7 days prior the laboratory test

    b. Platelets ≥30,000/μL and no transfusion support in 7 days prior the laboratory test

    c. Hemoglobin ≥8 g/dL and no transfusion or growth support in 7 days prior the laboratory test

9. Prothrombin time (PT)/international normalized ratio (INR) <1.5 × ULN and partial thromboplastin time (PTT) (activated PTT [aPTT]) <1.5 × ULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder).

10. Must sign an informed consent form (ICF) (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study. Assent is also required of children capable of understanding the nature of the study.

11. History of allo-HCT for underlying hematological disease.

12. A woman of childbearing potential must have a negative highly sensitive serum (β-human chorionic gonadotropin [β-hCG]) at screening and a negative urine pregnancy test at Day 1 prior to first dose of ibrutinib.

13. Before the first dose of ibrutinib, a woman must be either:

    a. Not of childbearing potential defined as:

        - postmenopausal
          A postmenopausal state is defined as no menses for 12 months without an

alternative medical cause.

- permanently sterile
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

b. Of childbearing potential* and

- practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly).

Examples of highly effective contraceptives include:

intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; sexual abstinence; combined (estrogen- and progestogen-containing) oral hormonal contraception

- agrees to remain on a highly effective method throughout the study and for at least 1 month after the last dose of ibrutinib.

*In this study, a premenarchal (defined as menarche has not yet occurred) woman is considered as having childbearing potential because menarche might occur during the study.

14. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for at least 1 month after receiving the last dose of ibrutinib.

15. During the study and for a minimum of 1 spermatogenesis cycle (defined as approximately 3 months) after receiving the last dose of ibrutinib, in addition to the highly effective method of contraception, a man

a. who is sexually active with a woman of childbearing potential must agree to use a double- barrier method of contraception (eg, condom with spermicidal foam/gel)
b. who is sexually active with a woman who is pregnant must use a condom
c. must agree not to donate sperms

Typical use failure rates may differ from those when used consistently and correctly. Contraceptive (birth control) use by men or women should be consistent with the Japanese regulations regarding the acceptable methods of contraception for those participating in clinical studies.

16. Must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Active acute GVHD

2. More than 3 previous systemic treatments for cGVHD. Treatment with glucocorticoids is considered a treatment for cGVHD and should be included in determining the number of previous treatments.

3. History of treatment with a tyrosine kinase inhibitor (eg, imatinib), purine analogs, or other cancer chemotherapy in the 4 weeks prior to starting ibrutinib. Participants may have received ibrutinib pretransplant for other reasons besides cGVHD such as for the treatment of leukemia or lymphoma.

4. History of treatment with monoclonal T and B cell antibodies in the 8 weeks prior to starting ibrutinib.

5. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of ibrutinib.

6. Received an investigational drug or used an invasive investigational medical device within 4 weeks before the first dose of ibrutinib.

7. Current treatment with sirolimus and either cyclosporine or tacrolimus

8. Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor (Attachment 7) with the exception of strong CYP3A inhibitors used for antifungal prophylaxis.

9. Concomitant use of warfarin or other Vitamin K antagonists.

10. More than 6 stools per day

11. Forced expiratory volume in 1 second (FEV1) <50% on pulmonary function tests.

12. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class III or IV 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 the first dose of ibrutinib.

13. Uncontrolled active systemic infection or infection requiring systemic treatment that was completed ≤7 days before the first dose of ibrutinib.

14. History of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV) infection. Subjects who are positive for hepatitis B core antibody, hepatitis B surface antibody (HBsAb), hepatitis B surface antigen (HBsAg), or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment.

Those who are PCR positive will be excluded.

15. Progressive underlying malignant disease including posttransplant lymphoproliferative disease (PTLD).

16. History of prior malignancy (not including the underlying malignancy that was the indication for transplant), except:

    a. Malignancy treated with curative intent and with no known active disease present for ≥24 months before enrollment;
    b. Adequately treated nonmelanoma skin cancer or lentigo maligna without evidence of disease;
    c. Adequately treated cervical carcinoma in situ without current evidence of disease;
    d. Malignancy, which is considered cured with minimal risk of recurrence.

17. Severe hepatic impairment (Child-Pugh classification, see Attachment 8).

18. Bleeding disorder (eg, von Willebrand's disease or hemophilia).

19. Stroke or intracranial hemorrhage within 6 months prior to enrollment.

20. Major surgery (eg, requiring general anesthesia), within 4 weeks of first dose of ibrutinib, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study.

21. Allergy or hypersensitivity to ibrutinib.

22. Unable to swallow capsules or malabsorption syndrome, disease significantly affecting GI function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.

23. Pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 1 month after the last dose of ibrutinib.

24. Plans to father a child while enrolled in this study or within 3 months after the last dose of ibrutinib.

25. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded

from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Refer to Section 8 Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

3. The following guidance should be applied during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving study medication:

    - For any surgery or invasive procedure requiring sutures or staples for closure, study medication should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure, and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.
    - For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis), study medication 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 study medication, it is not necessary to hold study medication for these procedures.
    - For emergency procedures, study medication should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

5. INTERVENTION ALLOCATION AND BLINDING

Intervention Allocation

As this is a single-arm study, all eligible subjects will receive treatment with ibrutinib.

Blinding

As this is an open study, blinding procedures are not applicable.

6. DOSAGE AND ADMINISTRATION

Ibrutinib 420 mg (3 × 140 mg capsules) will be administered orally once daily. It is expected that many subjects enrolled in the trial will require antifungal prophylaxis. Please see Section 8.3.1 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 approximately 240 mL of water. The capsules should be swallowed intact and subjects should not attempt to open capsules or

dissolve them in water. The first dose will be delivered at the study site on Week 1 Day 1, after which subsequent dosing will occur on an outpatient basis except for PK and PD sampling days on Week 1 Day 2, Week 2 Day 1, and Week 13 Day 1.

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.

Ibrutinib will be dispensed to subjects in bottles at each visit. Study-site personnel will instruct subjects on how to store study drug for at-home use as indicated for this protocol. Unused ibrutinib dispensed during previous visits must be returned to the site and drug accountability records updated at each visit. Returned capsules must not be redispensed to anyone.

6.1. Dose Modifications

6.1.1. Dose Modification for Adverse Reactions

The dose of ibrutinib must be modified according to the dose modification guidance in Table 4 and Table 5 if any of the following toxicities occur:

- Grade 4 neutropenia (ANC <500/µL) for more than 7 days
- 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 antiemetic and/or antidiarrheal therapy
- Any other Grade 4 or unmanageable Grade 3 toxicity

Table 4: Ibrutinib Dose Modifications

Occurrence	Action
First	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose level
Second	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (ie, 280 mg/day for 420 mg/day dose)
Third	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at 2 dose levels lower (ie, 140 mg/day for 420 mg/day dose)
Fourth	Discontinue ibrutinib

Table 5: Ibrutinib 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	--

Refer to Section 8.3.1 for instructions on dose modifications or temporary hold during concomitant administration of CYP3A inhibitors or inducers and Section 8.3.3 for subjects requiring the initiation of anticoagulants while receiving ibrutinib. Refer to Section 4.3 for

guidance on dose delays during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving 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.

Study drug may be held for a maximum of 28 consecutive days. Discontinue ibrutinib permanently if ibrutinib cannot be restarted within 28 days due to toxicity. If the dose of ibrutinib is reduced for a toxicity, at the investigator's discretion, the dose of ibrutinib may be reescalated after 8 weeks of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction.

When a toxicity which does not meet the above definition occurs and a dose modification is considered by the investigator due to the toxicity, the investigator should consult with the sponsor's medical monitor.

6.1.2. 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 6 below. If the elevation of bilirubin is due to a nonhepatic cause or Gilbert's Syndrome then no dose modifications are necessary.

Table 6: Ibrutinib Dose Modifications for Subjects with Hepatic Impairment

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

Bili = bilirubin; ULN = upper limit of normal
* In cases where the investigator wishes to restart ibrutinib after ibrutinib has been held for more than 28 days for hepatic impairment, please contact the medical monitor for approval.

6.1.3. Ibrutinib Hold After Withdrawal of All Immunosuppressants

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

- All systemic immunosuppressants used for the treatment of cGVHD have been discontinued.
- cGVHD response has been maintained for 12 weeks after complete withdrawal of all immunosuppressants (not including ibrutinib).
- The subject has received a minimum of 48 weeks of ibrutinib.

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

7. INTERVENTION COMPLIANCE

The first dose of ibrutinib will be delivered at the study site on Week 1 Day 1, after which subsequent dosing will occur on an outpatient basis. Intervention compliance will be assessed based on clinical interview with subjects at each study visit. Subjects will be instructed to return unused ibrutinib capsules dispensed during previous visits to the site. The theoretical number of ibrutinib capsules dispensed will be recorded and compared with the number returned and the drug accountability records will be updated by the study-site personnel at each visit.

During the study, the investigator or designated study-site personnel will be responsible for providing additional instruction to reeducate any subject who is not compliant with taking the study drug. Additional details may be provided in a pharmacy manual/study site investigational product and procedures manual that is provided separately and noted in Section 15, Study-specific Materials.

8. CONCOMITANT THERAPY

8.1. Permitted Concomitant Medications

8.1.1. 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, Attachment 9).[7] 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.

8.1.2. Systemic Immunosuppressant Therapy

Participants may be receiving other immunosuppressive therapies in addition to glucocorticoids. In addition, due to potential drug-drug interactions with ibrutinib, monitoring of drug levels for immunosuppressant agents such as cyclosporine, tacrolimus, or sirolimus are highly recommended during the clinical trial. The doses for these immunosuppressants should be adjusted (increased or decreased) per institutional practices based on the measured drug level. Concurrent use of sirolimus and a CI (tacrolimus or cyclosporine) are prohibited.

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

8.1.3. Systemic Steroids

Systemic corticosteroids may be decreased at the treating physician's discretion. The initial taper of corticosteroids may begin 2 weeks following initiation of ibrutinib if a clinical response is

seen. The recommendation is to not taper below 50% of the original dose by the 12-week assessment period unless there is a medical reason (eg, uncontrolled diabetes, infection) for steroid reduction below 50%. A specific steroid taper schedule will not be mandated.

By its nature, cGVHD is a protean disease with clinical manifestations that wax and wane over time. Closely spaced clinical evaluations will detect temporary exacerbations of cGVHD manifestations but may not accurately reflect the long-term trajectory of a subject's cGVHD and response to treatment. Therefore, in the event a participant experiences a flare of cGVHD, temporary reescalation of corticosteroids dose will be allowed at the physician's discretion. Tapering of increased corticosteroids dose for a flare will begin within 4 weeks. If criteria are met for progressive cGVHD, the participant will be scored as a treatment failure and dropped-off.

8.2. Prohibited Concomitant Medications

Any chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy is prohibited while the subject is receiving ibrutinib treatment. Localized, hormonal, or bone sparing treatment for malignancies, and localized radiotherapy for medical conditions other than the underlying disease may be considered with prior approval of the medical monitor. The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

8.3. Medications to be Used With Caution

8.3.1. CYP3A Inhibitors or Inducers

Ibrutinib is metabolized primarily by CYP3A4. Avoid coadministration with strong CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. The dose of ibrutinib should be adjusted for concomitant use of CYP3A inhibitors as per Table 7 below:

Table 7: Ibrutinib 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[a]	280 mg once daily
Strong CYP3A inhibitors	140 mg once daily or consider alternative with less CYP3A inhibitory potential

[a] Itraconazole and ketoconazole will be replaced with voriconazole for study subjects. Avoid concomitant use of clarithromycin with ibrutinib.

When these antifungal agents will be discontinued, the ibrutinib dose will be increased to 420 mg, considering the half-lives of the antifungal agents. Avoid concomitant use of strong CYP3A inducers. Consider alternative agents with less CYP3A induction. Grapefruit and Seville oranges should be avoided during the study period. A list of common CYP3A inhibitors and inducers is provided in Attachment 7. For further information, please refer to the current version of the ibrutinib IB and examples of inhibitors, inducers, and substrates may be found at

http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

8.3.2. Substrates of P-glycoprotein

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.

8.3.3. Antiplatelet Agents and Anticoagulants

Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. Ibrutinib should be withheld at least 3 to 7 days pre and postsurgery depending upon the type of surgery and the risk of bleeding (see Section 4.3).

For subjects requiring the initiation of therapeutic anticoagulation therapy (eg, atrial fibrillation), (other than warfarin or a vitamin K antagonist) the risks and benefits of continuing ibrutinib treatment should be considered. If therapeutic anticoagulation is clinically indicated during the course of the study, treatment with ibrutinib should be held and ibrutinib should 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 ibrutinib is restarted.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The TIME AND EVENTS SCHEDULE summarizes the frequency and timing of efficacy, PK, PD, and safety assessments applicable to this study. The study visits scheduled should occur at the times delineated in the TIME AND EVENTS SCHEDULE. The Week 1 and Week 2 visits should occur on the specified day and visits from Week 5 and onwards that are to occur every 4th week should occur within ±3 days of the scheduled visit date. Visits from Week 37 and onwards that are to occur every 12th week and all the other study visits in the treatment period should occur within ±7 days of the scheduled visit date. The End-of-treatment visit is scheduled after 30 days from last dose of ibrutinib. Posttreatment follow-up visit will occur every 12th week after End-of-treatment visit, until cGVHD progression. After cGVHD progression, survival status and the use of subsequent cGVHD treatment will be followed every 12th week by clinic visits or telephone contacts.

Lee cGVHD Symptom Scale assessment (whenever assessment is scheduled) should be conducted/completed before any tests, procedures, or other consultations to prevent influencing subject perceptions. Blood collections for PK and PD assessments should be kept as close to the specified time as possible. Actual dates and times (if applicable), of assessments will be recorded in the source documentation and case report form (CRF).

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator, to establish the absence of pregnancy at any time during the subject's participation in the study.

The total blood volume to be collected from each subject will be approximately 319.5 mL in the first year [from screening to Week 49], 135 mL per year after the first year [5 times visits per year], and 27 mL on the End of Treatment Visit. If a subject continues treatment phase until Week 109, the total blood volume is approximately 481.5 mL (255 mL for safety [85 mL for hematology and 170 mL for serum chemistry], 5 mL for coagulation studies, 3 mL for serology, 2 mL for serum β-hCG pregnancy test [women only], 77 mL for donor/host chimerism, 55 mL for quantitative serum immunoglobulins [Igs], 22 mL for PK, and 62.5 mL for PD). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.2. Screening Phase

The Screening Phase assessments will be performed within 42 days prior to study treatment initiation. The subjects (legally acceptable representatives [LARs], if the subject is incapable of providing consent) will be asked to sign the consent form at the screening visit before any study related procedures are conducted.

During the Screening Phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed. A relevant medical history and physical exam (including vital signs, height, and weight), along with medical history details of transplant history and indication will be captured. Karnofsky/Lansky performance status, malignant disease restaging for relapse and cGVHD activity assessment will be conducted. The subject’s baseline cardiovascular status will be assessed using an ECG. All concomitant medications including corticosteroids requirement, over-the counter drugs, vitamins and herbs will be recorded. Lee cGVHD Symptom Scale will be used for efficacy assessment. Laboratory test for Hematology, Serum chemistry, Coagulation studies: PT/INR, aPTT, Hepatitis serologies/PCR, and FEV1 by spirometry will be done. Serum pregnancy test will be done only for women of childbearing potential. Eligible subjects will have clinically determined cGVHD and are dependent on or refractory to steroids. Subjects may have had no more than 3 previous therapies for cGVHD.

Clinical assessment of cGVHD must be clinically stable or worsening for a minimum of 14 days between screening and first dose of ibrutinib. If cGVHD assessment shows clinical improvement during this period, subject may be reassessed. Reassessment should be performed at least 14 days later from the last assessment. If cGVHD assessment is stable or worsening between the last 2 assessments then the subject may receive first dose of ibrutinib. When cGVHD assessment is performed at the day of informed consent for this confirmation, clinical laboratory test results

which have been obtained in clinical practice at the same day before signing of the informed consent can be referred to the cGVHD assessment.

After reviewing all eligibility criteria, a subject will be enrolled in this study within 3 days before the planned first dose of ibrutinib. Adverse events and concomitant medication recording will start after the signing of the informed consent and will continue until 30 days after the last dose of ibrutinib or the time of starting a subsequent systemic treatment for cGVHD, if earlier.

9.1.3. Treatment Phase

On Day 1 of Study Week 1, subjects who satisfy all inclusion and exclusion criteria will start treatment with ibrutinib. All required tests and evaluations must be conducted before start of study drug administration on Day 1 of Study Week 1.

Subsequently, throughout the Treatment Phase, subjects will continue to receive ibrutinib unless they have intervening unacceptable toxicity or meet other criteria for subject discontinuation (see Section 10.2). All visit procedures will be performed as specified in the TIME AND EVENTS SCHEDULE.

During the Treatment Phase, efficacy and safety evaluations (See Section 9.2 and 9.5), sampling of PK and PD (See Section 9.3 and 9.4) will be performed according to the TIME AND EVENTS SCHEDULE. Adverse events and changes to concomitant medications will be recorded.

The measurements collected at the time closest to, but prior to, the first dose of study drug administration will be defined as the baseline values. The frequency of study procedures and assessment to be conducted during the Treatment Phase are outlined in the TIME AND EVENTS SCHEDULE. However, clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated.

For Week 1 Day 1 only, clinical laboratory tests and spirometry do not need to be repeated if the screening tests were performed within 3 days of the first dose of ibrutinib. The eligible subjects will be sequentially assigned to the study drug. Ibrutinib 420 mg (3 × 140 mg capsules) will be administered orally once daily. The first dose will be delivered at the study site on Day 1, after which subsequent dosing will occur on an outpatient basis except for PK and PD sampling days on Week 1 Day 2, Week 2 Day 1, and Week 13 Day 1 (see Section 9.3 and 9.4). Subjects should refrain from taking the study drug in the morning of the study visits designated for PK and PD sampling until seen at the site. When all evaluations will be completed, and it will be determined that the subject can continue treatment, ibrutinib capsules will be dispensed.

Ibrutinib will be dispensed to subjects in bottles. Study-site personnel will instruct subjects on how to store study drug for at-home use as indicated for this protocol. The evaluations will be done as per timepoints specified in the TIME AND EVENTS SCHEDULE. Subjects will be evaluated throughout the Treatment Phase for possible toxicities, and modifications in dosing will be made as required according to the criteria in Section 6.1.

Treatment will continue until study discontinuation criteria (refer Section 10.2) are met. If progressive cGVHD is confirmed, the subject will discontinue taking the study drug, complete the End-of-treatment Visit, and enter the Posttreatment Follow-up Phase.

For subjects who have reached the time of the study end in Treatment Phase, study treatment will be discontinued at the first visit after the study end. Then the End of Treatment Visit will be completed and the subject's study participation will be ended.

End of Treatment Visit

An End of Treatment Visit will be scheduled within 30 days after the last dose of study drug (+7 days) for all subjects, including those discontinuing treatment for any reason except for loss to follow-up, death, or withdrawal of consent for study participation. Subjects who are discontinued from treatment due to cGVHD progression, AEs, or other reasons should complete the End of Treatment Visit before starting any subsequent cGVHD treatment. If a subject is unable to return to the study site for the End of Treatment Visit, the subject should be contacted and any available information regarding AEs that occur within 30 days after the last dose of study drug or the time of starting a subsequent systemic treatment for cGVHD, if earlier should be collected.

9.1.4. Follow-up Phase

The Posttreatment Follow-up Phase will begin once a subject discontinued ibrutinib treatment.

Subjects who discontinue for reasons other than cGVHD progression (ie, for AE or Investigator decision) will complete an End-of-treatment Visit (30+7 days from the last dose of ibrutinib) and will be followed for the evaluations listed below until death, lost to follow-up, consent withdrawal, or study end, whichever occurs first:

- Continued cGVHD disease evaluations
- Follow-up for recurrence of malignancy
- Follow-up for new cGVHD treatments

Subjects who discontinue due to cGVHD progression will complete an End-of-treatment Visit and be followed for survival status and the use of subsequent cGVHD treatment (clinic visits or telephone contacts).

Investigators may recontact the subject to obtain long-term follow-up information regarding the subject's safety or survival status as noted in the ICF (refer to Section 16.2.3, Informed Consent and Assent Form).

Subjects will be instructed that study drug will not be made available to them after they have completed/discontinued study drug and that they should return to their primary physician to determine standard of care.

9.2. Efficacy

9.2.1. Efficacy Evaluations

NIH Consensus Panel Criteria for Overall Response

Response will be defined using the NIH Consensus Panel Chronic GVHD Activity Assessment (2014) (Attachment 4, Attachment 5, and Attachment 6). 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.
- cGVHD 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 cGVHD progression.
- Stable disease (SD): response that does not meet the criteria for CR, PR, or cGVHD progression.

Please refer to NIH Response Assessment Manual provided by the sponsor for further details.

Lee cGVHD Symptom Scale

All subjects in the study will complete the Lee cGVHD Symptom Scale (Attachment 3) at all response assessment visits.

9.3. Pharmacokinetics

Venous blood samples will be collected to determine plasma concentrations of ibrutinib and the metabolite PCI-45227 at the timepoints specified in TIME AND EVENTS SCHEDULE. Plasma samples used for PK evaluation may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period.

9.3.1. Evaluations

Venous blood samples of approximately 2 mL per sampling will be collected for measurement of plasma concentrations of ibrutinib and PCI-45227 according to the timepoints specified in the TIME AND EVENTS SCHEDULE and the BLOOD SAMPLING SCHEDULE FOR PK AND PD. Other metabolites of ibrutinib may be explored.

The subject should refrain from taking the study drug in the morning of study visits designated for PK sampling. The time of the last meal prior to the dosing is to be recorded in the CRF. The investigator or designee will supervise administration of the study drug and record the exact time of study drug administration and blood samplings.

9.3.2. Analytical Procedures

Plasma concentrations of ibrutinib and PCI-45227 will be determined using a validated, specific, and sensitive liquid chromatography/tandem mass spectrometry method under the supervision of the sponsor.

9.3.3. Pharmacokinetic Parameters

The plasma concentration data of ibrutinib and PCI-45227 will be used to determine PK parameters by noncompartment method. At least following PK parameters will be included: area under the plasma concentration-time curve from time zero to time of last measurable concentration (AUC_{last}), area under the plasma concentration-time curve from time zero to 24 hours (AUC_{24h}), maximum plasma concentration (C_{max}), time to reach the maximum plasma concentration (T_{max}), and elimination half-life ($t_{1/2}$).

In addition, the plasma concentration data of ibrutinib may be used for population PK analysis and further analyses to explore correlation between exposure and relevant clinical/PD information.

9.4. Pharmacodynamic Evaluations

Venous blood samples for PD evaluation (BTK and ITK binding site occupancy) will be collected according to the timepoints specified in the TIME AND EVENTS SCHEDULE and the BLOOD SAMPLING SCHEDULE FOR PK AND PD. The exact time of blood sampling will be recorded.

9.5. Safety Evaluations

The study will include the following evaluations of safety according to the timepoints outlined in the TIME AND EVENTS SCHEDULE. Any clinically relevant changes occurring during the study must be recorded on the AE section of the CRF. Any clinically significant abnormalities persisting at the end of the treatment/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached or until the end of the study.

Adverse Events

All AEs will be reported from the time a signed and dated ICF is obtained until 30 days following the last dose of ibrutinib or the time of starting a subsequent systemic treatment for cGVHD, if earlier. Adverse events reported after 30 days following the last dose of ibrutinib or the time of starting the subsequent systemic treatment for cGVHD should also be reported if considered related to ibrutinib. Progression of the disease under study is not considered an adverse event (or SAE), even if it results in death during the AE reporting period. If a clinical sign or symptom or a laboratory test abnormality is observed in a patient with disease progression, but is not related to progression of the disease under study, then the usual AE reporting requirements apply. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03.

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative). Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The laboratory reports must be filed with the source documents.

The following tests will be performed by the local laboratory:

- Hematology Panel

  -hemoglobin
  -platelet count
  -white blood cell (WBC) count
  -absolute neutrophil count (ANC)
  -absolute lymphocyte count
  -absolute eosinophil count

- Serum Chemistry Panel

  -sodium
  -potassium
  -glucose
  -total bilirubin
  -blood urea nitrogen (BUN)
  -creatinine
  -total protein
  -alkaline phosphatase
  -alanine aminotransferase (ALT)
  -lactic acid dehydrogenase (LDH)
  -uric acid
  -aspartate aminotransferase (AST)
  -albumin

- Coagulation Studies

Measurement of PT/INR and aPTT will be performed at local laboratory at screening.

- Pregnancy test:

Serum pregnancy tests are required at screening by local laboratory and only for women of childbearing potential. A urine pregnancy test will also be performed on Day 1 prior to first dose. If the test result is positive, the pregnancy must be ruled out by ultrasound to be eligible.

- Serology
  - Serologies include HIV antibody, hepatitis C antibody, HBsAb, HBsAg, and Hepatitis B core antibody (HBcAb) will be evaluated. If HBsAb, HBcAb, HBsAg or hepatitis C antibody is positive, then PCR to quantitate hepatitis B DNA or C RNA must be performed and must be negative prior to enrollment.
  - Clinical and laboratory signs of active HBV infection should be closely monitored for HBV carriers or subjects who have history of hepatitis B during and following study treatment, according to the Guidelines for Prevention of Immunosuppressive Therapy or Chemotherapy-Induced Reactivation of HBV Infection. Consultation with a hepatitis specialist is also recommended.

- Donor/Host Chimerism
  - Donor/host chimerism for the evaluation of engraftment status of the stem cell transplantation will be evaluated at local laboratory, except if donor/host chimerism cannot be performed due to any specific reason such as no donor information.
- Quantitative Serum Immunoglobulins
  - Testing for Ig A, IgG, and IgM levels will be performed at a local laboratory.

Electrocardiogram (ECG)

During the collection of ECGs, subjects will be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. At screening, ECG is mandatory to confirm eligibility. Other ECGs will be performed at the investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset of dyspnea.

Vital Signs

Vital signs will include blood pressure, pulse rate, respiratory rate, and body temperature. Blood pressure and pulse rate measurements will be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

Physical Examination

The complete physical examination will be performed at timepoints specified in the TIME AND EVENTS SCHEDULE and will include height (screening only) and weight, and examination per clinical practice. Review of symptoms should include inquiry of ocular symptoms; subjects should be referred to an ophthalmologist for a formal examination if any Grade ≥2 symptoms are reported.

Karnofsky/Lansky Performance Scale

The Karnofsky/Lansky Performance Scale is provided in Attachment 2. The Lansky scale is to be used for all subjects less than 16 years of age.

Forced Expiratory Volume in 1 Second

Subjects should be evaluated for FEV1 using spirometry at screening and Week 1 Day 1. After Week 1 Day 1, if the prior FEV1 result is abnormal then subsequent FEV1 measurements should be obtained every 12 weeks. If the prior FEV1 result is normal, then subsequent FEV1 measurements should be obtained every 24 weeks. If a subject has cGVHD features in lung, FEV1 evaluation other than these mandatory timepoints is encouraged in cGVHD activity assessment whenever possible. The NIH Lung score should be ascertained with every cGVHD activity assessment regardless of whether a FEV1 is performed.

9.6. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form. Instructions for the collection, handling, and shipment of samples are found in the laboratory manual that will be provided for sample collection and handling.

Refer to the TIME AND EVENTS SCHEDULE for the timing and frequency of all sample collections.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY INTERVENTION/ WITHDRAWAL FROM THE STUDY

10.1. Completion

The study will be terminated before the defined end of study (see Section 17.9) is reached if marketing approval is received for the indication under study from the Ministry of Health Labor and Welfare (MHLW) in Japan. A subject who is in the treatment period at this time will discontinue the study drug and will complete an End-of-treatment Visit before the study end. A subject who is in the follow-up period at this time will stop the further follow-up. Both subjects will be considered to have completed the study.

10.2. Discontinuation of Study Intervention/Withdrawal from the Study

Discontinuation of Study Intervention

A subject will not be automatically withdrawn from the study if he or she has to discontinue study drug before the end of the intervention regimen.

A subject's study drug must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study drug
- Subject begins treatment with another systemic therapy (including extracorporeal photopheresis) for cGVHD
- cGVHD progression
- Noncompliance with study medication
- Investigator’s decision (such as chronic noncompliance, significant protocol deviation, or best interest of the subject)
- Progression or relapse of the malignancy that was the indication for transplantation or development of posttransplant lymphoproliferative disease (PTLD)
- The subject becomes pregnant

If a subject discontinues study drug for any reason before the end of the study, posttreatment phase assessments should be obtained and scheduled assessments should be continued.

Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death
- Study termination by Sponsor

If a subject is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Additional subjects will not be entered. If a subject discontinues study drug and withdraws from the study, end-of-treatment and posttreatment assessments should be obtained, if possible. If the reason for withdrawal from the study is withdrawal of consent then no additional assessments are allowed.

11. STATISTICAL METHODS

Statistical analysis will be done by 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.

The primary analysis for all efficacy and safety endpoints will be conducted at the time when the last subject has completed the efficacy assessment at Week 37 or has discontinued treatment before Week 37. Final analysis will be conducted at the study end.

11.1. Subject Information

The following definitions will be used for the safety, efficacy, PK and PD (BTK and ITK binding site occupancy) analysis populations, respectively:

- **All treated population:** All enrolled subjects who will receive at least 1 dose of study drug.
- **Safety population:** All enrolled subjects who will receive at least 1 dose of study drug. Safety population is identical to all treated population.
- **Response evaluable population:** All enrolled subjects who will receive at least 1 dose of study drug and who have at least 1 adequate postbaseline efficacy assessment.
- **PK evaluable population:** All enrolled subjects who will receive at least 1 dose of study drug and have at least 1 postdose PK sample obtained.
- **PD evaluable population:** All enrolled subjects who will receive at least 1 dose of study drug and have at least 1 BTK and ITK binding site occupancy data.

11.2. Sample Size Determination

With a sample size of 17 subjects and assuming an expected overall cGVHD response rate of approximately 60%, it is expected to have at least 80% power to show the efficacious treatment effect (the lower bound of 95% confidence interval of the response rate >25%). At least 1 adolescent subject (12-17 years of age) will be enrolled in this study.

11.3. Efficacy Analyses

The all treated population will be used for all efficacy endpoints. The response evaluable population will be used for the overall cGVHD response rate as a sensitivity analysis.

Primary Endpoint

The overall cGVHD response rate (CR + PR) and its 95% confidence interval will be calculated with the exact test for binomial distribution in the all treated population. The study is considered to be positive if the lower limit of the exact 2-sided 95% confidence interval based on binominal distribution exceeds the threshold value (0.25).

Secondary Endpoints

Rate of sustained response for at least 20 weeks and cGVHD response rate at each timepoint of efficacy evaluation will be calculated with the exact 2-sided 95% confidence interval based on binominal distribution.

The DOR for responders will be calculated by the Kaplan-Meier method descriptively. Median DOR and the corresponding 95% confidence interval will be provided if estimable with Kaplan-Meier plot.

Corticosteroid requirement changes over time and change in symptom burden measured by the Lee cGVHD Symptom Scale will be summarized by descriptive statistics.

Exploratory Endpoints

The Kaplan-Meier method will be used to descriptively summarize the FFS. Median FFS and the corresponding 95% confidence interval will be provided if estimable with Kaplan-Meier plot.

The OS will be evaluated in the same manner as FFS, if necessary. Number and proportion of subjects with all immunosuppressants withdrawn will be summarized by descriptive statistics.

11.4. Pharmacokinetic Analysis

Pharmacokinetic evaluable population will be used for PK analyses. The individual plasma concentration data of ibrutinib and PCI-45227 will be listed and graphically displayed. Concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation. The data will be summarized at each timepoint using descriptive statistics (mean, standard deviation [SD], coefficient of variation, median, minimum and maximum) and mean (±SD) concentration-time profile will be graphically displayed. Concentration data below the lowest quantifiable concentration will be treated as zero in the

summary statistics. Additional analyses (eg, subgroup analyses by concomitant CYP3A inhibitors) may be performed as deemed necessary.

The individual PK parameters of ibrutinib and PCI-45227 derived by noncompartment method will be listed and summarized using descriptive statistics (mean, SD, coefficient of variation, geometric mean, median, minimum and maximum). Additional analyses (eg, subgroup analyses by concomitant CYP3A inhibitors) may be performed as deemed necessary.

Data or subjects will be excluded from the analysis if the data do not allow for accurate assessment of the PK. All subjects and samples excluded from the analysis will be clearly documented in the study report.

If the data is subjected to population PK analysis, details will be given in a population PK analysis plan and the results will be presented in a separate report. The data may be combined with data from other ibrutinib studies.

11.5. Pharmacodynamic Analyses

Pharmacodynamic evaluable population will be used for PD analyses. The BTK and ITK binding site occupancy will be tabulated and summarized at each timepoint using descriptive statistics (mean, SD, coefficient of variation, median, minimum and maximum). Additional analyses (eg, subgroup analyses by ibrutinib dose or concomitant CYP3A inhibitors) may be performed as deemed necessary.

11.6. Pharmacokinetic/Pharmacodynamic Analyses

Relationships between PK of ibrutinib and PD measures may be explored as deemed necessary.

11.7. Safety Analyses

Safety population will be used for safety analyses. The safety parameters to be evaluated are the incidence, intensity, relationship to study drug, action taken with regards to the study drug, and type of adverse events, vital signs measurements, and clinical laboratory results in the safety population. Exposure to and reasons for discontinuation from study treatment will be tabulated in the all treated population.

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events will be included in the analysis. Treatment-emergent adverse events are adverse events with onset during the treatment phase or that are a consequence of a preexisting condition that has worsened since baseline, and occur during treatment or within 30 days following the last dose of study treatment, or any adverse event that is considered study treatment-related regardless of the start date of the event. The number and percent of subjects with treatment-emergent adverse events will be summarized according to intensity using the NCI-CTCAE (Version 4.03), drug relationship, and outcome. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized. Summaries, listings, datasets, or

subject narratives may be provided, as appropriate, for those subjects who die, who discontinue study drug due to an adverse event, or who experience a severe or an SAE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled timepoint. Frequency tabulations of the changes from baseline results will be presented in pre versus postintervention cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the abnormalities will be made. A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

Parameters with predefined NCI-CTCAE toxicity grades will be summarized. Change from baseline to the worst adverse event grade experienced by the subject during the study will be provided as shift tables.

Vital Signs

Descriptive statistics of temperature, pulse rate, respiratory rate, and blood pressure (systolic and diastolic) supine values and changes from baseline will be summarized at each scheduled timepoint. The percentage of subjects with values beyond clinically important limits will be summarized.

12. 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.

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily

have a causal relationship with the intervention. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

An SAE based on ICH and European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality), other than progression of cGVHD.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For ibrutinib, the expectedness of an adverse event will be determined by whether or not it is listed in the IB.

Adverse Event Associated With the Use of the Intervention

An adverse event is considered associated with the use of the intervention if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2, Attribution Definitions.

12.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the intervention.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the intervention. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the intervention. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the NCI-CTCAE Version 4.03. The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study drug

- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the CRF.

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of ibrutinib, or the start of subsequent cGVHD treatment, if earlier. Adverse events reported after 30 days following the last dose of ibrutinib or the time of starting the subsequent systemic treatment for cGVHD should also be reported if considered related to ibrutinib. Resolution information after 30 days should be provided, if it can be obtained. All Grade 3 or Grade 4 adverse events considered related to ibrutinib must be followed until recovery to baseline or Grade ≤1 or until no further improvement is expected. Cardiac adverse events of Grade 2 or higher will be followed until improvement to baseline or Grade ≤1 or until no further improvement is expected. The unresolved aforementioned events will be followed for a maximum of 24 weeks. All adverse events of special interest as defined in Section 12.3.3 related to bleeding or resulting in bleeding complications must be followed until recovery or until there is no further improvement. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of ibrutinib, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Progressive disease of cGVHD should not be reported as an adverse event, but symptoms/clinical signs in a patient with disease progression may be reported (see Section 12.3.2). Otherwise, all events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent

Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number

12.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the CRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax).

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)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility).

- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience the investigator may choose to hospitalize the subject for the duration of the intervention period.
- The administration of blood or platelet transfusion. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.

Progression of the disease under study is not considered an adverse event (or SAE), even if it results in death during the AE reporting period. If a clinical sign or symptom or a laboratory test abnormality is observed in a patient with disease progression, but is not related to progression of the disease under study, then the usual AE reporting requirements apply.

12.3.3. Adverse Events of Special Interest

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities by the sponsor. These events, meeting the definition of major hemorrhage listed below, will be reported to the sponsor within 24 hours of awareness irrespective of seriousness (ie, serious and nonserious AEs) following the procedure described above for SAEs and will require enhanced data collection.

Major hemorrhage is defined as:

- Any treatment-emergent hemorrhagic adverse event of Grade 3 or higher. All hemorrhagic events requiring a transfusion of red blood cells should be reported as Grade 3 or higher adverse events per NCI-CTCAE.
- Any treatment-emergent SAE of bleeding of any grade.
- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade.

12.3.4. Other Malignancies

In addition to all routine adverse event reporting; all new malignant tumors, including solid tumors, skin malignancies, and hematologic malignancies; are to be reported for the duration of study treatment and during any protocol-specified follow-up periods including postprogression follow up for overall survival.

12.3.5. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study intervention.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY INTERVENTION INFORMATION

14.1. Physical Description of Study Drug

Ibrutinib capsules are provided as a hard gelatin capsule containing 70 mg and 140 mg of ibrutinib. It will be manufactured and provided under the responsibility of the sponsor. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the IB for a list of excipients.

14.2. Packaging

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

14.3. Labeling

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

14.4. Preparation, Handling, and Storage

Ibrutinib capsules should be stored according to the storage conditions indicated on the label. The recommended storage condition for ibrutinib capsules is 15°C to 25°C with excursions permitted to 30°C. Current stability data indicate that the capsules will be stable for the duration of the clinical study under the labeled storage conditions. Study staff will instruct subjects on how to store medication for at-home use as indicated for this protocol. Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on study intervention preparation, handling, and storage.

14.5. Intervention Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the intervention accountability form. Subjects or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study drug. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers. The subjects must return unused study drug to the study site.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the subject, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the intervention return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the intervention return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to

the same subject. Whenever a subject brings his or her study drug to the study site for pill count, this is not seen as a return of supplies. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure
- Pharmacy manual/study site investigational product and procedures manual
- Laboratory manual
- NCI-CTCAE Version 4.03
- Patient reported outcome (PRO) questionnaires and PRO completion guidelines
- Electronic data capture (eDC) Manual
- Sample ICF
- Subject diaries

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

This is an open-label, single-arm study and all subjects will receive the study drug. For the study population (Japanese patients with steroid dependent/refractory cGVHD), there are currently no standard treatment options. As ibrutinib has been approved in the US for the treatment of adult patients with cGVHD after failure of one or more lines of systemic therapy based on beneficial results of phase 1b/2 PCYC-1129-CA study in subjects with steroid dependent/refractory cGVHD, ibrutinib may also demonstrate clinical benefit for the population of this study. The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

When referring to the signing of the ICF, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each subject, his or her parent(s) (preferably both parents, if available) or legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be

obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies. For the purposes of this study, all references to subjects who have provided consent (and assent as applicable) refers to the subjects and his or her parent(s) or the subject's legal guardian(s) or legally acceptable representative(s) who have provided consent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parent(s) still want them to participate.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This

approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study, the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent and Assent Form

Each subject or a legally acceptable representative must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) and assent form that is/are used

must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject or legally acceptable representative is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed. The physician may also recontact the subject for the purpose of obtaining consent to collect information about his or her survival status.

The subject or legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's or his or her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject or legally acceptable representative is obtained.

Children (minors) or subjects who are unable to comprehend the information provided can be enrolled only after obtaining consent of a legally acceptable representative. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies. Written assent should be obtained from subjects who are able to write. A separate assent form written in language the subject can understand should be developed for adolescents. After having obtained the assent, a copy of the assent form must be given to the subject, and to the subject's parent or if applicable legally acceptable representative.

When prior consent of the subject is not possible and the subject's legally acceptable representative is not available, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or legally acceptable representative must be informed about the study as soon as possible and give consent to continue.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject or his or her legally acceptable representative includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject or a legally acceptable representative has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory PD, PK and PK/PD research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for nonacceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be

promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required

- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth (as allowed by local regulations). In cases where the subject is not enrolled into the study, the date seen and date of birth (as allowed by local regulations) will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; intervention receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable. The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the CRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the CRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and

study-site personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after their return to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. The data will be entered into the study database and verified for accuracy and consistency with the data sources.

The sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

For CRF completed on pressure-sensitive paper, a copy is to be retained in the archives of the sponsor. A second copy must be archived by the investigator.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will use a combination of monitoring techniques (central, remote, or on-site monitoring) to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first postinitiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site. Central monitoring will take place for data identified by the sponsor as requiring central review.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the last scheduled study assessment shown in the TIME AND EVENTS SCHEDULE for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding ibrutinib or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of ibrutinib, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of exploratory analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will

not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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Attachment 1: 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)	
Genitalia	Lichen planus-like features Lichen sclerosus-like features	Erosions Fissures Ulcers		
Females	Vaginal scarring or clitoral/labial agglutination			
Males	Phimosis or urethral/meatus scarring or stenosis			

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)
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]	
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; CT= computed tomography; GI= gastrointestinal; GVHD= graft versus host disease; ITP, idiopathic thrombocytopenic purpura.

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

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)

[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.
[e] Pulmonary entities under investigation or unclassified.
[f] Diagnosis of chronic GVHD requires biopsy.

Source:
Jagasia MH, Greinix HT, Arora M, et al. Biol Blood Marrow Transplant.2015;21:389-401.[23]

Attachment 2: 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

Attachment 3: Lee cGVHD Symptom Scale

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

Attachment 4: Chronic GVHD Activity Assessment-Clinician

FORM A **Current Patient Weight:**

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

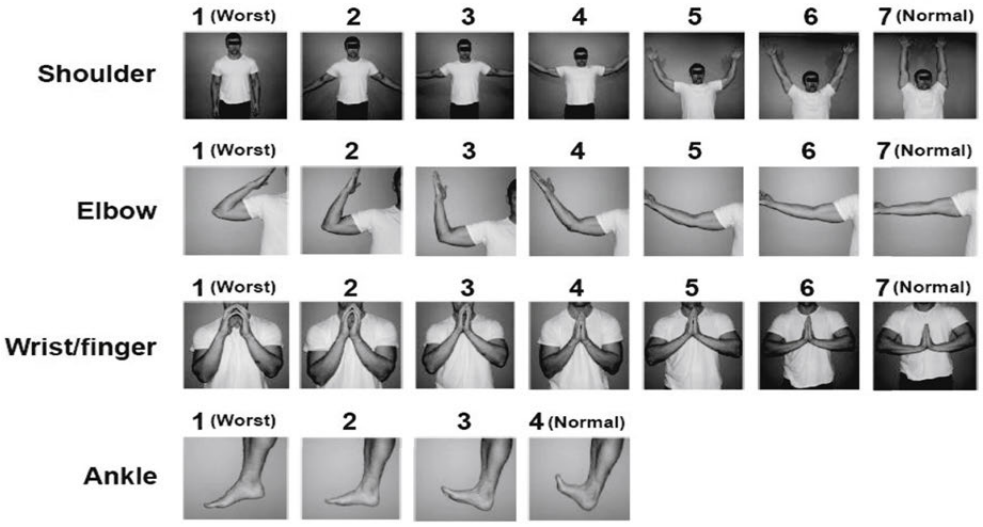
Mouth	**Erythema**	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3
	Lichenoid	None	0	Lichen-like changes (<25%)	1	Lichen-like changes (25-50%)	2	Lichen-like changes (>50%)	3
	Ulcers	None	0			Ulcers involving (≤20%)	3	Severe ulcerations (>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. Biol Blood Marrow Transplant. 2015;21:984-999.[31]

Attachment 5: 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.

*Liver score 1 or more in Diagnosis and Staging Working Group Report by NIH cGVHD Consensus Development Project (2014) [23]:

Score 0: Normal total bilirubin and ALT or alkaline phosphatase <3 x ULN

Score 1: Normal total bilirubin with ALT ≥3 to 5 x ULN or alkaline phosphatase ≥3 x ULN

Score 2: Elevated total bilirubin but ≤3 mg/dL or ALT >5 ULN

Score 3: Elevated total bilirubin >3 mg/dL

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.
- cGVHD 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 cGVHD progression.
- Stable disease (SD): response that do not meet the criteria for CR, PR, or cGVHD 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 timepoint, to confirm progression, before discontinuing study drug. If progression is confirmed, time to progression will be calculated using first date of cGVHD progression. Lack of Response includes categories of cGVHD progression or stable disease.

Reference:
Lee SJ, Wolff D, Kitko C, et al. Biol Blood Marrow Transplant. 2015;21:984-999.[31]
Jagasia MH, Greinix HT, Arora M, et al. Biol Blood Marrow Transplant.2015;21:389-401.[23]

Attachment 6: Chronic GVHD Activity Assessment − Patient Self Report

FORM B

CHRONIC GVHD ACTIVITY ASSESSMENT-PATIENT SELF REPORT

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

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

Patient Global Ratings:

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

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

0 1 2 3 4 5 6 7 8 9 10

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

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

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

Reference:
Lee SJ, Wolff D, Kitko C, et al. Biol Blood Marrow Transplant. 2015;21:984-999. [31]

Attachment 7: Inhibitors and Inducers of CYP3A

Inhibitors and inducers of CYP3A enzymes are defined as follows. Refer to Section 6.1 and 8.3.1 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[a]	modafinil
Itraconazole[b]	oxcarbazepine
Ketoconazole[b]	pioglitazone
nefazodone	troglitazone
saquinavir	pioglitazone
suboxone	**Strong CYP3A inducers**
telithromycin	avasimibe
cobicistat	carbamazepine
boceprevir	phenobarbital
mibefradil	phenytoin
telaprevir	rifabutine
troleandomycin	St. John's Wort
posaconazole	
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. Avoid concomitant use of clarithromycin with ibrutinib
b. Itraconazole and ketoconazole will be replaced with voriconazole for study subjects

Attachment 8: Child-Pugh Score

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

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

Source:

Child CG, Turcotte JG. "Surgery and portal hypertension". In Child CG. The liver and portal hypertension. Philadelphia: Saunders. 1964. pp. 50-64.[8]

Pugh RN, Murray-Lyon IM, Dawson L, et al. "Transection of the oesophagus for bleeding oesophageal varices". The British Journal of Surgery, 1973;60: 646-9.[43]

Attachment 9: 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.[20, 32]	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.[32]	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.
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	Occupational and physical therapy to prevent falls and improve function, treatment of neuropathic syndromes with tricyclic antidepressants, SSRI, or anticonvulsants.[48] Orthotics and assistive devices (canes and walkers). Bracing, splinting or surgical release for entrapment neuropathies.

Organ System	Organ-Specific Intervention*	
	Prevention	Treatment
	wounds in insensate patients.	
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; UVA, ultraviolet-A; UVB, ultraviolet-B, PUVA, psoralen ultraviolet A; HSV, herpes simplex virus; HPV, human papilloma virus; CMV, cytomegalovirus; EMG, electromyography; VZV, varicella zoster virus; ROM, range of motion.
*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.

References:

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.[7]

Inamoto Y, Savani BN, Shaw BE, et al. Secondary solid cancer screening following hematopoietic cell transplantation. Bone Marrow Transplant. 2015;50:1013-1023.[20]

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.[32]

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.[48]

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Pharmaceutical K.K

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

SIGNATURES

Signed by	Date	Justification
PPD	24Jul2018, 11:35:28 AM, UTC	Document Approval

Janssen Pharmaceutical K.K.*

Clinical Protocol

COVID-19 Appendix

Protocol Title
A Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib in Subjects with Steroid Dependent/Refractory Chronic Graft Versus Host Disease (cGVHD)

Protocol 54179060GVH3001; Phase 3

JNJ-54179060 (Ibrutinib)

* This study is being conducted by Janssen Pharmaceutical K.K. in Japan. The term "sponsor" is used throughout the protocol to represent Janssen Pharmaceutical K.K.

Status: Approved
Date: 14 May 2020
Prepared by: Janssen Pharmaceutical K.K.
EDMS number: EDMS-RIM-61817, 1.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

COVID-19 APPENDIX

GENERAL GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by subjects and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study-related subject management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of subjects and site staff. If at any time the investigator assesses that the risk of treatment may outweigh the benefits, study treatment will be interrupted, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, subjects will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Subjects will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for subjects on study treatment, including follow up. Modifications to protocol-required assessments may be permitted after consultation between the subject and investigator, and with the agreement of the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study treatment and withdrawal from the study should be documented with the prefix “COVID-19-related” in the Comments electronic case report form (eCRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL:

Subject Visits and Assessments

- For subjects who are unable to come to the site for Response Follow-up Visits, the visit should be postponed and rescheduled as soon as possible.
- For subjects who are unable to come to the site for Treatment Phase Visits, contact (eg, telephone, videoconference, or other channels) with the subject should be made in advance, to collect information on the subject's current health status and any new or ongoing adverse events and concomitant medications. The remote method that is used for contact with the subject must be allowable per local regulations and fully documented in the subject source record. Protocol-specified laboratory assessments and physical examinations should be obtained locally, if possible. Where local laboratories are used, it is important to ensure appropriate documentation of laboratory reference ranges. After reviewing all available information, and if the investigator assesses that continued treatment is acceptable, contact the site manager to discuss alternative solutions for the provision of study treatment to subjects (see alternatives below). The remote contact with the subject, the local laboratory results, and the sponsor discussion should be documented in the subject source record. Similarly, at a minimum, a comment must be entered in the Comments eCRF clearly designating as "COVID-19-related" and acknowledging the discussion between the investigator and the sponsor.
- If the subject is not willing or able to go to a local clinic/laboratory, remote contact (eg, telephone, videoconference, or other channels) with the subject is recommended, as well as a thorough review of the subject's medical history, prior labs, and most recent disease evaluation. The remote method chosen must be allowable per local regulations and fully documented in the subject source record. If appropriate, treatment should be interrupted until new laboratory assessments are made. However, if the investigator assesses that continued treatment is acceptable despite the absence of new laboratory tests, contact the site manager to discuss alternative solutions for the provision of study medication to subjects (see possible alternatives below). Proper documentation of all discussions and decisions should be made in the subject source record and in the Comments eCRF.
- If any change in subject status is identified that may impact the subject's safety, then study treatment should be interrupted until the subject can be assessed. Any changes in study treatment (dose, frequency, interruption) needs to be clearly documented as "COVID-19-related". When pandemic conditions improve, travel restrictions are lifted, and the subject is willing and able to come to the clinic, subjects should be scheduled for an in-clinic, follow-up visit.
- All deviations from protocol-required assessments should be documented in detail within the subject's source record and should be clearly designated as "COVID-19-related". It must be documented if a visit is conducted remotely. Source documentation should detail how each assessment was collected (eg, remote vs. on-site, central vs. local laboratory, vital signs taken at home by caretaker vs. delegated in-home nursing).

Study Drug Supply

If a subject is unable to travel to the site for a scheduled visit where study drug would be dispensed, the following alternate measures should be discussed with the study monitor and may be considered to ensure continuity of treatment, upon sponsor's approval:

- A caregiver or family member may pick up study drug on behalf of the subject if first discussed and agreed by the subject. The conversation with the subject must be documented in the subject source records. The subject must name the individual who will pick up study drug on their behalf. This is necessary for site staff to confirm the study drug is provided to the appropriate individual, ensure proper chain of custody of study drug, and to maintain subject privacy. Identification of who will pick up the study drug must be confirmed and documented in the subject source record.
- Investigative site staff may deliver study drug directly to the subject's home. The chain of custody and transit conditions must be clearly documented within the subject source record.
- If no other alternative is feasible, direct-to-patient shipment of study drug from the site may be considered with prior approval from the sponsor. Site staff need to obtain permission from the subject and record this in the subject source record for direct-to-patient shipments. It is important to note this process must be allowed by the local health authority and a specific approval process must be followed with the sponsor before moving forward. If requested by the site, the sponsor will investigate local requirements and confirm health authority requirements for direct-to-patient shipment. If approval is granted by the sponsor, specific procedures including shipment conditions, preferred courier services, and documentation requirements will be communicated by the sponsor to the site.

If a subject is able to come to the site for a Treatment Phase Visit but anticipates being unable to come to the next visit, the investigator may dispense study treatment for the current visit and an additional visit, after agreement with the sponsor's medical monitor. Prior to continuing treatment with the additional study treatment, the subject should obtain protocol-specified laboratory assessments and physical examinations locally, if possible, and the investigator should conduct a remote contact as described above. After reviewing all available information, if the investigator assesses that continued treatment is acceptable, the subject may continue treatment using the previously supplied additional study treatment. Proper documentation of all discussions and decisions should be made in the subject source record and in the Comments eCRF.

For subjects who have reason to believe they have been exposed to COVID-19 but do not yet have a confirmed diagnosis and/or are not showing symptoms of infection:

- The investigator should consider the risk/benefit of continuing ibrutinib based on the individual subject's underlying condition and the potential risks associated with COVID-19.
- If the subject becomes symptomatic at any point, refer to guidance below for subjects with symptomatic COVID-19 infection.

For subjects who have been diagnosed with COVID-19:

- The investigator should contact the sponsor's responsible medical officer to discuss plans for study treatment and follow-up.
- The investigator should consider the risk/benefit of continuing ibrutinib based on the nature and status of the subject's underlying condition and the potential risks associated with COVID-19.
- As with all infections, the investigator should follow the protocol guidance which is to interrupt therapy for Grade 4 or unmanageable Grade 3 toxicity (see Section 6.1.1), and resume once infection has resolved to Grade 1 or baseline (recovery). Given that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new pathogen, a more cautious approach would be appropriate, with interruption for confirmed cases of SARS-CoV-2 infection of any grade.

On-site Monitoring Visits

In case on-site monitoring visits are not possible, as per institution policies, the sponsor's site managers may contact the investigator to arrange remote monitoring visits. Additional on-site monitoring visits may be needed in the future to catch up on source data verification.

All of the above measures are recommended for consideration on a temporary basis during the COVID-19 pandemic to enable continuity of treatment and to ensure that subject assessments, particularly those assessing disease progression and safety, continue as outlined in the protocol without imposing health risk to subjects, their families, and site staff. Every effort should be made to complete all protocol-required assessments. Investigators should use their clinical judgment and risk/benefit assessment in determining if a subject can continue study treatment in the absence of on-site clinic visits. If remote visits are not possible, or if in the investigator's judgment, appropriate safety monitoring is not feasible in a remote setting, the investigator should consider temporarily interrupting study treatment (for a maximum of 28 consecutive days, unless reviewed and approved by the sponsor) or discontinuing study treatment.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

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Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

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_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Pharmaceutical K.K.

Signature: electronic signature appended at the end of the protocol Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	14-May-2020 12:01:18 (GMT)	Document Approval