Official Title: **An Open-Label Phase 1/2 Study of Itacitinib (INCB039110) in Combination With Ibrutinib in Subjects With Relapsed or Refractory Diffuse Large B-Cell Lymphoma**

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Clinical Study Protocol

INCB 39110-206

An Open-Label Phase 1/2 Study of INCB039110 in Combination With Ibrutinib in Subjects With Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Product:	**INCB039110**
IND Number:	[redacted]
EudraCT Number:	**2017-002773-19**
Phase of Study:	**1/2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol (Version 0):	**30 MAR 2016**
Amendment (Version) 1:	**27 JUN 2016**
Amendment (Version) 2:	**11 MAY 2017**
Amendment (Version) 3:	**05 FEB 2018**
Amendment (Version) 4:	**01 MAR 2018**
Amendment (Version) 5:	**18 JUN 2020**

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study Protocol, Good Clinical Practices as defined in Title 21 of the US Code of Federal Regulations Parts 50, 54 56, 312, and Part 11 as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

INVESTIGATOR'S AGREEMENT

I have read the INCB 39110-206 Protocol Amendment 5 (Version 5 dated 18 JUN 2020) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

SYNOPSIS

Name of Investigational Product: INCB039110

Title of Study: An Open-Label Phase 1/2 Study of INCB039110 in Combination With Ibrutinib in Subjects with Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Protocol Number: INCB 39110-206	**Study Phase:** 1/2

Phase 1

Primary Objective:

The primary objective of Phase 1 is to evaluate the safety and tolerability of INCB039110 in combination with ibrutinib in subjects with relapsed or refractory diffuse large B-cell lymphoma (DLBCL).

Secondary Objective:

The secondary objective of Phase 1 is to evaluate the efficacy of INCB039110 in combination with ibrutinib in terms of objective response rate (ORR).

[redacted]

Phase 2

Primary Objective:

The primary objective of Phase 2 is to evaluate the efficacy of INCB039110 in combination with ibrutinib in subjects with relapsed or refractory non-GCB DLBCL as demonstrated by ORR.

Secondary Objectives:

The secondary objectives of Phase 2 are as follows:

- To evaluate efficacy in terms of duration of response (DOR), durable response rate, and progression-free survival (PFS).
- To evaluate the safety and tolerability of the treatment combination.

[redacted]

Endpoints:

Phase 1:

Efficacy endpoints will be assessed using the Lugano Classification; adverse events (AEs) will be assessed using National Cancer Institute CTCAE v4.03.

Primary Endpoint:

Safety and tolerability will be assessed by evaluating the frequency, duration, and severity of AEs (including serious adverse events [SAEs] and dose-limiting toxicities [DLTs]), and changes in clinical and laboratory assessments.

Secondary Endpoints:

Efficacy will be assessed by ORR, defined as the percentage of subjects achieving either a complete response (CR) or partial response (PR).

[redacted]

Phase 2

Primary Endpoint:

Efficacy will be assessed by ORR, defined as the percentage of subjects achieving either a CR or PR.

Secondary Endpoints:

- DOR, defined as the time from earliest date of disease response until earliest date of disease progression.
- Durable response rate, defined as the percentage of subjects achieving a CR or PR for > 16 weeks.
- PFS, defined as the time from enrollment until the earliest date of disease progression determined by objective radiographic disease assessments, or death due to any cause.
- Safety and tolerability via assessment of the frequency, duration, and severity of AEs and SAEs, and changes in clinical and laboratory assessments.

[redacted]

Overall Study Design:

This is an open-label, single-group, Phase 1/2 study of INCB039110 in combination with ibrutinib in subjects with relapsed or refractory DLBCL. Phase 1 will evaluate the safety and tolerability of INCB039110 when combined with ibrutinib in subjects with DLBCL (ABC, GCB, or unclassifiable) using a 6 + 3 design; Phase 2 will evaluate the efficacy of the combination in subjects with ABC or unclassifiable DLBCL at the dose determined in Phase 1 using a Simon 2-stage expansion design. Subjects may continue to receive study treatment until evidence of disease progression, unacceptable toxicity, or consent withdrawal.

Phase 1

The starting dose of INCB039110 will be 300 mg once daily (QD). Depending on tolerability, the dose of INCB039110 in combination with ibrutinib (560 mg QD) could be increased to 400 mg QD (Cohort 2) or decreased to 200 mg QD (Cohort -1). The dose selected for study in Phase 2 will be the dose tolerated by at least two-thirds of subjects who did not require a dose reduction within the first 28 days of treatment. In order to be included in the tolerability review, a subject must have received the cohort-specific dose of INCB039110 and ibrutinib for at least 75% of the days during the 28-day surveillance period, or have experienced a DLT. Additional subjects may be enrolled to achieve a minimum cohort size of 6 should withdrawal or dose interruptions/reductions result in a subject being nonevaluable.

Dose cohorts are outlined in the table below:

Cohort	Subjects	Regimen	Subjects With DLT	Action
-1	6	INCB039110 200 mg QD + ibrutinib 560 mg QD	≤ 1	Begin expansion portion of the study
			2	Enroll 3 additional subjects (9 subjects total)
			≥ 3	Terminate study
1 (Starting dose)	6	INCB039110 300 mg QD + ibrutinib 560 mg QD	≤ 1	Escalate to Cohort 2
			2	Enroll 3 additional subjects (9 subjects total); if no new DLTs, escalate to Cohort 2
			≥ 3	Reduce to Cohort -1
2	6	INCB039110 400 mg QD + ibrutinib 560 mg QD	≤ 1	Begin Phase 2
			2	Enroll 3 additional subjects (9 subjects total); if no new DLTs, begin Phase 2 study
			≥ 3	Begin Phase 2 of the study using Cohort 1 dose

Phase 2:

Subjects with ABC or unclassifiable DLBCL will receive the recommended Phase 2 dose of INCB039110 combination with ibrutinib as determined in Phase 1. Phase 2 will use a Simon 2-stage design with a stopping rule to allow early termination of the study at the end of Stage 1 if there is lack of sufficient efficacy. During Stage 1, if 9 or fewer of the first 22 evaluable subjects achieve an objective response (defined as a CR or PR), then the study may be terminated. If 10 or more subjects achieve an objective response, then the study will continue and accrue 38 additional subjects to Stage 2. Subjects who were enrolled but did not receive treatment will be excluded from the efficacy analysis and replaced. A timely assessment of response will be made to avoid risk of overenrollment before accrual to Stage 2. At the end of Stage 2, ORR will be assessed for sufficient efficacy to warrant further study. The study will be considered successful if the total number of objective responders is 29 or more. The study will end once all subjects have discontinued study treatment.

Study Population:

Key Inclusion Criteria:

- Male or female, 18 years or older.
- Histologically documented diagnosis of DLBCL.
  - For Phase 1, subjects may have any DLBCL subtype.
  - For Phase 2, subjects must have ABC or unclassifiable subtypes of DLBCL confirmed by immunohistochemistry using the Hans algorithm.

  Subjects having a computed tomography (CT) scan abnormality with uncertain interpretation following completion of the most recent treatment regimen must have biopsy confirmation of residual DLBCL before study entry.
- Relapsed or refractory DLBCL, defined as having received at least 1 but no more than 3 prior treatment regimens and ineligible for high-dose chemotherapy/autologous stem cell transplant.
- Fluorodeoxyglucose-avid disease (based on local evaluation) per the Lugano Classification. Fluorodeoxyglucose-avid disease is defined as disease with a 5-point scale score of 4 or 5.
- Subjects must have archived tumor tissue (block or 15-20 unstained slides) available, or be willing to undergo an incisional or excisional lymph node biopsy of accessible adenopathy (or, in less accessible lymph nodes, 4 to 8 core biopsies).

- At least 1 measurable (≥ 2 cm in longest dimension) lesion on CT scan or magnetic resonance imaging (MRI).
- Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.
- Adequate bone marrow, renal, and hepatic function, per local reference laboratory ranges (values must not be achieved with growth factors) as follows:
  - Absolute neutrophil count ≥ 1.5×10^9/L.
  - Platelet count ≥ 75×10^9/L.
  - Hemoglobin ≥ 8.0 g/dL (transfusions are permitted to achieve required hemoglobin level).
  - Serum creatinine ≤ 2.0 g/dL or measured or calculated creatinine clearance ≥ 30 mL/min by the Cockcroft-Gault Equation.
  - Aspartate aminotransferase and ALT ≤ 2.5 × institutional upper limit of normal (ULN) or ≤ 5 × ULN for subjects with known hepatic metastases.
  - Total bilirubin ≤ 1.5 × ULN if no liver metastases or < 3 × ULN in the presence of liver metastases or presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia). Further evaluation should be performed to confirm and document origin of increase.
- Prothrombin time/international normalized ratio < 1.5 × ULN and activated partial thromboplastin time < 1.5 × ULN.

Key Exclusion Criteria:

- Transformed DLBCL or DLBCL with coexistent histologies (eg, follicular or mucosa-associated lymphoid tissue lymphoma).
- Primary mediastinal (thymic) large B-cell lymphoma.
- Known central nervous system lymphoma (either primary or metastatic).
- Autologous stem cell transplant within the previous 3 months, allogeneic stem cell transplant within the previous 6 months, or active graft versus host disease following allogeneic transplant.
- Use of immunosuppressive therapy within 28 days of starting study treatment. Immunosuppressive therapy includes but is not limited to cyclosporine A, tacrolimus, or high-dose corticosteroids. Subjects receiving corticosteroids must be at a dose level ≤ 10 mg/day within 7 days of initiating study treatment.
- Prior or concurrent therapy with a Janus kinase inhibitor or Bruton's tyrosine kinase inhibitor.
- Receipt of anticancer medications or investigational drugs within the following intervals before starting study treatment (unless otherwise approved by the sponsor):
  - < 6 weeks for mitomycin-C or nitrosoureas.
  - < 28 days for any investigational agent for any indication.
  - < 21 days or 5 half-lives (whichever is greater) for all other cytotoxic anticancer medications.
  - < 4 weeks for monoclonal antibodies used as anticancer treatment.
  - < 10 weeks or 5 half-lives from completion of any radio- or toxin-immunoconjugates.
- Major surgery within 28 days before starting study treatment.
- Prior treatment-related toxicities that have not resolved to Grade 1, with the exception of ≤ Grade 2 neuropathy and any grade of alopecia.
- Chronic or current active infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment.

- Clinically significant cardiac disease, including unstable angina, acute myocardial infarction, and/or cardiac conduction issues within 6 months of Day 1; New York Heart Association Class II to IV congestive heart failure; uncontrolled arrhythmias.
- Known bleeding disorders (eg, von Willebrand's disease) or hemophilia.
- History of stroke or intracranial hemorrhage within 6 months of entering the study entry.
- Significant concurrent, uncontrolled medical condition including, but not limited to renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, neurological, cerebral, or psychiatric disease.
- Current or previous other malignancy within 3 years of study entry or not cured with treatment, except cured basal or squamous cell skin cancer, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma *in situ*, or other noninvasive or indolent malignancy without sponsor approval.
- Subjects who are currently receiving therapy with a strong cytochrome P450 3A4 inducer or inhibitor.
- Subjects who are currently receiving therapy with warfarin or vitamin K antagonists such as coumarin-based anticoagulants (eg, fluindione and phenindione).
- Unable to swallow oral medication, malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach or small bowel, ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
- Known human immunodeficiency virus infection.
- Known hepatitis B virus (HBV) or hepatitis C virus (HCV) or at risk for HBV reactivation. Hepatitis B virus DNA and HCV RNA must be undetectable. At risk for HBV reactivation is defined as hepatitis B surface antigen–positive or anti–hepatitis B core antibody positive.

Study Drug, Dosage, and Mode of Administration:

The starting dose of INCB039110 in Phase 1 will be 300 mg QD (3 × 100 mg tablets); dose cohorts may be escalated to 400 mg QD or decreased to 200 mg QD depending on observed DLTs. The recommended Phase 2 dose identified during Phase 1 will be the starting dose in Phase 2. Subjects may have dose reductions of INCB039110 during the course of treatment based upon clinical and laboratory assessments.

Reference Therapy, Dosage, and Mode of Administration:

Ibrutinib will be administered at a dose of 560 mg QD (4 × 140 mg capsules). Subjects may have dose reductions of ibrutinib during the course of treatment based upon clinical and laboratory assessments.

Study Schedule/Procedures:

During screening and every 28 days from the start of study treatment (Day 1), a study visit will be conducted that includes a physical examination, clinical laboratory tests, and assessments of vital signs, ECOG status, concomitant medications, and AEs. [redacted] Treatment compliance will also be assessed during the treatment portion of the study.

During screening, subjects will have a bone marrow biopsy and an objective assessment of disease status performed by positron emission tomography (PET) using [18F] fluorodeoxyglucose and diagnostic quality CT scan or MRI. Disease status will be subsequently assessed by CT/MRI at Week 8, Week 16, and every 16 weeks thereafter until disease progression. On-treatment bone marrow biopsies will be required only if needed to confirm a CR. PET-CT will be subsequently used to confirm CR/PR.

Subjects withdrawn from study treatment for reasons other than disease progression will be assessed per standard of care until disease progression, initiation of new anticancer therapy, or death, whichever occurs first.

Estimated Duration of Participation:

Subject participation is expected to average 6 months, which includes the following:

- A screening period lasting up to 28 days.
- A treatment period lasting as long as the subject has not met withdrawal criteria (approximately 4 months).
- A safety follow-up period lasting 30 days.

Estimated Number of Subjects:

Phase 1: Up to 18 subjects

Phase 2: Approximately 60 subjects (22 in Stage 1; 38 in Stage 2)

Principal Coordinating Investigator: [redacted] MD

Statistical Methods:

Sample size determination:

The study will lead to a decision between 2 prespecified hypotheses about the probability of an ORR, p. The null hypothesis H_0: p = 40% reflects a response rate that would be of no clinical benefit, and the alternative hypothesis H_A: p = 55% is a response rate that might lead to larger, confirmatory studies. Using a Simon 2-stage optimal design, a total of 60 subjects will be needed for 80% power at 1-sided alpha = 0.1 level. If there are 9 or fewer objective responders from the first 22 evaluable subjects, the null hypothesis will be considered as supported, and the study will be terminated. Otherwise, 38 additional subjects will be enrolled (Stage 2). Subjects who did not receive study treatment will be excluded from the analysis of Stage 1 and replaced.

Primary efficacy analysis: The study will be considered successful if the total number of objective responders is ≥ 29 in Phase 2. A 90% confidence interval will be calculated for the ORR.

Secondary efficacy [redacted] **analysis:** Median DOR and durable response rate (CR or PR ≥ 16 weeks) will be estimated with a 90% confidence interval. Median PFS will be estimated with 90% confidence intervals. [redacted]

Safety Analysis: Safety data will be tabulated with summary statistics.

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LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this clinical study Protocol.

Term	Explanation
5PS	5-point scale
aaIPI	age-adjusted International Prognostic Index
ABC	activated B-cell
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ASCT	autologous stem cell transplant
[redacted]	[redacted]
BCL	B-cell lymphoma
BCR	B-cell receptor
BR	bendamustine and rituximab
BTK	Bruton's tyrosine kinase
CFR	Code of Federal Regulations
cHL	classical Hodgkin lymphoma
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CI	confidence interval
CR	complete response
CRP	C-reactive protein
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DFS	disease-free survival
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
FCR	fludarabine, cyclophosphamide, and rituximab

Term	Explanation
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
GCB	germinal center B-Cell
GCP	Good Clinical Practice
HBc	hepatitis B core
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDC	high-dose chemotherapy
HIPAA	Health Insurance Portability and Accountability Act of 1996
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IL	interleukin
ILD	interstitial lung disease
IN	Investigator Notification
INR	international normalized ratio
IPI	International Prognostic Index
IRB	Institutional Review Board
ITT	intent to treat
IVRS	Interactive Voice Response System
JAK	Janus kinase
LDH	lactate dehydrogenase
LDi	longest transverse diameter of lesion
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
MYD88	myeloid differentiation primary response 88
NCI	National Cancer Institute
NF-κB	nuclear factor kappa light chain enhancer of activated B cells
NHL	non-Hodgkin lymphoma
ORR	objective response rate
OS	overall survival

Term	Explanation
PET	positron emission tomography
[redacted]	[redacted]
PFS	progression-free survival
PI3K	phosphoinositide 3-kinase
[redacted]	[redacted]
PMBL	primary mediastinal (thymic) large B-cell lymphoma
PO	orally
PP	per protocol
PPD	cross product of the longest transverse diameter of lesion and perpendicular diameter
PR	partial response
pSTAT3	phosphorylated signal transducer and activator of transcription 3
PT	prothrombin time
QD	once daily
RA	rheumatoid arthritis
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SDi	shortest axis perpendicular to the LDi
SEER	Surveillance, Epidemiology, and End Results Program
SPD	sum of the product of the perpendicular diameters for multiple lesions
STAT	Signal transducer and activator of transcription
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
TYK	tyrosine kinase
ULN	upper limit of normal
WBC	white blood cell

1. INTRODUCTION

1.1. Overview of Diffuse Large B-Cell Lymphoma

Non-Hodgkin lymphoma (NHL) is the most common hematologic malignancy, with over 385,000 new cases diagnosed in 2012 (Torre et al 2015). Incidence rates of NHL tend to be higher in North America, Western Europe, Northern Europe, and Australia compared with the rest of the world; it has been estimated that over 80,000 new cases of NHL and approximately 20,000 deaths due to NHL will occur in the United States in 2015 (Siegel et al 2015). Between 1975 and 2011, the incidence of new cases of NHL in the United States has nearly doubled from 11 to 20 cases per 100,000 people, but the proportion of deaths has slowly decreased (NCI 2015).

Diffuse large B-cell lymphoma (DLBCL) is a clinically and pathologically heterogeneous group of lymphoid malignancies and is the most common subtype of NHL observed in adults. Diffuse large B-cell lymphoma (BCL) accounts for approximately 25% of all NHLs in the developed world and up to 58% in some reports. The incidence is higher in men than women and generally increases with age, with the median age at onset generally occurring within the sixth decade (Swerdlow et al 2008).

Clinical presentation, histology, natural history, and prognosis are variable and are determined primarily by the site(s) of extranodal disease. Approximately 60% of all patients have advanced disease, with bone marrow involvement reported in up to 30% of cases (Armitage and Weisenberger 1998). The International Prognostic Index (IPI) and the age-adjusted IPI (aaIPI) are considered to be the most reliable prognostic benchmarks for all NHL subtypes and DLBCL in particular. More recently, advances in molecular diagnostics have further defined DLBCL prognostic factors. Gene expression profiling suggests the emergence of at least 3 distinct subtypes of DLBCL: germinal center B-cell (GCB) type, activated B-cell (ABC) type, and Type 3 (primary mediastinal) DLBCL (Rosenwald et al 2002). The ABC subtype has been associated with a particularly poor prognosis, suggesting that molecular subtyping may be a more relevant predictor than IPI. Prognosis varies across patients with DLBCL; subtype, patient characteristics, disease burden, and response to therapy all affect clinical outcome, but all subtypes are considered aggressive and fatal if left untreated (Martelli et al 2013). Survival outcomes for patients with GCB versus ABC subtypes are statistically different as shown below in Figure 1 and Table 1 (Roschewski et al 2013, Dunleavy et al 2013).

Figure 1: Using Biologic Predictive Factors to Direct Therapy of DLBCL

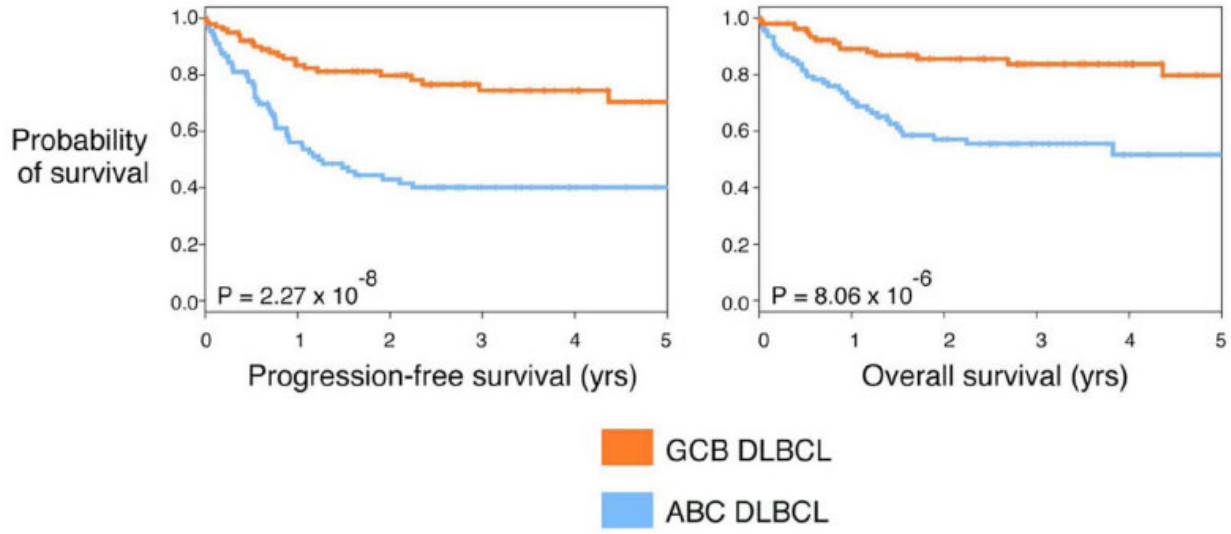


Table 1: Progression-Free Survival and Overall Survival by DLBCL Subtype

Molecular Subtype	Regimen	3-Year PFS Rate	3-Year OS Rate
ABC DLBCL	R-CHOP	40%	Approximately 45%
GCB DLBCL	R-CHOP	74%	Approximately 80%
PMBL	DA-EPOCH-R	100%	97% (at 5 years)

OS = overall survival; PFS = progression-free survival; PMBL = primary mediastinal B-cell lymphoma; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

In addition, gene mutations and rearrangements have been associated with poorer prognosis. The combined frequency of BCL-6 mutations and rearrangements approaches 100% in DLBCL; increased expression of this gene results in downregulation of downstream tumor suppressor genes, allowing cells to avoid apoptosis (Phan and Dalla-Favera 2004, Migliazza et al 1995). B-cell lymphoma 6 and BCL-2 rearrangements have been reported in 22% of patients with Stage II to IV disease. The presence of BCL-2 rearrangements did not significantly affect OS or disease-free survival (DFS); however, high BCL-2 protein expression did adversely affect both outcomes. The p53 gene is responsible for inducing growth inhibition; deletions and mutations have been reported in 20% of DLBCL cases and have been associated with a poorer clinical prognosis when compared with that of patients with wild-type p53 (Ichikawa et al 1997). Overexpression of nuclear factor kappa light chain enhancer of activated B cells (NF-κB), c-myc, and Ki-67 has also been associated with poor outcomes (Friedberg 2011).

1.1.1. Treatment for Advanced DLBCL

First-line treatment for DLBCL is based on the patient's IPI score and age using 3 major subgroups: elderly patients (> 60 years, aaIPI = 0-3); young patients with low risk (< 60 years, aaIPI = 0-1); and young patients with high risk (<60 years, aaIPI = 2-3). Rituximab, an anti-CD20 chimeric monoclonal antibody, has emerged as the standard of care for patients with DLBCL when administered in combination with cyclophosphamide, doxorubicin, vincristine,

and prednisone (R-CHOP) chemotherapy every 14 or 21 days. Complete response rates of 76% to 78% have been reported in elderly patients (> 60 years) and up to 86% in younger (≤ 60 years) patients (Coiffier et al 2010, Pfreundschuh et al 2008, Feugier et al 2005, Satterthwaite and Witte 2000, Sehn et al 2005, Coiffier et al 2002). It is recommended that after completing systemic therapy, select patient subsets should receive additional therapy, patients with bulky disease should receive consolidation radiation therapy, and those with high lactate dehydrogenase (LDH) and multiple extranodal sites or orbital and testicular involvement should receive prophylactic central nervous system (CNS) radiation therapy. The use of high-dose chemotherapy (HDC) supported by autologous stem cell transplant (ASCT) in the first-line setting was evaluated in a series of recent randomized studies, but results were not conclusive. In some cases, HDC/ASCT has been recommended for young patients (< 65 years) diagnosed with DLBCL who did not achieve a complete response (CR) after first-line chemotherapy or for patients with chemosensitive DLBCL at relapse (Martelli et al 2013).

1.1.2. Treatment for Relapsed/Refractory DLBCL

Although the use of first-line rituximab has been associated with substantial reduction in relapse rates, up to 20% of patients with low IPI risk and up to 50% of patients with IPI score > 2 will relapse. Relapsed patients and patients with disease that fails to respond to first-line therapy have a poor prognosis (Martelli et al 2013, Cultrera and Dalia 2012). Patients in this setting are generally divided into 2 categories: those with chemosensitive disease who are potentially eligible for HDC/ASCT, and those who are refractory to chemotherapy or are not medically fit for an aggressive chemotherapy regimen. Salvage chemotherapy is generally inadequate; response rates range from 30% to 60%, but less than 10% of patients achieve long-term DFS. The PARMA study demonstrated the benefit of HDC/ASCT versus standard chemotherapy for relapsed or refractory DLBCL; OS and 5-year event-free survival were significantly improved in transplanted patients compared with nontransplanted patients (Philip et al 1991). For patients ineligible for ASCT or relapsed after transplant, bendamustine in combination with rituximab demonstrated encouraging results; in a multicenter Phase 2 study, an overall response rate of 59% was observed (Fischer et al 2011). In addition, a number of novel agents are undergoing evaluation for DLBCL, including immunomodulating agents, mammalian target of rapamycin (mTOR) inhibitors, proteasome inhibitors, histone deacetylase inhibitors, and antiangiogenic agents.

1.2. Study Rationale

1.2.1. Inhibition of Janus Kinase as a Target for Cancer Therapy

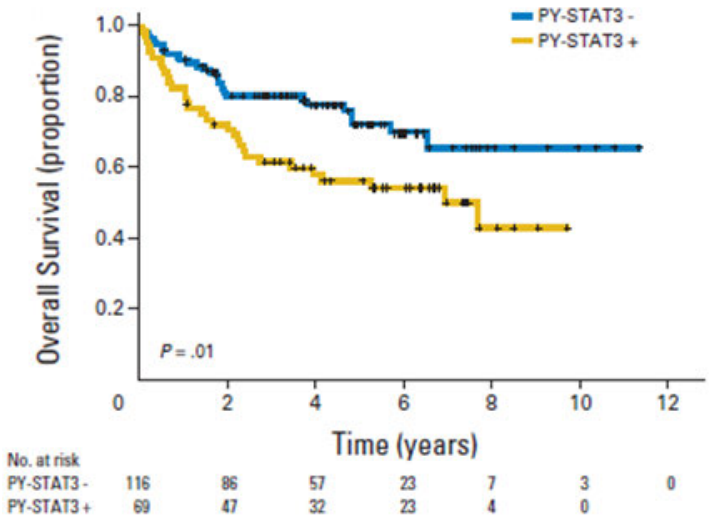
The Janus kinase (JAK) enzymes play an obligatory role in transducing intracellular signals generated by cytokine and growth factor receptors. Upon cytokine and growth factor binding to their cognate receptors, tyrosine phosphorylation of the intracellular domains of the receptors by JAKs enables them to serve as docking sites for signal transducer and activator of transcription (STAT) factors, which are also phosphorylated. Tyrosine-phosphorylated STATs are released from the receptors, form homodimers, and translocate to the nucleus where they bind canonical sequences and modulate transcription of genes that regulate a number of cellular functions. In contrast to normal cells, in which STAT tyrosine phosphorylation occurs transiently, STAT proteins, especially STAT3, are persistently phosphorylated in most malignancies

(Sansone and Bromberg 2012). The persistent or constitutive phosphorylation of STAT3 in cancers may occur via a variety of mechanisms, including increased expression of cytokines and cytokine receptors, decreased expression of the negative regulatory proteins such as suppressors of cytokine signaling through promoter methylation, and loss of tyrosine phosphatases that dephosphorylate JAKs and STATs.

Neoplastic progression involves JAK/STAT pathway activity through cell autonomous and noncell autonomous mechanisms. Cell autonomous mechanisms refer to tumor cell intrinsic alterations that facilitate the gain of neoplastic properties. The ability of STAT3 to sustain cell proliferation and block apoptosis (Lesina et al 2011); mediate cell cycle progression during oncogenic stress (Toyonaga et al 2003, Thoennissen et al 2009); control invasiveness, metastasis, and angiogenesis; and confer chemotherapeutic resistance (Catlett-Falcone et al 1999) are major mechanisms contributing to cancer. Noncell autonomous mechanisms refer to the extrinsic effects mediated by tumor microenvironment, stroma, immune system, and stellate cells (Masamune et al 2005); these play an integral role in many cancers and are substantially shaped to a great extent by JAK/STAT signaling. In addition, JAK/STAT-dependent inflammatory cytokines such as interleukin (IL)-6 and interferon gamma are critical mediators of cancer cachexia, a significant cause for cancer morbidity and mortality. Based on this evidence, we hypothesize that inhibition of JAK kinases may directly affect malignant cell proliferation and may suppress the inflammatory state leading to improvements in nutritional status, fatigue, tolerance to therapy, and prolonged survival in patients with advanced cancers that are driven by these intrinsic and extrinsic pathways influenced by STATs. This hypothesis is supported by evidence that JAK/STAT inhibitors are able to slow tumor cell growth and prolong survival in *in vivo* models (Iwanski et al 2010, Thoennissen et al 2009, Toyonaga et al 2003).

Aberrant activation of JAKs, through production of cytokines and growth factors, has also been associated with increased malignant cell proliferation and survival in a number of tumor types. JAKs activate a number of downstream pathways implicated in the proliferation and survival of malignant cells including the STATs, a family of important latent transcription factors. In DLBCL, JAK pathway activation occurs through both autocrine and paracrine mechanisms. In the tumor cells, B-cell receptor (BCR) signaling leads to increased IL-6 and IL-10 production through activation of the NF-κB pathway (Lam et al 2008). A subset of DLBCLs has been characterized as having high expression of STAT3, IL-6, and/or IL-10, and it has been shown that JAK inhibition is cytotoxic in these DLBCL cell lines and synergizes with NF-κB inhibitors. In addition to JAK/STAT pathway activation through autocrine pathways, the stromal compartment can also provide a source of these cytokines in a paracrine manner (Hodge et al 2005). High phosphorylated STAT3 (pSTAT3) levels are associated with poor survival in DLBCL with difference more significant in non-GCB than GCB subtype. Figure 2 shows gene expression profiling that identified an 11-gene signature of STAT3 activation in DLBCL. Survival differences based on STAT3 gene signature are similar to pSTAT3-based STAT-3 activation.

Figure 2: STAT Activation Predicts Poor Prognosis in DLBCL



Of clinical relevance, levels of serum IL-10 and IL-6, which signal through the JAKs, have been found to be elevated in patients with DLBCL when compared with normal controls. Further, patients with high serum IL-10 levels were shown to have a shorter event-free survival (Gupta et al 2012). Within the JAK family of kinases, JAK1 has been shown to cooperate with JAK2, JAK3, and tyrosine kinase (TYK) 2 and to play a dominant role in mediating the signaling of a number of inflammatory cytokines, including IL-6 and IL-10.

Inhibiting the phosphoinositide 3-kinase (PI3K) or JAK-STAT pathways may also be therapeutic in B-cell malignancies due to their contribution to tumor growth and survival and effects on the tumor microenvironment. Blocking both pathways may be synergistic due to JAK-STAT augmentation of BCR activation of the NF-κB pathway. A Phase 1 study recently evaluated INCB039110 in combination with INCB040093, a PI3Kδ inhibitor, in 17 subjects with relapsed/refractory classical Hodgkin lymphoma (cHL). In the dose-escalation portion of the study, responses were observed in 6 of the 9 evaluable subjects receiving INCB040093 and INCB039110. In an expansion cohort, objective response rate (ORR) in the cHL cohort was 50% in subjects treated with INCB040093 and 75% (1 CR) in subjects treated with INCB040093 plus INCB039110 (Forero-Torres et al 2015).

1.2.2. Inhibition of JAK With INCB039110

INCB039110 is a small molecule inhibitor of the JAK family of protein TYKs, with selectivity for JAK1. Members of the JAK family play an important role in signal transduction after cytokine and growth factor binding to their receptors; aberrant production of cytokines and growth factors has been associated with a number of cancers. Activated JAKs then phosphorylate tyrosine residues on cytokine receptors and are the principal kinases associated with phosphorylation and activation of the STAT. Aberrant production of cytokines and growth factors has been associated with myeloproliferative neoplasms and other chronic inflammatory conditions; thus, inhibition of their signaling may represent a therapeutic option. INCB039110 potently inhibits JAK1 (IC_{50} = 3.6 nM at 1 mM adenosine triphosphate concentration), with 22- to > 500-fold selectivity for the other JAK family members, JAK2, JAK3, and TYK2. Moreover, INCB039110 is potent (IC_{50} values of approximately 10-100 nM) in cytokine-driven

cell-based assays, such as IL-2–stimulated phosphorylation of JAKs and STATs, and IL-2–induced proliferation of primary human T cells. INCB039110 potently inhibits the phosphorylation of STAT proteins and the production of proinflammatory factors (eg, IL-17, monocyte chemotactic protein-1) induced by other cytokines, such as IL-23 and IL-6, with IC_{50} values in the range of approximately 30 to 100 nM. Additional preclinical and pharmacological details can be found in the Investigator's Brochure (IB).

1.2.3. Inhibition of Bruton's Tyrosine Kinase as a Target for Cancer Therapy

Ibrutinib (IMBRUVICA®) is a first-in-class, potent, orally administered, covalently binding inhibitor of Bruton's tyrosine kinase (BTK).

Ibrutinib has been approved in many regions, including the United States and Europe, for the treatment of patients with mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL) who have received at least 1 prior therapy, first-line treatment of patients with CLL with a deletion of the short arm of chromosome 17 (del17p) or a TP53 mutation, and patients with Waldenström's macroglobulinemia. Ibrutinib is currently under investigation in various indications as a single agent and in combinations.

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

The process of B-cell maturation, including immunoglobulin chain rearrangement and somatic mutation, is tightly regulated. It is thought that BCLs and CLL result from mutations and translocations acquired during normal B-cell development (Shaffer et al 2002). Several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B-cell malignancies.

The role of BTK in BCR signal transduction is demonstrated by the human genetic immunodeficiency disease X-linked agammaglobulinemia and the mouse genetic disease X-linked immunodeficiency, both caused by a mutation in the BTK gene. These genetic diseases are characterized by a reduction in BCR signaling and a failure to generate mature B-cells. The BTK protein is expressed in most hematopoietic cells with the exception of T-cells and natural killer cells, but the selective effect of BTK mutations suggests that its primary functional role is in antigen receptor signaling in B-cells (Satterthwaite and Witte 2000).

In a Phase 1/2 study of 80 subjects with relapsed or refractory DLBCL, CRs or partial responses (PRs) were reported in 37% (14/38) of subjects with ABC DLBCL treated with ibrutinib, but in only 5% (1/20) of subjects with GCB DLBCL. Subjects whose ABC tumors harbored BCR mutations responded to ibrutinib frequently (5/9; 55.5%), especially those with concomitant myeloid differentiation primary response 88 (MYD88) mutations (4/5; 80%). This is consistent with the hypothesis of *in vitro* cooperation between the BCR and MYD88 pathways. Responses also occurred in subjects whose ABC tumors lacked BCR mutations (9/29; 31%), suggesting that oncogenic BCR signaling in ABC does not require BCR mutations and might be initiated by other mechanisms (Wilson et al 2015).

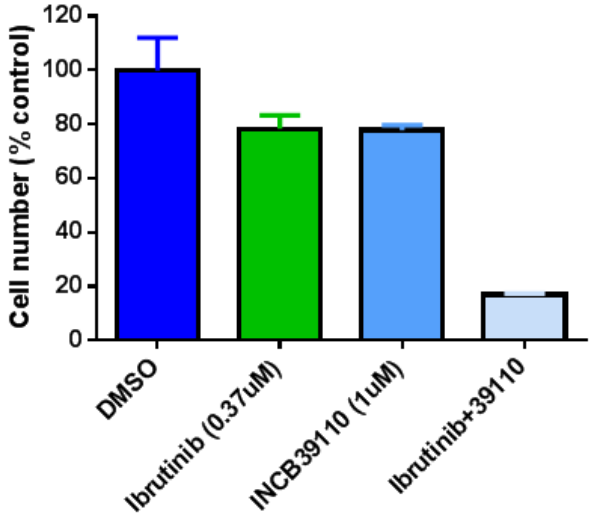
For the most comprehensive nonclinical and clinical information regarding ibrutinib background, safety, efficacy, and *in vitro* and *in vivo* preclinical activity and toxicology of ibrutinib, refer to the latest version of the ibrutinib IB.

1.2.4. Combined Inhibition of JAK and BTK in DLBCL

A number of B-cell malignancies, including DLBCL, have been shown to be particularly dependent upon BCR survival signals as evidenced by their sensitivity to genetic and pharmacological inhibition of BCR signaling components *in vitro*. In DLBCL, JAK pathway activation also occurs through both autocrine and paracrine mechanisms. In the tumor cells, BCR signaling leads to increased IL-6 and IL-10 production through activation of the NF-κB pathway (Lam et al 2008). A subset of DLBCLs has been characterized as having high expression of STAT3, IL-6, and/or IL-10 and it has been shown that JAK inhibition is cytotoxic in these DLBCL cell lines and synergizes with NF-kB inhibitors. In addition to JAK/STAT pathway activation through autocrine pathways, the stromal compartment can also provide a source of these cytokines in a paracrine manner (Hodge et al 2005). Within the JAK family of kinases, JAK1 has been shown to cooperate with JAK2, JAK3, and TYK2 and to play a dominant role in mediating the signaling of a number of inflammatory cytokines, including IL-6 and IL-10.

Preclinical data demonstrate that the presence of IL-10, a cytokine shown to be elevated in DLBCL patients and correlated with decreased survival, reduces the potency of the BTK inhibitor, ibrutinib, to block cell growth. The addition of a JAK1 inhibitor, although it has no inhibitory effect as a single agent, reverses this effect. The combination of both inhibitors demonstrates marked synergy in blocking cell growth and inducing apoptosis by inhibiting multiple signaling pathways (Figure 3). Together, these data suggest that both the JAK/STAT and BTK pathways may contribute to driving tumor growth and survival in DLBCL, and combination therapies that block both pathways may prove more beneficial in these diseases due to the central role that JAK-mediated cytokine signaling plays in augmenting BCR-mediated activation of the NF-κB pathway.

Figure 3: Inhibition of JAK Synergizes With B-Cell Receptor Signaling Inhibition in DLBCL *In Vitro*



According to the Phase 1/2 study results for ibrutinib in DLBCL (Section 1.2.3), ABC subtype appears to be more driven by BCR signaling, and ibrutinib has demonstrated enhanced efficacy in this subtype. The primary objective for Phase 1 of this study is to determine the safety and tolerability of the combination, INCB039110 and ibrutinib; thus, DLBCL subjects of all subtypes may be included in this part of the study. However, in Phase 2 of the study, efficacy is the primary endpoint, and the selection of the sample size and response rate for continuation of the study into Stage 2 for the Simon 2-stage design are based on the objective response rate in DLBCL ABC subtype subjects treated in the above Phase 1/2 ibrutinib study.

1.3. Potential Risks and Benefits of the Treatment Regimen

1.3.1. INCB039110

As of 13 DEC 2016, 9 Phase 1, 4 Phase 1/2, and 5 Phase 2 clinical studies with INCB039110, including studies of INCB039110 in combination with chemotherapeutic agents, corticosteroids, pembrolizumab (anti– programmed cell death 1 monoclonal antibody), and investigational PI3Kδ (INCB040093 and INCB050465) and indoleamine 2,3-dioxygenase 1 (epacadostat) inhibitors, have either been completed or are ongoing. A total of 777 subjects were enrolled in these studies and received at least 1 dose of INCB039110. In completed clinical pharmacology studies, INCB039110 has been administered to 197 healthy adult subjects as a single dose, repeat single doses, or multiple doses for up to 10 days.

In the ongoing and completed clinical pharmacology studies, INCB039110 was generally safe and well tolerated in healthy subjects, with few discontinuations. The majority of treatment-emergent adverse events (TEAEs) were mild in severity. There have been no clinically significant, unanticipated safety findings or trends observed. The main drug effect identified was a rapidly reversible dose related decrease in neutrophil counts presumably caused by neutrophil margination; neutrophil decreases generally resolved within 24 to 48 hours of dose discontinuation. Other reversible hematologic abnormalities, including decreased reticulocyte count, were observed after multiple-dose administration of higher dose levels at which JAK2 inhibition was noted.

Adverse events (AEs) that have been reported by more than 5% of healthy subjects in an individual study receiving INCB039110 included fatigue, headache, neutropenia, nausea, contact dermatitis, ecchymosis, reticulocyte count decreased, excoriation, and nasal congestion. Adverse events reported by more than 10% of subjects receiving INCB039110 in the psoriasis study included nasopharyngitis. Adverse events reported by more than 10% of subjects in the MF study included fatigue, thrombocytopenia, nausea, diarrhea, upper respiratory tract infection, constipation, cough, dyspnea, peripheral edema, pyrexia, dizziness, abdominal pain, night sweats, pain in extremity, arthralgia, contusion, headache, pruritus, vomiting, and increased bilirubin/hyperbilirubinemia. In the RA study, there were no TEAEs reported by more than 10% of subjects.

Events reported in ≥ 5 subjects in any study in which INCB039110 was given in conjunction with chemotherapy were as follows: anemia, fatigue, thrombocytopenia, nausea, pyrexia, neutropenia, diarrhea, dysgeusia, peripheral edema, headache, alopecia, cough, dyspnea, constipation, decreased appetite, epistaxis, vomiting, and hypoalbuminemia.

In lymphoid malignancies where INCB039110 was given in combination with INCB040093, a PI3Kδ inhibitor (N = 71), TEAEs observed in ≥ 10% of subjects included nausea, cough, diarrhea, pyrexia, thrombocytopenia/platelet count decreased, vomiting, fatigue, neutropenia/neutrophil count decreased, chills, night sweats, aspartate aminotransferase increased, constipation, decreased appetite, headache, back pain, dyspnea, oropharyngeal pain, rash, alanine aminotransferase (ALT) increased, abdominal pain, anemia, asthenia, blood cholesterol increased, leukocytosis, upper respiratory tract infection, peripheral edema, dizziness, and pain in extremity. Serious AEs reported in more than 1 subject included *Pneumocystis jirovecii* pneumonia (5 subjects), pyrexia (5 subjects), pneumonia (3 subjects), urinary tract infection (3 subjects), cardiac arrest (2 subjects), and respiratory failure (2 subjects).

Because of the potential for myelosuppression, subjects will have hematologic parameters closely monitored during clinical studies. If there are clinically relevant declines in hematology parameters, therapy may be interrupted until resolution or discontinuation. As INCB039110 also has the potential to cause white blood cell (WBC) margination (ie, a transient decrease in absolute neutrophil count [ANC]), assessment of hematology parameters should be performed before study drug administration at all applicable study visits.

Results from each of these studies are summarized in the INCB039110 IB.

1.3.2. Ibrutinib

1.3.2.1. Summary of Clinical Safety

Pooled safety data for a total of 423 subjects treated with various therapies in combination with ibrutinib from 4 studies conducted in B-cell malignancies, which included 1 randomized control study, are summarized in Table 2. Therapies used in combination with ibrutinib in these studies, included BR (bendamustine and rituximab), FCR (fludarabine, cyclophosphamide, and rituximab), ofatumumab, and R-CHOP.

Table 2: Most Frequently Reported TEAEs in Subjects Receiving Ibrutinib in Combination Therapy (N = 423)

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

For more detailed information, refer to the current version of the ibrutinib IB.

1.3.2.2. Risks

1.3.2.2.1. Bleeding-Related Events

There have been reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events, such as contusion, epistaxis, and petechiae, and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied. See Section 5.7 for guidance on concomitant use of anticoagulants, antiplatelet therapy, and/or supplements. See Section 5.8 for guidance on ibrutinib management with surgeries or procedures.

1.3.2.2.2. Infections

Fatal and nonfatal infections have occurred with ibrutinib therapy. At least 25% of subjects with MCL and 35% of subjects with CLL had Grade 3 or greater infections per NCI CTCAE v4.03 (NCI 2010). The most commonly reported infections include pneumonia, cellulitis, urinary tract infection, and sepsis. Although causality has not been established, cases of progressive multifocal leukoencephalopathy have occurred in patients treated with ibrutinib.

1.3.2.3. Cytopenias

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

1.3.2.4. Atrial Fibrillation

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. For atrial fibrillation that persists, the risks and benefits of ibrutinib treatment should be considered, and the Protocol dose modification guidelines should be followed (see Section 5.5.1.2).

1.3.2.5. Second Primary Malignancies

Second primary malignancies, most frequently skin cancers, have occurred in subjects treated with ibrutinib. Second primary malignancies, including nonskin carcinomas (SCC and BCC), have occurred in patients treated with ibrutinib. The most frequent second primary malignancy was non-melanoma skin cancer.

1.3.2.6. Tumor Lysis Syndrome

There have been reports of tumor lysis syndrome events in subjects treated with single-agent ibrutinib or in combination with chemotherapy. Subjects at risk of tumor lysis syndrome are those with comorbidities and/or risk factors, such as high tumor burden before treatment, increased uric acid (hyperuricemia), elevated LDH, bulky disease at baseline, and pre-existing kidney abnormalities.

1.3.2.7. Diarrhea

Diarrhea is the most frequently reported nonhematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe. Should symptoms be severe or prolonged follow the Protocol dose modification guidelines (see Section 5.5.1.2).

1.3.2.8. Rash

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

1.3.2.9. Interstitial Lung Disease

Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib. Randomized, controlled Phase 3 studies did not show an increased incidence rate of ILD in subjects treated with ibrutinib as compared to subjects treated with active control. Subjects should be monitored and evaluated for symptoms (eg, dyspnea, cough or pyrexia) and treated symptomatically, including interruption of the suspected agent as appropriate.

1.3.3. Potential Risks and Benefits for the Combination of INCB039110 and Ibrutinib

Treatment-emergent cytopenias have been reported with INCB039110 monotherapy and ibrutinib monotherapy; it is not known whether the combination of INCB039110 and ibrutinib would precipitate more frequent, more severe, and/or new cytopenias (or other toxicities) or risk for infections as compared with each agent individually. Both INCB039110 and ibrutinib are primarily metabolized in the liver by cytochrome P450 (CYP) 3A4; [redacted].

The combination of INCB039110 and ibrutinib is being tested for the first time in this clinical study and, therefore, any potential benefit is hypothesized based on preclinical studies. As described in Section 1.2.4, preclinical data suggest that both the JAK/STAT and BTK pathways may contribute to driving tumor growth and survival in DLBCL, and combination therapies that block both pathways may prove more beneficial in these diseases due to the central role that JAK-mediated cytokine signaling plays in augmenting BCR-mediated activation of the NF-κB pathway.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Phase 1

2.1.1.1. Primary Objective

The primary objective of Phase 1 is to evaluate the safety and tolerability of INCB039110 in combination with ibrutinib in subjects with relapsed or refractory DLBCL).

2.1.1.2. Secondary Objective

The secondary objective of Phase 1 is to evaluate the efficacy of INCB039110 in combination with ibrutinib in terms of ORR.

[redacted]

2.1.2. Phase 2

2.1.2.1. Primary Objective

The primary objective of Phase 2 is to evaluate the efficacy of INCB039110 in combination with ibrutinib in subjects with relapsed or refractory non-GCB DLBCL as demonstrated by ORR.

2.1.2.2. Secondary Objectives

The secondary objectives of Phase 2 are as follows:

- To evaluate efficacy in terms of duration of response (DOR), durable response rate, and PFS.
- To evaluate the safety and tolerability of the treatment combination.

[redacted]

2.2. Study Endpoints

2.2.1. Phase 1

Efficacy endpoints will be assessed using the Lugano Classification (Cheson et al 2014); AEs will be assessed using NCI CTCAE v4.03 (NCI 2010).

2.2.1.1. Primary Endpoint

Safety and tolerability will be assessed by evaluating the frequency, duration, and severity of AEs (including SAEs and dose-limiting toxicities [DLTs]) and changes in clinical and laboratory assessments.

2.2.1.2. Secondary Endpoint

Efficacy will be assessed by ORR, defined as the percentage of subjects achieving either a CR or PR.

[redacted]

2.2.2. Phase 2

2.2.2.1. Primary Endpoint

Efficacy will be assessed by ORR, defined as the percentage of subjects achieving either a CR or PR.

2.2.2.2. Secondary Endpoints

- DOR, defined as the time from earliest date of disease response until earliest date of disease progression.
- Durable response rate, defined as the percentage of subjects achieving a CR or PR for > 16 weeks.
- PFS, defined as the time from enrollment until the earliest date of disease progression determined by objective radiographic disease assessments, or death due to any cause.
- Safety and tolerability via assessment of the frequency, duration, and severity of AEs and SAEs, and changes in clinical and laboratory assessments.

[redacted]

3. SUBJECT ELIGIBILITY

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or subject safety. Therefore, adherence to the criteria as specified in the Protocol is essential.

3.1. Subject Inclusion Criteria

The following criteria are required for inclusion in the study:

1. Male or female, 18 years of age or older.
2. Histologically documented diagnosis of *de novo* DLBCL.
   a. For Phase 1, subjects may have any DLBCL subtype.
   b. For Phase 2, subjects must have ABC or unclassifiable subtypes of DLBCL confirmed by immunohistochemistry (IHC) using the Hans algorithm.

   Subjects having a computed tomography (CT) scan abnormality with uncertain interpretation following completion of the most recent treatment regimen must have biopsy confirmation of residual DLBCL before study entry.
3. Relapsed or refractory DLBCL, defined as having received at least 1 but no more than 3 prior treatment regimens and ineligible for HDC/ASCT.
4. Fluorodeoxyglucose-avid disease (based on local evaluation) per the Lugano Classification (Cheson et al 2014). Fluorodeoxyglucose-avid disease is defined as disease with a 5-point scale (5PS) score of 4 or 5.
5. Subjects must have archived tumor tissue (block or 15-20 unstained slides) available, or be willing to undergo an incisional or excisional lymph node biopsy of accessible adenopathy (or, in less accessible lymph nodes, 4 to 8 core biopsies).
6. At least 1 measurable ($\geq$ 2 cm in longest dimension) lesion on CT scan or magnetic resonance imaging (MRI).
7. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.
8. Adequate bone marrow, renal, and hepatic function, per local reference laboratory ranges (values must not be achieved with growth factors) as follows:
   a. ANC $\geq 1.5 \times 10^9$/L.
   b. Platelet count $\geq 75 \times 10^9$/L.
   c. Hemoglobin $\geq$ 8.0 g/dL (transfusions are permitted to achieve required hemoglobin level).
   d. Serum creatinine $\leq$ 2.0 g/dL or measured or calculated creatinine clearance $\geq$ 30 mL/min by the Cockcroft-Gault Equation.

e. Aspartate aminotransferase (AST) and ALT ≤ 2.5 × institutional upper limit of normal (ULN) or ≤ 5 × ULN for subjects with known hepatic metastases.
f. Total bilirubin ≤ 1.5 × ULN if no liver metastases or < 3 × ULN in the presence of liver metastases or presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia). Further evaluation should be performed to confirm and document the origin of increase.

9. Prothrombin time (PT)/international normalized ratio (INR) < 1.5 × ULN and activated partial thromboplastin time (aPTT) < 1.5 × ULN.
10. Willingness to avoid pregnancy or fathering children based on the criteria below:
    a. Woman of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea).
    b. Woman of childbearing potential who has a negative serum pregnancy test at screening and before the first dose on Day 1 and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through up to 3 months after ending treatment. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.
    c. Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through up to 3 months after ending treatment. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.
11. Ability to comprehend and willingness to sign an informed consent form (ICF).

3.2. Subject Exclusion Criteria

If met, any of the following criteria will lead to subject exclusion from the study:

1. Transformed DLBCL or DLBCL with coexistent histologies (eg, follicular or mucosa-associated lymphoid tissue lymphoma).
2. PMBL.
3. Known CNS lymphoma (either primary or metastatic).
4. Autologous stem cell transplant within the previous 3 months, allogeneic stem cell transplant within the previous 6 months, or active graft versus host disease following allogeneic transplant.
5. Use of immunosuppressive therapy within 28 days of starting study treatment. Immunosuppressive therapy includes, but is not limited to, cyclosporine A, tacrolimus, or high-dose corticosteroids. Subjects receiving corticosteroids must be at a dose level ≤ 10 mg/day within 7 days of initiating study treatment.
6. Prior or concurrent therapy with a JAK inhibitor or BTK inhibitor.

7. Receipt of anticancer medications or investigational drugs within the following intervals before starting study treatment (unless otherwise approved by the sponsor):
    a. < 6 weeks for mitomycin-C or nitrosoureas.
    b. < 28 days for any investigational agent for any indication.
    c. < 21 days or 5 half-lives (whichever is greater) for all other cytotoxic anticancer medications.
    d. < 4 weeks for monoclonal antibodies used as anticancer treatment.
    e. < 10 weeks or 5 half-lives from completion of any radio- or toxin-immunoconjugates.
8. Major surgery 28 days before starting study treatment.
9. Prior treatment-related toxicities that have not resolved to ≤ Grade 1, with the exception of Grade ≤ 2 neuropathy and any grade of alopecia.
10. Chronic or current active infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment.
11. Clinically significant cardiac disease, including unstable angina, acute myocardial infarction, and/or cardiac conduction issues within 6 months of Day 1; New York Heart Association Class II to IV congestive heart failure; or uncontrolled arrhythmia.
12. Known bleeding disorders (eg, von Willebrand's disease) or hemophilia.
13. History of stroke or intracranial hemorrhage within 6 months before study entry.
14. Significant concurrent, uncontrolled medical condition including, but not limited to, renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, neurological, cerebral, or psychiatric disease.
15. Current or previous other malignancy within 3 years of study entry or not cured with treatment, except cured basal or squamous cell skin cancer, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma *in situ*, or other noninvasive or indolent malignancy without sponsor approval.
16. Subjects who are currently receiving therapy with a strong CYP3A4 inducer or inhibitor.
17. Subjects who are currently receiving therapy with warfarin or vitamin K antagonists, such as coumarin-based anticoagulants (eg, fluindione and phenindione).
18. Unable to swallow oral medication, malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach or small bowel, ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
19. Known human immunodeficiency virus infection.
20. Known hepatitis B virus (HBV) or hepatitis C virus (HCV) or at risk for HBV reactivation. Hepatitis B virus DNA and HCV RNA must be undetectable. At risk for HBV reactivation is defined as hepatitis B surface antigen (HBsAg) positive or anti-hepatitis B core (HBc) antibody positive.
21. Unwilling to be transfused with blood components.

22. Pregnant or breastfeeding women or subjects unwilling to take appropriate measures to avoid pregnancy.
23. Any condition that would jeopardize the safety of the subject or compliance with the Protocol.
24. Previous reaction to any component of or INCB039110 or ibrutinib, or known hypersensitivity to either active substance or any of their excipients.
25. Prior radiotherapy within 2 weeks before starting study treatment. A 1-week washout period is permitted for palliative radiation to non–central nervous system (CNS) disease with medical monitor approval.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is an open-label, single-group, Phase 1/2 study of INCB039110 in combination with ibrutinib in subjects with relapsed or refractory DLBCL. Phase 1 will evaluate the safety and tolerability of INCB039110 when combined with ibrutinib in subjects with DLBCL (ABC, GCB, or unclassifiable) using a 6 + 3 design; Phase 2 will evaluate the efficacy of the combination in subjects with ABC or unclassifiable DLBCL at the dose determined in Phase 1 using a Simon 2-stage expansion design. Subjects may continue to receive study treatment until evidence of disease progression, unacceptable toxicity, or consent withdrawal.

4.1.1. Phase 1

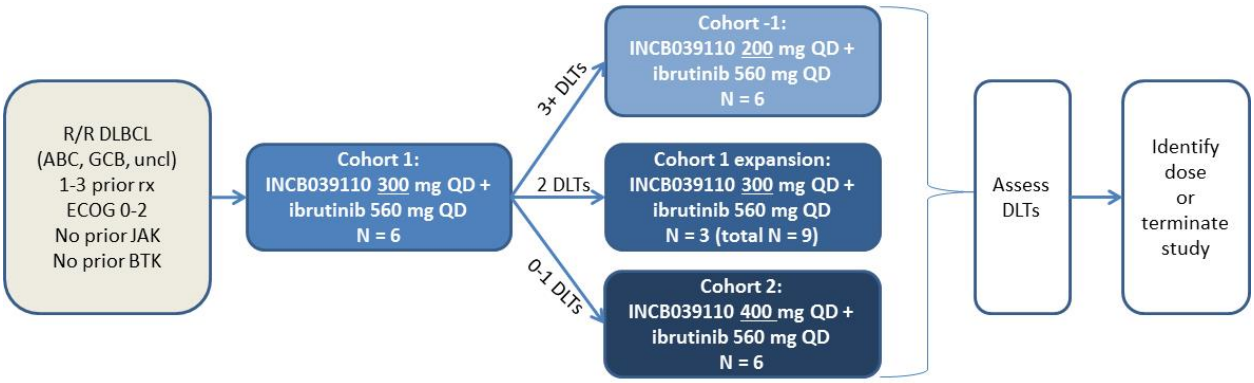
The starting dose of INCB039110 will be 300 mg once daily (QD). Depending on tolerability, the dose of INCB039110 in combination with ibrutinib (560 mg QD) could be increased to 400 mg QD (Cohort 2) or decreased to 200 mg QD (Cohort -1). The dose selected for study in Phase 2 will be the dose tolerated by at least two-thirds of subjects who did not require a dose reduction within the first 28 days of treatment. In order to be included in the tolerability review, a subject must have received the cohort-specific dose of INCB039110 and ibrutinib for at least 75% of the days during the 28-day DLT surveillance period or have experienced a DLT. Additional subjects may be enrolled to achieve a minimum cohort size of 6 should withdrawal or dose interruptions/reductions result in a subject being nonevaluable.

Dose cohorts are outlined in Table 3, and the design is depicted in Figure 4.

Table 3: Phase 1 Dose Cohorts

Cohort	Number	Regimen	Subjects With DLT	Action
-1	6	INCB039110 200 mg QD + ibrutinib 560 mg QD	≤ 1	Begin expansion portion of the study
			2	Enroll 3 additional subjects (9 subjects total)
			≥ 3	Terminate study
1 (Starting dose)	6	INCB039110 300 mg QD + ibrutinib 560 mg QD	≤ 1	Escalate to Cohort 2
			2	Enroll 3 additional subjects (9 subjects total); if no new DLTs, escalate to Cohort 2
			≥ 3	Reduce to Cohort -1
2	6	INCB039110 400 mg QD + ibrutinib 560 mg QD	≤ 1	Begin Phase 2 study
			2	Enroll 3 additional subjects (9 subjects total); if no new DLTs, begin Phase 2 study
			≥ 3	Begin Phase 2 study using Cohort 1 dose

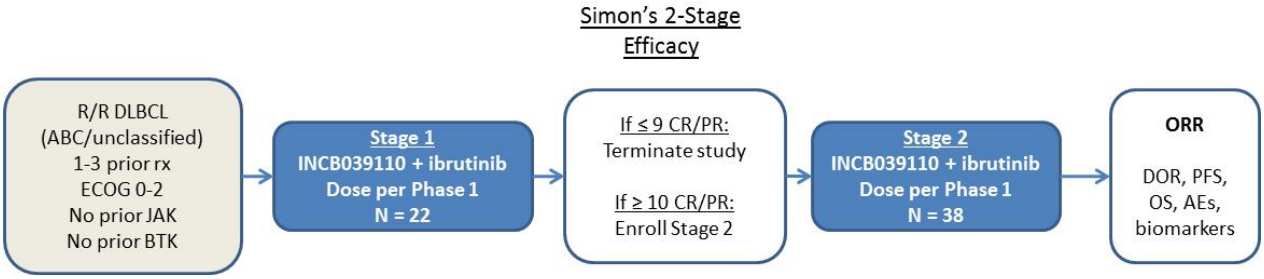
Figure 4: Phase 1 Design Schema



4.1.2. Phase 2

Subjects with ABC or unclassifiable DLBCL will receive the recommended Phase 2 dose (RP2D) of INCB039110 in combination with ibrutinib as determined in Phase 1. Phase 2 will use a Simon 2-stage design with a stopping rule to allow early termination of the study at the end of Stage 1 if there is lack of sufficient efficacy. During Stage 1, if 9 or fewer of the first 22 evaluable subjects achieve an objective response (defined as a CR or PR), then the study may be terminated. If 10 or more subjects achieve an objective response, then the study will continue and accrue 38 additional subjects to Stage 2. Subjects who were enrolled but did not receive treatment will be excluded from the efficacy analysis and replaced. A timely assessment of response will be made to avoid risk of overenrollment before accrual to Stage 2. At the end of Stage 2, ORR will be assessed for sufficient efficacy to warrant further study. The study will be considered successful if the total number of objective responders is 29 or more. The design is depicted in Figure 5.

Figure 5: Phase 2 Design Schema



4.2. Measures Taken to Avoid Bias

Measurements of safety and efficacy will be objectively assessed using NCI CTCAE v4.03 (NCI 2010) and Lugano Classification (Cheson et al 2014), respectively.

4.3. Number of Subjects

4.3.1. Planned Number of Subjects

Up to 18 subjects will be enrolled in Phase 1, and approximately 60 subjects will be enrolled in Phase 2 (22 in Stage 1 and 38 in Stage 2).

4.3.2. Replacement of Subjects

Additional subjects may be enrolled in Phase 1 to achieve a minimum cohort size of 6 should withdrawal or dose interruptions/reductions result in a subject being nonevaluable.

4.4. Duration of Treatment and Subject Participation

After signing the ICF, screening assessments may be completed over a period of up to 28 days. Each subject enrolled in the study may continue to receive study treatment until treatment discontinuation criteria are met. If the subject discontinues all study treatment (INCB039110 and ibrutinib), then the treatment period will end, and the subject will enter the follow-up period (see Section 6.4). Study participation is expected to average approximately 6 months per individual subject.

4.5. Overall Study Duration

The study begins when the first subject signs the ICF. The end of Phase 1 will occur when all subjects have completed the DLT surveillance period; Phase 2 will end once the last subject is assessed for response.

Once the last subject is evaluable for response, a database lock of the study will occur to allow the analysis of the study data. Any remaining subjects may continue to receive study treatment and be seen by the investigator per usual standard of care for this population. Provisions will be made to ensure access to treatment for subjects who are continuing to benefit from study treatment at the time of study termination.

The investigator will be expected to monitor for and report any SAEs, AEs of special interest, and pregnancies, as detailed in Section 8. The remaining subjects are considered to be on study until a discontinuation criterion is met and written notification is provided to the sponsor.

The study will end once all subjects have discontinued study treatment and safety follow-up.

4.6. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator is to notify the institutional review board (IRB)/independent ethics committee (IEC) in writing of the study's completion or early termination, send a copy of the notification to the sponsor or sponsor's designee, and retain 1 copy for the site study regulatory file.

The sponsor may terminate the study electively due to ethical concerns, insufficient subject recruitment, alterations in accepted clinical practice, emerging data, or if required by regulatory decision. If the study is terminated prematurely, then the sponsor will notify the investigators, the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study.

5. TREATMENT

5.1. Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

Study sites will enter subject demographic and baseline data into the interactive voice response system (IVRS) in order to receive a subject number and treatment allocation.

All subject numbers will be 6 digits; the first 3 digits will be the site number, and the last 3 digits will be the subject's number. This subject number will be maintained throughout the study and will not be reassigned. Subjects who withdraw consent or discontinue from the study after being assigned a subject number will retain their initial number.

Site staff will contact the IVRS to allocate the subject to treatment assignment and obtain the initial study drug assignment. The investigator or designee will select the assigned bottles of study drug from their stock that correspond to the number provided by the IVRS and dispense the study drug to the subject. All subsequent dispensing of study drug should follow this process. Refer to the IVRS manual for detailed information.

If a subject is mistakenly given a bottle of study drug that is not the bottle assigned by the IVRS, then the IVRS help desk must be notified immediately. The reason for the misallocation of the study drug must be documented by the study site and reported to the IRB/IEC.

For subjects who signed an ICF but are not allocated study drug and for subjects who are allocated study drug but were not treated, refer to the electronic case report form (eCRF) Completion Guidelines for instruction on which eCRFs to complete.

5.1.2. Randomization and Blinding

Not applicable.

5.2. INCB039110

5.2.1. Description and Administration

INCB039110 drug substance is a white to off-white powder. INCB039110 100 mg (free base equivalent) sustained release tablets (SR3 formulation) contain the active ingredient, hypromellose, microcrystalline cellulose, lactose monohydrate, and magnesium stearate.

In Phase 1, INCB039110 tablets will be administered orally (PO) at the cohort-specific dose (eg, 3 × 100 mg tablets) QD. In Phase 2, INCB039110 tablets will be administered PO at the RP2D identified in Phase 1. The use of strong CYP3A inhibitors/inducers, grapefruit, and pomegranate should be avoided for the duration of the study (Appendix B).

[redacted]

Due to the potential for WBC margination, blood samples should be collected before study treatment administration at all applicable study visits.

Subjects may have dose reductions of INCB039110 during the course of treatment based on AEs, clinical evaluation, and laboratory assessments. See Section 5.5.1 for INCB039110 dose modification guidance.

Subjects are permitted to remain on INCB039110 until withdrawal from study treatment is considered necessary as per Section 5.6.

5.2.2. Supply, Packaging, and Labeling

INCB039110 will be provided to sites as 100 mg tablets packaged in high-density polyethylene bottles as applicable by Incyte. No preparation is required.

All Incyte investigational product labels will be in the local language and will comply with the legal requirements of each country.

5.2.3. Storage

INCB039110 should be stored at ambient conditions (15°C to 30°C, or 59°F to 86°F) as per the IB.

5.2.4. Instruction to Subjects for Handling INCB039110

The subject must be instructed in the handling of INCB039110 as follows:

- Store the study medication at room temperature.
- Remove only the number of tablets from the study drug bottle needed at the time of administration.
- Do not remove doses in advance of the next scheduled administration.
- Make every effort to take doses on schedule.
- Report any missed doses.

- Take study medication with a glass of water.
- Do not take another dose if vomiting occurs after taking study medication.
- Do not take study medication on the day of clinic visits until after blood samples are collected.
- [redacted]
- Keep study drug in a safe place and out of reach of children.
- Bring all used and unused study medication kits to the site at each visit.

5.3. Ibrutinib

5.3.1. Description and Administration

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

Ibrutinib 560 mg (4 × 140 mg capsules) will be administered PO QD. The capsules should be taken around the same time each day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact, and subjects should not attempt to open capsules or dissolve them in water. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study (Appendix B).

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

The first dose will be delivered in the clinic on Day 1, after which subsequent dose administration is typically on an outpatient basis. [redacted] Ibrutinib will be dispensed to subjects in bottles at each visit. Unused ibrutinib dispensed during previous visits must be returned to the site, and drug accountability records must be updated at each visit. Returned capsules must not be dispensed to anyone.

5.3.2. Supply, Packaging and Labeling

Ibrutinib capsules will be packaged in child-resistant, opaque, high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies.

5.3.3. Storage

Ibrutinib capsules must be stored in accordance with storage conditions and shelf life as indicated in the manufacturer's approved label.

5.3.4. Instruction to Subjects for Handling Ibrutinib

The subject must be instructed in the handling of ibrutinib as follows:

- Store the study medication in accordance with the manufacturer's storage conditions.
- Remove only the number of tablets from the study drug bottle needed at the time of administration.
- Do not remove doses in advance of the next scheduled administration.
- Make every effort to take doses on schedule.
- Report any missed doses.
- Take study medication with a glass of water.
- Do not open capsules nor dissolve them in water.
- Do not take another dose if vomiting occurs after taking study medication.
- If a dose of ibrutinib is not taken at the scheduled time, it should 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.
- [redacted]
- Keep study drug in a safe place and out of reach of children.
- Bring all used and unused ibrutinib kits to the site at each visit.

5.3.5. Overdose

Any dose of ibrutinib in excess of that specified in this Protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any SAE criterion must be reported as a SAE in the appropriate timeframe and documented as clinical sequelae to an overdose. There is no specific experience in the management of ibrutinib overdose in patients. No maximum tolerated dose was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg per day (1400 mg/day). Healthy subjects were exposed up to a single dose of 1680 mg. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Subjects who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

5.4. Treatment Compliance

Compliance with all study-related treatments should be emphasized to the subject by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with INCB039110 and ibrutinib will be calculated by the sponsor based on the drug accountability documented by the site staff and monitored by the sponsor/designee (tablet counts). Subjects will be instructed to bring all study drugs with them to the study visits in order for site personnel to conduct tablet counts to assess study drug accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

5.5. Treatment Interruptions and Adjustments

5.5.1. Dose Modifications

5.5.1.1. Dose Modification of INCB039110

Treatment with INCB039110 may be delayed up to 2 weeks (14 days) to allow for resolution of toxicity. Subjects may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the subject unsuitable for further participation in the study. The treating investigator should contact the sponsor to discuss the case of any subject whose treatment has been delayed for more than 14 days before restarting treatment with INCB039110.

Because subjects may enter the study with extensive pretreatment and/or severe bone marrow infiltration by the primary disease, dose interruption and reduction rules are provided as guidelines (see Table 4 and Table 5). Individual decisions regarding dose reduction should be made using clinical judgment and in consultation with the sponsor's medical monitor, taking into account relatedness of the AE to the study drug and the subject's underlying condition. Adverse events that have a clear alternative explanation or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose-reduction rules.

Table 4: Guidelines for Interruption and Restarting Study Drug

ADVERSE EVENT	ACTION TAKEN
Chemistry	
• AST and/or ALT > 3.0 × ULN Note: In subjects with bone metastasis–related elevations at baseline, contact sponsor to discuss clinical management and possible dose reductions.	**Step 1:** Interrupt INCB039110 up to 14 days until the toxicity has resolved to ≤ Grade 1 (unless approved otherwise by the medical monitor). **Step 2:** Restart INCB039110 at same dose. If assessed as related to INCB039110, restart at next lower dose. Monitor as clinically indicated.
Hematology	
• ANC ≤ 1.0×10^9/L unless due to underlying disease • Platelet count is < 60×10^9/L unless due to underlying disease	**Step 1:** Interrupt INCB039110 up to 14 days until the toxicity has resolved to ≤ Grade 1 or pretherapy baseline. **Step 2:** Restart INCB039110 at same dose; monitor as clinically indicated.
• Grade 4 ANC (< 0.5×10^9/L) • ≥ Grade 3 ANC with an oral temperature of at least 38.5°C OR with ≥ Grade 3 infection. • Platelet count is < 35×10^9/L	**Step 1:** Interrupt INCB039110 up to 14 days until the toxicity has resolved to ≤ Grade 1. **Step 2:** Restart INCB039110 at same dose. If assessed as related to INCB039110, restart at next lower dose. Monitor as clinically indicated.

Table 4: Guidelines for Interruption and Restarting Study Drug (Continued)

ADVERSE EVENT	ACTION TAKEN
Other toxicities	
• Any Grade 1 or Grade 2 toxicity	Continue study treatment and treat the toxicity; monitor as clinically indicated.
• Any Grade 3 toxicity, if clinically significant and not manageable by supportive care	**Step 1:** Interrupt INCB039110 up to 14 days until the toxicity has resolved to ≤ Grade 1. **Step 2:** Restart INCB039110 at same dose. If assessed as related to INCB039110, restart at next lower dose. Monitor as clinically indicated.
• Any recurrent Grade 3 toxicity after 2 dose reductions	Discontinue study drug administration and follow-up per Protocol. Exceptions require approval of sponsor.
• Any other Grade 4 toxicity	Discontinue study drug administration and follow-up per Protocol. Exceptions require approval of sponsor.

Table 5: Dose Reduction Levels for INCB039110

Current Dose	First Dose Reduction	Second Dose Reduction
300 mg QD	200 mg QD	Discontinue
400 mg QD	300 mg QD	200 mg QD
200 mg QD	Discontinue	Discontinue

5.5.1.2. Dose Modification for Ibrutinib

The dose of ibrutinib should be modified according to the dose modification guidelines in Table 6 if any of the following toxicities occur:

- Grade 4 ANC ($< 0.5 \times 10^9$/L) for more than 7 days.
- Grade 3 thrombocytopenia ($< 50 \times 10^9$/L) in the presence of clinically significant bleeding events.
- Grade 4 thrombocytopenia ($< 25 \times 10^9$/L).
- 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.

For Grade 3 or 4 atrial fibrillation or persistent atrial fibrillation of any grade, the risks and benefits of ibrutinib treatment should be considered.

Ibrutinib is metabolized in the liver. For subjects who develop mild liver impairment while on study (Child-Pugh Class A), the recommended dose reduction for ibrutinib is to a level of 280 mg daily (2 capsules). For subjects who develop moderate liver impairment while on study (Child-Pugh Class B), the recommended dose reduction is to a level of 140 mg daily (1 capsule). Subjects who develop severe hepatic impairment (Child-Pugh Class C) must withhold study drug

until resolved to moderate impairment (Child-Pugh Class B) or better and could be re-treated according to resolved hepatic conditions (ie, 140 mg or 280 mg for moderate or mild impairment, respectively). Subjects should be monitored for signs of toxicity and follow dose modification guidance as needed.

If the dose of ibrutinib is reduced, at the investigator's discretion, the dose of ibrutinib may be re-escalated after 56 days of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction. Dose changes must be recorded in the appropriate eCRF.

Table 6: Dose Modifications for Ibrutinib

Toxicity Occurrence	**Action to be Taken**
First	Withhold study drug until recovery to Grade ≤ 1 or baseline; may restart at original dose level.
Second	Withhold study drug until recovery to Grade ≤ 1 or baseline; may restart at 1 dose level lower (ie, 280 mg/day for 420 mg/day dose; 420 mg/day for 560 mg/day dose).
Third	Withhold study drug until recovery to Grade ≤ 1 or baseline; may restart at 1 dose level lower (ie, 140 mg/day for 420 mg/day dose; 280 mg/day for 560 mg/day dose).
Fourth	Discontinue study drug.

5.5.2. Dose-Limiting Toxicity and Determination of Recommended Phase 2 Dose

A DLT will be defined as the occurrence of any toxicities in Table 7 occurring up to and including Study Day 28, except those with a clear alternative explanation (eg, disease progression) or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination. All DLTs will be assessed by the investigator using CTCAE v4.03 criteria (NCI 2010). In order to be included in the tolerability review, subjects must have received the cohort-specific dose of INCB039110 and ibrutinib for at least 75% of the days during the 28-day surveillance period or have experienced a DLT. Additional subjects may be enrolled to achieve a minimum cohort size should withdrawal or dose interruptions/reductions result in subjects being nonevaluable.

Individual subject dose reductions may be made based on events observed at any time during treatment with study drug; however, for the purposes of dose cohort escalation/de-escalation, expanding a dose cohort, and determining the RP2D, decisions will be made based on events that are observed from the first day of study drug administration through and including Day 28. A lower RP2D may subsequently be determined based on relevant toxicities that become evident after Day 28.

Table 7: Criteria for Defining Dose-Limiting Toxicity

Toxicity
Nonhematologic
• Any ≥ Grade 3 nonhematologic toxicity, EXCEPT the following: – Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms. – Nausea, vomiting, and diarrhea adequately controlled with medical therapy within 48 hours. – Singular or nonfasting elevations in blood glucose (ie, blood glucose excursions will be considered toxicities if fasting blood glucose is elevated on 2 separate sequential occasions).
Hematologic
• Grade 3 thrombocytopenia with bleeding. • Grade 4 thrombocytopenia. • Febrile neutropenia (ANC < 1.0×10^9/L and fever > 101°F/38.5°C). • Grade 4 neutropenia that does not recover to ≤ Grade 2 in ≤ 3 days after interrupting study drug. • Grade 4 anemia unresponsive to treatment. **Note:** "INCB039110 is suspected to cause transient decreases in ANC as a result of margination; therefore, DLT rules require neutropenia to persist after holding INCB039110 for 2 to 3 days. If the clinical status of the subject allows, investigators are encouraged to wait 24 hours before starting growth factors, to determine if WBC margination is contributing to the degree of neutropenia."

5.5.2.1. Management of Dose-Limiting Toxicities or Other Urgent Situations

In all cases, investigators may employ any measures or concomitant medications necessary to optimally treat the subject following discussion with the sponsor whenever possible.

5.5.2.2. Follow-Up of Dose-Limiting Toxicities

Any DLT should be followed until it resolves to baseline or Grade 1 or appears to have stabilized for a minimum of 4 weeks. During follow-up, subjects should be seen as often as medically indicated to assure safety.

5.6. Withdrawal of Subjects From Study Treatment

The decision to discontinue study treatment (eg, INCB039110 and ibrutinib) will not constitute study completion (see Section 5.6). In the event that the decision is made to discontinue study treatment, the treatment phase will be considered complete and the follow-up phase will begin.

5.6.1. Withdrawal Criteria

Subjects **must** be withdrawn from study treatment (INCB039110 and ibrutinib) for the following reasons:

- The subject has experienced an unacceptable toxicity.
- The subject is unable to tolerate INCB039110 at a dose of 200 mg QD.
- There is evidence of disease progression from radiographic tumor assessment.

- Further participation would be injurious to the subject's health or well-being, in the investigator's medical judgment.
- The subject becomes pregnant.
- Consent is withdrawn.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority or IRB or IEC.

A subject **may** be withdrawn from study treatment in the following situations:

- If a subject is found not to have met eligibility criteria, then the medical monitor and investigator will collaborate to determine whether the subject should be withdrawn from the study.
- If a subject is noncompliant with study procedures or study drug administration in the opinion of the investigator, then the sponsor should be consulted for instruction on handling the subject.

5.6.2. Withdrawal Procedures

In the event that the decision is made to permanently discontinue study treatment, the subject will be withdrawn from the study, and the end-of-treatment (EOT) visit should be conducted. Reasonable efforts should be made to have the subject return for a follow-up visit as described in Section 6.

Subjects who discontinue study treatment for reasons other than disease progression will be assessed per standard of care until disease progression, initiation of new anticancer treatment, or death, whichever occurs first.

If a subject is withdrawn from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the subject's medical record and in the eCRF.
- The EOT visit should be performed.
- Subjects must be followed for safety until the time of the follow-up visit or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer.

5.7. Concomitant Medications

All concomitant medications and treatments must be recorded in the eCRF. Any prior medication received up to 30 days before enrollment will be recorded in the eCRF. Concomitant treatments and/or procedures that are required to manage a subject's medical condition during the study will also be recorded in the eCRF.

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

American Society of Clinical Oncology guidelines (Smith et al 2015). Transfusions may be given in accordance with institutional policy.

Short courses (≤ 14 days) of steroid treatment for non–cancer related medical reasons (eg, joint inflammation, asthma exacerbation, rash, antiemetic use, infusion reactions) at doses that do not exceed prednisone 20 mg per day or equivalent are permitted.

Localized hormonal or bone-sparing treatment for non–B-cell malignancies and localized radiotherapy for medical conditions other than the underlying B-cell malignancies may be considered if necessary. Palliative (ie, nontherapeutic) radiotherapy for control of DLBCL-related symptoms is allowed.

5.7.1. Restricted Medications

The following medications have restrictions on use during the treatment phase of the study:

- Aspirin in doses exceeding 81 mg/day is not permitted. Low-dose aspirin (≤ 81 mg/day) is permitted. Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs; eg, ibuprofen) are permitted.
- Co-administration with strong CYP3A4 inhibitors; alternative agents with less CYP3A inhibition should be considered (Appendix B). Differences in individual sensitivity and variation CYP enzyme inhibition may result in the need for dose reduction of INCB039110 and/or ibrutinib. The sponsor medical monitor may be consulted for advice when using these agents.
- Co-administration with CYP3A4 moderate/weak inducers (Appendix B).
- If concomitant administration of an anticoagulant/antiplatelet medication is indicated, then caution and enhanced monitoring is required. History of thrombocytopenia and any concurrent INCB039110-related thrombocytopenia should be a factor in the choice of anticoagulant and dose.
- Systemic corticosteroid doses greater than the equivalent of 10 mg prednisolone per day are not permitted from the screening visit through the follow-up visit, except with medical monitor approval.
- Any medications known to cause QT prolongation should be used with caution; periodic electrocardiogram (ECG) and electrolyte monitoring should be considered.
- Supplements such as fish oil and vitamin E preparations should be avoided. Ibrutinib should be used with caution in subjects requiring other anticoagulants or medications that inhibit platelet function.

- For subjects requiring the initiation of therapeutic anticoagulation therapy (eg, atrial fibrillation), the risks and benefits of continuing ibrutinib treatment should be considered. If therapeutic anticoagulation is clinically indicated, then treatment with ibrutinib should be withheld and not restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted. Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib.

5.7.2. Prohibited Medications and Measures

The following medications are prohibited during the treatment:

- Any concurrent anticancer therapy (eg, chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, hormonal therapy, or tumor embolization) other than those specified in the Protocol.
- Any investigational medication before withdrawing from the study.
- Corticosteroids for the treatment of the underlying malignancy.
- Potent inducers of CYP3A4.
- Warfarin or vitamin K antagonists.

5.8. Procedural Restrictions

5.8.1. Minor Surgical Procedures

For minor procedures (eg, a central line placement, needle biopsy, thoracentesis, paracentesis), ibrutinib should be withheld for at least 3 days before 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 receiving ibrutinib, it is not necessary to withhold ibrutinib for these procedures.

5.8.2. Major Surgical Procedures

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

5.8.3. Emergency Procedures

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

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedule of assessments in Table 8; the order of assessments is suggested by the order of mention within the schedule. Laboratory assessments are shown in Table 9.

Table 8: Schedule of Assessments

Procedure	Section	Screening	Treatment				EOT	Follow-Up	Comments
		Day -28 to -1	Day 1	Day 8 (± 3 days)	Day 15 (± 3 days)	Day 28/Q28D (± 3 days)		EOT + 30-35 Days	
Informed consent	7.1	X							
Contact IVRS	7.2	X	X			X	X		
Inclusion and exclusion criteria	3.1 3.2	X	X						
Demography and medical history	7.3.1	X							
Prior/concomitant medications	7.3.2	X	X	X	X	X	X	X	
Physical exam/ weight/height	7.4.2 7.4.3	X*	X	X	X	X	X	X	*Comprehensive exam at screening; targeted physical exam thereafter. Height required at screening only.
Vital signs	7.4.4	X	X	X	X	X	X	X	
12-lead ECG	7.4.5	X*	X*	X**					*Triplicate ECGs will be performed during screening and on Day 1 before starting study treatment. **Triplicate ECGs will be performed predose and 2 hours (± 15 minutes) after receiving INCB039110 on Day 8. Additional ECGs may be performed as clinically indicated.
ECOG status	7.6.1	X	X			X	X	X	
AE assessment	7.4.1	X	X	X	X	X	X	X	
CT or MRI	7.5.1	X				X*	X		*Week 8, Week 16, and then every 16 weeks ± 1 week. Also required to confirm CR.
FDG-PET scan/PET-CT	7.5.2	X				X*			*Required at baseline and to confirm CR or if clinically indicated.

Table 8: Schedule of Assessments (Continued)

Procedure	Section	Screening	Treatment				EOT	Follow-Up	Comments
		Day -28 to -1	Day 1	Day 8 (± 3 days)	Day 15 (± 3 days)	Day 28/Q28D (± 3 days)		EOT + 30-35 Days	
Bone marrow exam	7.5.3	X*							*Required as a screening assessment unless performed as per standard of care within 60 days of Day 1. Repeat to confirm CR or if clinically indicated.
Dispense study drug	5.1		X			X			
Study drug accountability	5.4		X	X	X	X	X		
INCB039110 administration	5.2.1		X*	X*	X*	X*			*Subjects should refrain from taking INCB039110 on clinic visit days until after local laboratory blood samples are collected.
Ibrutinib administration	5.3.1		X*	X*	X*	X*			*Subjects should refrain from taking ibrutinib on clinic visit days until after local laboratory blood samples are collected.

FDG = fluorodeoxyglucose; PET = positron emission tomography.

Table 9: Laboratory Assessments

Laboratory Tests	Section	Screen	Day 1	Day 8 (± 3 days)	Day 15 (± 3 days)	Day 28/Q28D (± 3 days)	EOT	Follow-Up	Details
Local Laboratory Samples									
Serum chemistries	7.4.6.1	X	X		X	X	X	X	Day 1 laboratory tests may be omitted if the screening tests occurred in preceding 7 days. All lab draws should be performed before dose administration.
Hematology	7.4.6.2	X	X	X	X	X	X	X	Day 1 laboratory tests may be omitted if the screening tests occurred in preceding 7 days. All lab draws should be performed before dose administration.
Coagulation panel	7.4.6.2	X	X			X*	X		Day 1 laboratory tests may be omitted if the screening tests occurred in preceding 7 days. All lab draws should be performed before dose administration. *After Day 28, should be repeated every 3 months, ie., Day 112, Day 196, etc.
Serology	7.4.6.5	X							
Serum pregnancy	7.4.6.4	X					X		All female subjects of childbearing potential; negative pregnancy test must be obtained within 7 days of first dose of study treatment.
Urine pregnancy	7.4.6.4		X						Only as medically indicated for females of childbearing potential.
[redacted]									

Table 10: Table of Required Laboratory Analytes

Serum Chemistries	Serology	Hematology	Coagulation
Albumin	HBsAg	Hemoglobin	PT
Alkaline phosphatase	Anti-HBsAg	Hematocrit	PTT
ALT	Anti-HB core IgG	Platelet count	aPTT
AST	HCV antibody	Red blood cell count	INR
Bicarbonate	HCV-RNA	White blood cell count	
Blood Urea Nitrogen	HBV-DNA	Differential cell count:	
Calcium		Basophils	
Chloride		Eosinophils	
Creatinine		Lymphocytes (absolute)	
Glucose		Monocytes	
LDH		Neutrophils (absolute)	
Phosphate			
Potassium			
Sodium			
Total bilirubin[a]			
Direct bilirubin[a]			
Indirect bilirubin			
Total serum protein			
Total cholesterol			
CRP			

CRP = C-reactive protein.
[a] Only required if total bilirubin is elevated.

6.1. Screening

The screening period is the interval between the signing of the ICF and the day that the subject is enrolled in the study (Day 1). Screening may not exceed 28 days. Informed consent must be obtained before performing any study-specific procedures. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during this phase.

Procedures conducted as part of the subject's routine clinical management (eg, blood count, imaging study) and obtained before signing of informed consent may be used for screening or baseline purposes provided that the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study. Results from the screening visit evaluations will be reviewed to confirm subject eligibility before enrollment or the administration of study drug. Tests with results that fail eligibility requirements may be repeated once during the screening phase if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before enrollment will be used to determine subject eligibility. Treatment should start as soon as possible, but within 2 days after the date of enrollment. Additionally, a subject who fails screening may repeat the screening process 1 time if the investigator believes there has been a change in eligibility status (eg, following recovery from an infection).

6.2. Treatment

The treatment period begins on the day that the subject receives the first dose of study drug (Day 1). This day must be no more than 28 days after the subject has signed the ICF. Dates for subsequent study visits will be determined based on this day and should occur within the visit windows outlined in the schedule of assessments (Table 8) unless delayed for safety reasons.

6.3. End of Treatment

There is no predefined EOT. If a decision is made that the subject will permanently discontinue study treatment, then the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, then the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT page in the eCRF. The subject should be encouraged to return for follow-up visits.

6.4. Follow-Up

6.4.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 to 35 days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). Adverse events and SAEs must be reported up until at least 30 days after the last dose of study drug, the date of the follow-up visit, or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable effort should be made to have the subject return for the follow-up visit and report any AEs that may occur during this phase.

If a subject is scheduled to begin a new anticancer therapy before the end of the safety follow-up period, the safety follow-up visit should be performed before new anticancer therapy is started.

6.4.2. Disease Status Follow-Up

Subjects who discontinue study treatment for a reason other than disease progression will move into the disease status follow-up period and should be assessed per standard of care to monitor disease status. Every effort should be made to collect information regarding disease status until:

- The start of new antineoplastic therapy.
- Disease progression.
- Death.
- The end of the study.

6.5. Unscheduled Visits

Unscheduled visits may be held at any time at the investigator's discretion, and appropriate clinical and laboratory measurements performed based on AEs or other findings.

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7.1. Administration of Informed Consent Form

Valid informed consent must be obtained from the study subject before conducting any study-specific procedures using an ICF approved by the local IRB/IEC that contains all elements required by ICH E6 and describes the nature, scope, and possible consequences of the study in a form understandable to the study subject. Local and institutional guidelines for ICF content and administration must be followed; the original signed ICF must be retained by the investigator, and a copy of the signed ICF must be provided to the study subject. The informed consent process for each subject must be documented in writing within the subject source documentation.

7.2. Interactive Response Technology Procedure

The IVRS will be contacted to obtain a subject ID number when a subject enters screening. Upon determining that the subject is eligible for study entry, the IVRS will be contacted to obtain treatment assignment. Additionally, the IVRS will be contacted during visits when study drug is resupplied.

7.3. Demography and History

7.3.1. Demographics, Medical History, Disease History

Demographic data and a complete medical and medication history, including date of diagnosis of DLBCL, histology, current staging, sites of disease, prior surgery, radiation, and other details related to the disease under study, will be collected at screening.

7.3.2. Prior and Concomitant Medications and Procedures

Prior and concomitant medications and procedures will be reviewed to determine study eligibility. All concomitant medications and measures must be recorded in the eCRF, and any medication received or procedure performed within 30 days before enrollment and up to the safety follow-up visit will be recorded in the eCRF. The medication record will be maintained after signing the ICF to document concomitant medications, including any changes to the dose or regimen. Concomitant medications include any prescription, over-the-counter, or natural/herbal preparations taken or administered during the study period. Concomitant treatments and/or procedures that are required to manage a subject's medical condition during the study will also be recorded in the eCRF.

7.4. Safety Assessments

7.4.1. Adverse Events

Adverse events will be monitored from the time the subject signs the ICF through the safety follow-up. Subjects will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study. In order to avoid bias in eliciting AEs, subjects will be asked general, nonleading questions such as "How are you feeling?" All AEs (serious and nonserious) must be recorded on the source documents and eCRFs regardless of the assumption

of a causal relationship with the study drug. The definition, reporting, and recording requirements for AEs are described in Section 8.

7.4.2. Comprehensive Physical Examination

Physical examinations must be performed by a medically qualified individual, such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, as local law permits.

The comprehensive physical examination will include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; lymph nodes; a brief neurological examination (eg, reflexes, strength, Romberg's test, vibration sense, and gross sensory perception); and body weight (within 1 lb or 0.5 kg). The initial comprehensive physical examination should include an accurate measurement of the subject's height.

7.4.3. Targeted Physical Examination

A targeted physical examination will be a symptom-directed evaluation conducted by the investigator or designee. The targeted physical examination will include assessment(s) of the body systems or organs, as indicated by subject symptoms, AEs, subject's weight, or other findings.

7.4.4. Vital Signs

Vital sign measurements (blood pressure, pulse, respiratory rate, and body temperature) will be taken with the subject in the recumbent, semirecumbent, or sitting position after 5 minutes of rest. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

7.4.5. Twelve-Lead Electrocardiograms

All 12-lead ECGs will be performed with the subject in a recumbent or semirecumbent position after 5 minutes of rest. Triplicate ECGs will be performed during screening and on Day 1 before starting study treatment. Triplicate ECGs will be performed predose and 2 hours (± 15 minutes) after receiving INCB039110 on Day 8. When triplicate ECGs are being obtained, individual measurements should be performed 5 ± 3 minutes apart.

All 12-lead ECGs obtained at subsequent timepoints will be compared with the baseline 12-lead ECGs as follows:

- For ECG morphology, all postdose ECG recordings will be compared with Day 1 predose ECGs.
- For the calculation of changes in cardiac intervals (eg, QT interval), the intervals from the screening and Day 1 predose (triplicate) ECGs will be computed and averaged and used as the baseline for comparison of all postdose intervals.

The investigator or another appropriately trained individual will perform the initial ECG analysis of the data collected for each subject. Electrocardiogram data will be reviewed as necessary by a qualified cardiologist at the study site. If a pattern of abnormalities is observed, the sponsor

reserves the right to have copies (electronic or hard) of any and all ECGs sent to a central ECG laboratory for review.

Electrocardiograms that are identified as abnormal and clinically meaningful compared with the screening assessment should be reported as AEs. For such AEs, the findings of the abnormal ECGs and the corresponding baseline ECG findings must be reported in the eCRF, and copies of the abnormal tracings and corresponding baseline tracings will also be sent to the sponsor and/or sponsor's designee as indicated in the study manual.

Additional ECGs may be performed at the investigator's discretion as clinically indicated.

7.4.6. Laboratory Assessments

Blood draws for laboratory assessments will occur at study visits indicated in Table 9. Blood draws will be completed before the subject receives the morning dose of INCB039110. Specific laboratory assessments are listed in Table 10. The screening portion of the study will require a maximum of 16 mL of blood, the first 28 days on study will require a maximum of 35 mL of blood, and each subsequent 28 days on study will require a maximum of 11 mL of blood for local safety laboratory assessments.

All laboratory assessments will be performed at a local laboratory using institutional best practices. Results and normal reference ranges will be entered into the eCRF.

7.4.6.1. Chemistry

All chemistry and coagulation panel assessments will be performed from blood samples collected using institutional best practices before administration of INCB039110. Results and normal reference ranges will be entered to the eCRF.

7.4.6.2. Hematology

Hematology assessments, including complete blood count with differential, will be performed at a local (site) laboratory using institutional best practices before administration of INCB039110. Results and normal reference ranges will be entered to the eCRF.

7.4.6.3. Urinalysis

Not applicable.

7.4.6.4. Pregnancy Testing

A serum pregnancy test will be performed at screening and EOT. Urine pregnancy test will be performed only if pregnancy is suspected during treatment; positive results must be confirmed with a serum pregnancy test. Pregnancy testing will only be required for women of childbearing potential.

7.4.6.5. Serology

Serology will be performed by local laboratory using institutional best practices on samples drawn at the screening visit.

7.5. Efficacy Assessments

Subjects will have an objective assessment of disease status using PET and diagnostic-quality computed tomography (CT) scan or MRI.

7.5.1. Computed Tomography Scan or Magnetic Resonance Imaging

Subjects will undergo a diagnostic-quality CT or MRI to evaluate measurable disease during the screening phase. If CT/MRI assessment was performed as standard of care before signing of the ICF but within 28 days of Day 1, the results from that assessment may be recorded in the eCRF in lieu of a study-specific assessment.

On-treatment assessments should be repeated at Week 8, Week 16, and every 16 weeks thereafter.

This assessment schedule also applies to those subjects who discontinue study treatment for reasons other than disease progression until disease progression, start of new anticancer therapy, withdrawal of consent, end of the study, or death, whichever occurs first. Scheduled assessments should always be calculated from the first dose of study treatment. Imaging should not be delayed for delays in treatment.

7.5.2. FDG-PET or Combined PET-CT

Positron emission tomography (PET) using [^{18}F] fluorodeoxyglucose (FDG), or combined PET-CT is required to evaluate disease burden during the screening phase. If FDG-PET assessment was performed as standard of care before signing of the ICF but within 28 days of Day 1, then the results from that assessment may be recorded in the eCRF in lieu of a study-specific assessment.

Subsequently, FDG-PET or PET-CT will be repeated in order to confirm response assessments of CR or if clinically indicated.

This assessment schedule also applies to those subjects who discontinue study treatment for reasons other than disease progression until disease progression, start of new anticancer therapy, withdrawal of consent, end of the study, or death, whichever occurs first. Scheduled assessments should always be calculated from the first dose of study treatment. Imaging should not be delayed for delays in treatment.

7.5.3. Bone Marrow Examination

Bone marrow examination is required as a screening assessment unless performed as per standard of care within 60 days of Day 1. Otherwise, a bone marrow biopsy will be performed only to confirm CR or as clinically indicated. The pathology report result from the bone marrow examination will be captured in the eCRF.

7.5.4. Response Criteria – the Lugano Classification

The Lugano Classification (Cheson et al 2014) will be used to assess response to treatment (see Table 11). As PET assessment is required to confirm CR or PR, PET-based response should be applied in most circumstances. Computed tomography/MRI-based response criteria are provided in the event that PET scans cannot be interpreted.

Table 11: Lugano Classification for Response Assessment

Site	PET-Based Response	CT-Based Response
	Complete metabolic response	**Complete radiologic response (all of the following)**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 with or without a residual mass on 5PS.[a]	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi.
Nonmeasured lesion	Not applicable.	Absent.
Organ enlargement	Not applicable.	Regress to normal.
New lesions	None.	None.
Bone marrow	No evidence of FDG-avid disease in marrow.	Normal by morphology; if indeterminate, IHC negative.
	Partial metabolic response	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	• Score 4 or 5[a] with reduced uptake compared with baseline and residual mass(es) of any size. • At interim, these findings suggest responding disease. • At EOT, these findings suggest residual disease.	• ≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites. • When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default. • When no longer visible, 0 × 0 mm. For a node > 5 mm × 5 mm but smaller than normal, use actual measurement.
Nonmeasured lesions	Not applicable.	Absent/regressed, but no increase.
Organ enlargement	Not applicable.	Spleen must have regressed by > 50% in length beyond normal.
New lesions	None.	None.
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consider further evaluation with MRI or biopsy.	Not applicable.

Table 11: Lugano Classification for Response Assessment (Continued)

Site	PET-Based Response	CT-Based Response
	No metabolic response	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score of 4 or 5[a] with no significant change in FDG uptake from baseline at interim or EOT.	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met.
Nonmeasured lesions	Not applicable.	No increase consistent with progression.
Organ enlargement	Not applicable.	No increase consistent with progression.
New lesions	None.	None.
Bone marrow	No change from baseline.	Not applicable.
	Progressive metabolic disease	**Progressive disease (requires at least 1 of the following)**
Individual target nodes/nodal lesions	Individual target nodes/nodal lesions: • Score 4 or 5a with an increase in intensity of uptake from baseline and/or • New FDG-avid foci consistent with lymphoma at interim or EOT assessment. Extranodal lesions: • New FDG-avid foci consistent with lymphoma at interim or EOT assessment. New lesions: • New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered. Bone marrow: • New or recurrent FDG-avid foci.	PPD progression: • An individual node/lesion must be abnormal with all of the following: – LDi > 1.5 cm. – Increase by ≥ 50% from PPD nadir. – Increase in LDi or SDi from nadir: ▪ 0.5 cm for lesions ≤ 2 cm. ▪ 1.0 cm for lesions > 2 cm. • In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15 cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. • New or recurrent splenomegaly. • New or clear progression of preexisting nonmeasured lesions. • Regrowth of any previously resolved lesions. • A new node > 1.5 cm in any axis. • A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma. • Assessable disease of any size unequivocally attributable to lymphoma. • New or recurrent involvement of the bone marrow

LDi = longest transverse diameter of lesion; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

[a] PET 5-point scale: 1) no uptake above background; 2) update ≤ mediastinum; 3) uptake > mediastinum but ≤ liver; 4) uptake moderately > liver; 5) uptake markedly higher than liver and/or new lesions; X) new areas of uptake unlikely to be related to lymphoma.

7.6. Performance Status Assessments

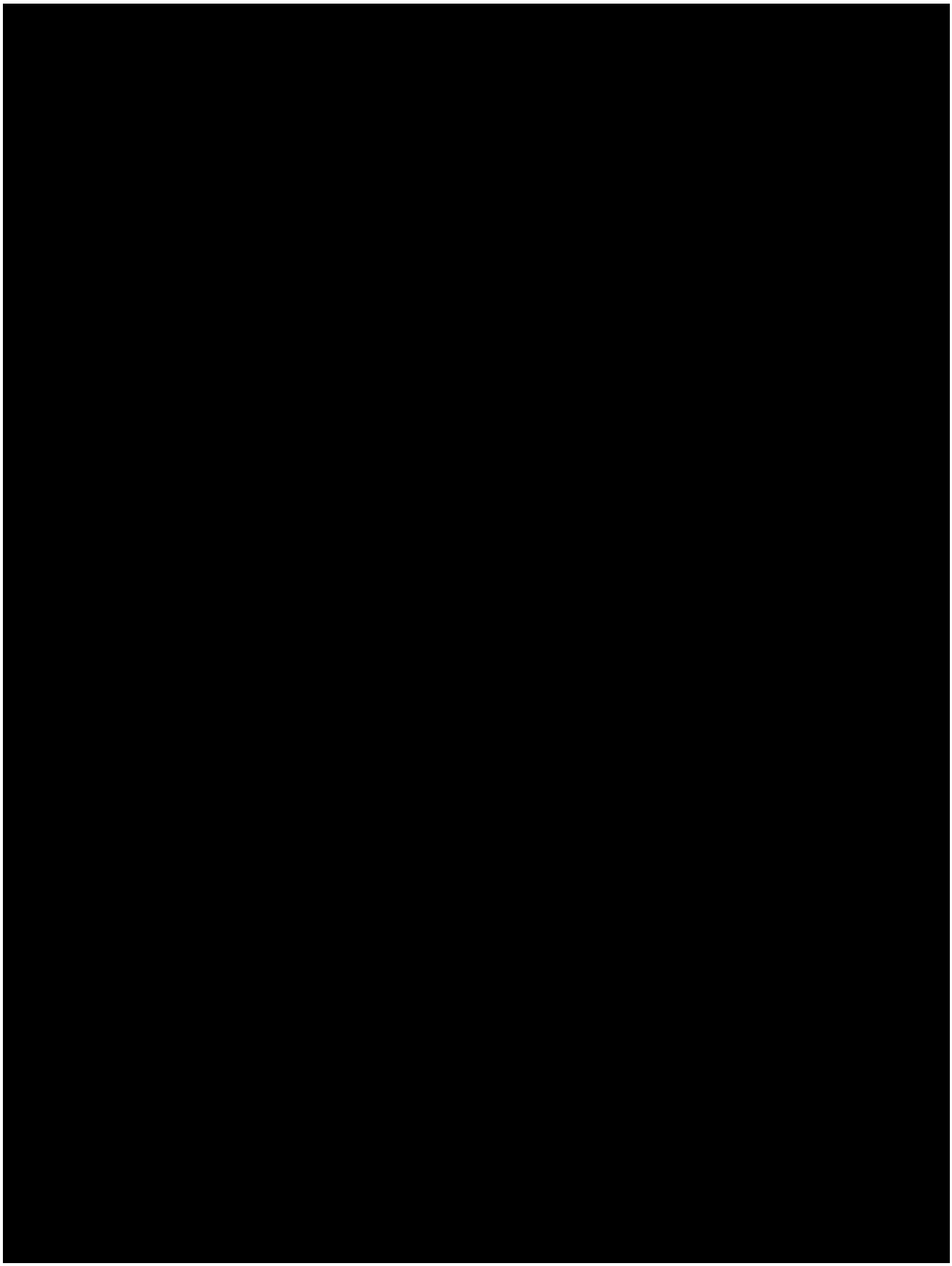
7.6.1. ECOG Performance Status

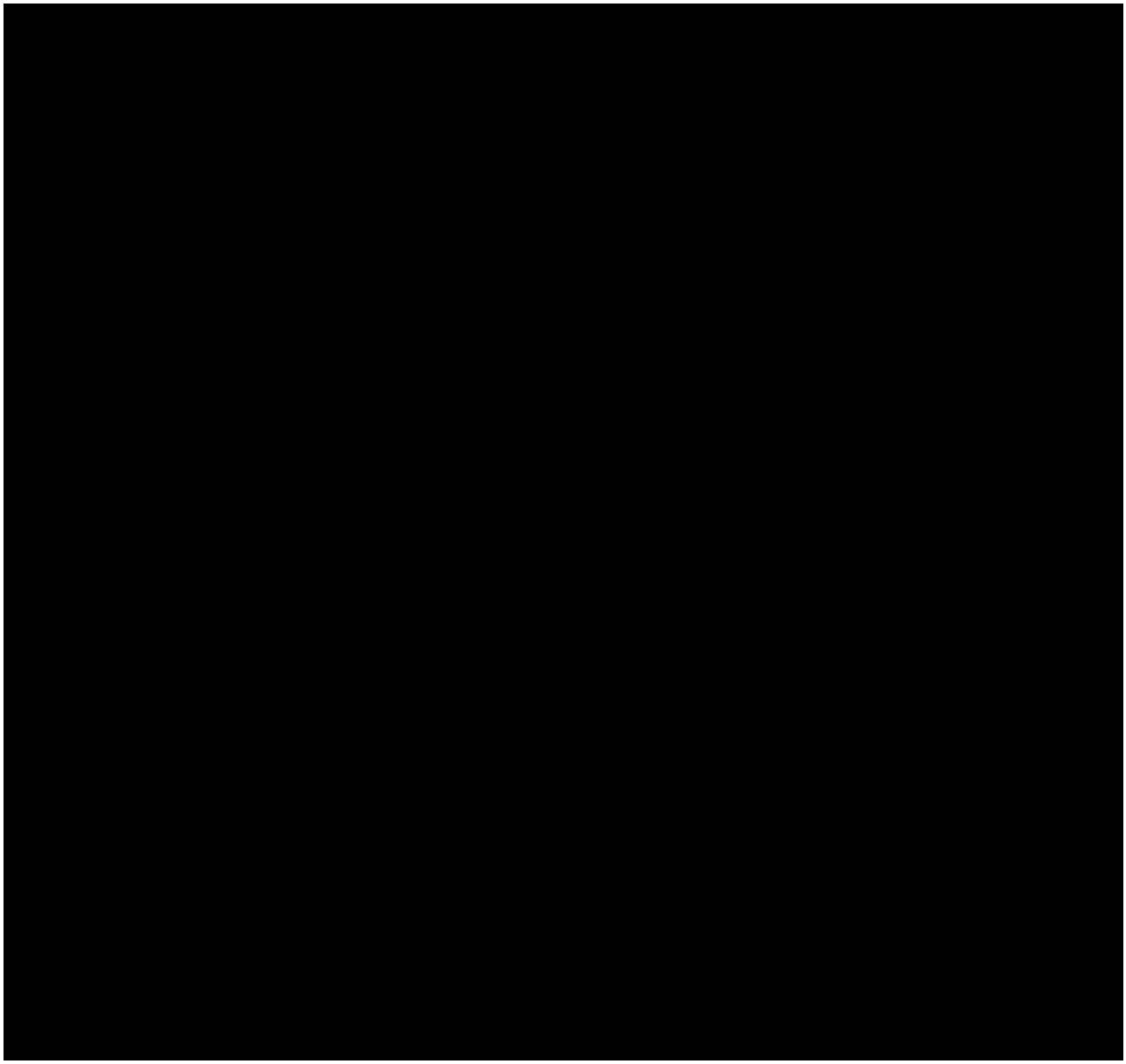
ECOG performance status (Oken et al 1982; Table 12) will be required at screening to evaluate eligibility and will be assessed at other study visits per Table 8. Performance status must be assessed by a medically qualified individual and recorded in the eCRF.

Table 12: ECOG Performance Scores

Grade	Performance Status
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

[redacted]





7.9. Other Study Procedures

7.9.1. Distribution of Subject Reminder Cards

Subjects will be provided with a reminder card at each visit. The subject reminder card will indicate the date/time of the next visit and will also remind the subject that they should not take their morning dose of study drug on Day 1, Day 8, and Day 15, as they will take it after blood draws have been completed for safety evaluation. The reminder cards for the Day 1, 8, and 15 visits will have an area on which the date and time of the last dose taken (from the previous evening) and the time of their last meal before the visit should be recorded.

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions

For the purposes of this Protocol, an adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related, that occurs after a subject provides informed consent. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically meaningful, require therapy (eg, hematologic abnormality that requires transfusion), or require changes in the study drug(s).

8.1.2. Reporting

Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events form of the eCRF. Conditions that were already present at the time of informed consent should be recorded on the Medical History form in the eCRF. Monitoring for the occurrence of new AEs should be continued for at least 30 days after the last dose of study drug. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

The term "disease progression" should be recorded as an AE/SAE only if there are no other identifiable AEs/SAEs associated with the disease progression at the time of reporting. For events associated with disease progression, the relevant signs and symptoms should be reported using a diagnosis whenever possible rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE. If the events resulting from disease progression meet the criteria for an SAE (eg, resulted in hospitalization, a life-threatening event, or death), the specific event(s) should be reported as an SAE(s) as described in Section 8.3.2. In both cases (ie, AEs or SAEs related to disease progression), it should be indicated that each event (reported as a diagnosis or as signs and symptoms) is related to disease progression on the Adverse Events form of the eCRF.

The severity of AEs will be assessed using CTCAE v4.03 Grades 1 through 4. The CTCAE v4.03 severity of Grade 5 will not be used; AEs resulting in death will be graded accordingly using Grades 1 through 4 and have the outcome noted as fatal. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity.

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
Grade 4	Life-threatening consequences; urgent intervention indicated.

The occurrence of AEs should be sought by nondirective questioning of the subject during the screening process after signing the ICF and at each visit during the study. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. To the extent possible, each AE should be evaluated to determine:

- The severity grade (CTCAE Grade 1 to 4).
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no).
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug.
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per serious adverse event (SAE) definition provided in Section 8.3.1.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements (see Section 8.3.2).

All AEs should be treated appropriately. If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on Adverse Event form and the treatment should be specified on the Prior/Concomitant Medications or Procedures and Non-Drug Therapy form in the eCRF.

Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome.

When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves. For example, 2 separate AEs will be reported if a subject has Grade 1 diarrhea, meeting the definition of an AE that lasts for 3 days before worsening to a Grade 3 severity. The Grade 1 event will be reported as an AE with a start date equal to the day the event met the Grade 1 AE definition and a stop date equal to the day that the event increased in severity from Grade 1 to Grade 3. The Grade 3 event will also be reported as an AE, with the start date equal to the day the event changed in

intensity from Grade 1 to Grade 3 and a stop date equal to the day that the event either changed severity again or resolved.

8.2. Laboratory Test Abnormalities

8.2.1. Definitions and Reporting

Laboratory abnormalities that constitute an AE in their own right (considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug) should be recorded on the Adverse Event form in the eCRF. Whenever possible, a diagnosis rather than a symptom should be provided (eg, "anemia" instead of "low hemoglobin"). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory test result corresponds to a sign or symptom of a previously reported AE, it is not necessary to separately record the laboratory test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 (severe) AE does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1. A dose modification for the laboratory abnormality may be required (see Section 5.5) and should not contribute to the designation of a laboratory test abnormality as an SAE.

8.3. Serious Adverse Events

8.3.1. Definitions

An SAE is defined as an event that meets at least 1 of the following criteria:

- Is fatal or life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
  - A routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
  - An elective surgery or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF.
  - A treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE and not resulting in hospital admission.
  - Any social reasons and respite care, in the absence of any deterioration in the subject's general condition.
- Results in persistent or significant disability, incapacity, or a substantial disruption of a person's ability to conduct normal life functions.
- Constitutes a congenital anomaly or birth defect.
- Is considered to be an important medical event or a medically significant event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event

may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above.

8.3.2. Reporting

Every SAE, regardless of suspected causality (eg, relationship to study drug(s) or study procedure or disease progression), occurring after the subject has signed the ICF through the last study visit (or 30 days after the last dose of study drug, whichever is later) must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. Any SAEs occurring more than 30 days after the last dose of study drug should be reported to the sponsor or its designee only if the investigator suspects a causal relationship to the study drug.

Information about all SAEs is collected and recorded on the Adverse Event form of the eCRF. The investigator must assess and record the causal relationship of each SAE to the study treatment.

The investigator must also complete the Incyte Serious Adverse Event Report Form, in English, and send the completed and signed form to the sponsor or designee within 24 hours of becoming aware of the SAE. The investigator must provide a causality assessment, that is, assess whether there is at least a reasonable possibility that the SAE is related to the study treatment: suspected (yes) or not suspected (no). Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.

The contact information of the sponsor's study-specific representatives is listed in the investigator manual provided to each site. The original copy of the SAE Report Form and the confirmation sheet must be kept at the study site.

Investigational site personnel must report any new information regarding the SAE within 24 hours of becoming aware of the information in the same manner that the initial SAE Report Form was sent. Follow-up information is recorded on an amended or new SAE Report Form, with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous SAE Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or subject disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

If the SAE is not documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

All new malignant tumors including solid tumors, skin malignancies, and hematologic malignancies will be reported as SAEs, regardless of the treatment group that the subject is enrolled in.

This includes any second primary malignancy, regardless of causal relationship to study drug(s), occurring at any time for the duration of the study, from the time of signing the informed consent to 5 years after the last study drug treatment.

Events of second primary malignancy are to be reported using the SAE form; these events must also be documented in the appropriate page(s) of the eCRF and in the subject's source documents. Documentation of the diagnosis of the second primary malignancy must be provided at the time of reporting as an SAE (eg, any confirmatory histology or cytology results, x-rays, CT scans).

8.4. Adverse Events of Special Interest

Specific AEs, or groups of AEs, will be followed as part of standard safety monitoring activities. These events (regardless of seriousness) will be reported per the SAE reporting timelines.

8.4.1. Major Hemorrhage

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic AEs of Grade 3 or higher.
- Any treatment-emergent SAEs of bleeding of any grade.
- Any treatment-emergent CNS hemorrhage/hematoma of any grade.

All hemorrhagic events requiring transfusion of red blood cells should be reported as Grade 3 or higher per CTCAE Events meeting the definition of major hemorrhage will be captured as an AE of special interest according to Section 8.4.

8.5. Emergency Unblinding of Treatment Assignment

Not applicable.

8.6. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a subject during maternal or paternal exposure to study drug, the following procedures should be followed in order to ensure subject safety:

- The study drug must be discontinued immediately (female subjects only; see Section 5.5 for the maximum permitted duration of study drug interruption).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any

birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

Any SAE occurring during pregnancy must be recorded on the SAE report form and submitted to the sponsor or designee.

8.7. Warnings and Precautions

Special warnings or precautions for the study drug, derived from safety information collected by the sponsor or its designee, are presented in the Investigator's Brochure (IB). Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications (INs). Any important new safety information should be discussed with the subject during the study, as necessary. If new significant risks are identified, they will be added to the ICF.

8.8. Data Monitoring Committee

The sponsor will continuously monitor safety through frequent contact with the treating investigators, review of the clinical data, and formal study meetings. Routine (at least biweekly) teleconferences will be held among participating study sites to provide subject-by-subject updates on current study status, interim toxicities reported, and any other pertinent information. Adverse event and laboratory data entered into the clinical database will be reviewed periodically for trends and evolving safety signals. Lastly, formal review meetings will be conducted with investigators during the study to establish consensus on the safety and tolerability of a given dose, based on the collective experience of the group.

8.9. Product Complaints

The sponsor collects product complaints on study drugs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by the sponsor or its designee will be reported to the sponsor. All product complaints associated with other study material will be reported directly to the respective manufacturer.

The investigator or his/her designee is responsible for reporting a complete description of the product complaint via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be reported as described in Section 8.1.2 of this Protocol.

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint communication with the product.

9. STATISTICS

9.1. Study Populations

The populations to be analyzed include the following:

- Intent-to-treat (ITT) population: Subjects enrolled into the Phase 2 portion of the study.
- Per-protocol (PP) population: Subjects in the ITT population who received at least 80% of the assigned study drug regimen, met all inclusion/exclusion criteria, and had no significant Protocol violations as determined by sponsor. A subject who is discontinued because of disease progression is considered to be evaluable for the PP population.
- Safety evaluable population: Subjects enrolled in the Phase 2 portion of the study who received at least 1 dose of study drug.
- Safety run-in population: Subjects enrolled in the Phase 1 portion of the study who received at least 1 dose of study drug.

[redacted]

9.2. Selection of Sample Size

9.2.1. Sample Size in Safety Run-in Phase

For the safety run-in phase, the decision to de-escalate the dose will be driven by the number of observed toxicities and can be calculated based on the binomial distribution. A 6 + 3 dose escalation design will be used in this study. The probability of this occurrence based on the true toxicity rate is shown in Table 14.

Table 14: Probability to De-Escalate INCB039110

True Toxicity Rate	Probability to De-Escalate INCB039110
0.25	0.341
0.3	0.469
0.35	0.591
0.4	0.700
0.45	0.790

9.2.2. Sample Size in Expansion Phase

The study will lead to a decision between 2 prespecified hypotheses about the probability of an ORR, p. The null hypothesis H_0: p = 40% reflects a response rate that would be of no clinical benefit, and the alternative hypothesis H_A: p = 55% is a response rate that might lead to larger, confirmatory studies. Using a Simon 2-stage optimal design, a total of 60 subjects will be needed for 80% power at 1-sided alpha = 0.1 level. If there are $\leq$ 9 objective responders from

the first 22 evaluable subjects, then this will support the null hypothesis, and the study will be terminated. Otherwise, 38 additional subjects will be enrolled (Stage 2).

9.3. Level of Significance

The level of significance for the primary endpoint is 1-sided 10%, which is deemed acceptable for a proof-of-concept study.

9.4. Statistical Analyses

9.4.1. Primary Analyses

The primary endpoint is ORR; a subject will be considered as a responder if his or her best overall response is PR or better based on the Lugano Classification (Cheson et al 2014). The rate of responders will be estimated using the observed rate, and its 90% CI will be calculated using the method of Koyama and Chen (2008) that accounts for the early termination rules of the Simon 2-stage design. The study will be considered successful if the total number of objective responders is ≥ 29 in Phase 2.

9.4.2. Secondary Analyses

The DOR is defined as the difference of the end of response and the start of response for subjects who have achieved a response. The start of a response will be the first visit where the subject achieves PR or better based on the Lugano Classification. [redacted] Duration of response will be assessed using Kaplan-Meier method for subjects who achieve a response. Median duration and 90% CI will be estimated. Subjects who are still responding at the time of database freeze or discontinuation will be censored at the last valid radiologic assessment visit.

The durable response rate is defined as CR or PR for ≥ 16 weeks as determined by Lugano Classification. The rate of responders will be estimated together with 90% CI.

Progression-free survival (PFS) will be determined from the enrollment date until the earliest date of disease progression, as measured by investigator assessment of objective radiographic disease assessments per Lugano Classification, or death due to any cause if earlier. Progression-free survival data will be analyzed using Kaplan-Meier method, treating subjects with no observed death or progression as censored at the last valid radiologic assessment visit. Median PFS and 90% CI will be estimated.

[redacted] All the efficacy endpoints (ORR, DOR, and PFS) of subjects from the safety run-in population will be summarized separately as appropriate with data availability.

Subgroup analyses for the subtypes will be explored, including but not limited to response by IPI as well as other disease characteristics.

[redacted]

[redacted]

9.4.4. Safety Analyses

The safety analyses will be conducted for the safety evaluable and safety run-in populations separately. Summary statistics for safety data will be provided.

9.4.4.1. Adverse Events

Adverse events will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the CTCAE v4.03 (NCI 2010).

The subset of AEs considered by the investigator to have a relationship to study drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, then the AE will be considered treatment-related. The incidence of AEs and treatment-related AEs will be tabulated.

9.4.4.2. Clinical Laboratory Tests

Laboratory test values outside the normal range will be assessed for severity based on the normal ranges for the clinical reference laboratory. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated.

Laboratory data will be classified into CTCAE grades for AEs using CTCAE v4.03. The following summaries will be produced for the laboratory data:

- Number and percentage of subjects with worst postbaseline CTCAE grade (regardless of baseline value). Each subject will be counted only for the worst grade observed postbaseline.
- Shift tables using CTCAE grades to compare baseline with the worst postbaseline value will be produced with CTCAE grade.
- For laboratory parameters where CTCAE grades are not defined, shift tables to the worst postbaseline value will be produced using the low/normal/high classifications based on laboratory reference ranges.

9.4.4.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities (see Table 15), and subjects exhibiting clinically notable vital sign abnormalities will be listed. A value will be considered an "alert" value if it is outside of the established range and shows a > 25% change from baseline.

Table 15: Criteria for Clinically Notable Vital Signs Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 mmHg	< 85 mmHg
Diastolic blood pressure	> 100 mmHg	< 40 mmHg
Pulse	> 100 bpm	< 45 bpm
Temperature	> 38°C	< 35.5°C
Respiratory rate	> 24/min	< 8/min

[redacted]

9.5. Interim Analysis

No interim analysis is planned.

10. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

10.1. Investigator Responsibilities

This study will be performed in accordance with ethical principles that originate in the Declaration of Helsinki and conducted in adherence to the study Protocol; GCPs as defined in Title 21 of the US CFR Parts 11, 50, 54, 56, and 312; ICH E6 GCP consolidated guidelines; and local regulatory requirements as applicable to the study locations.

The investigator will be responsible for:

- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and subject records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all subjects.
  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study- related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.
- Obtaining informed consent and ensuring that the study subjects' questions have been answered and the subjects fully understand study procedures:
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the subject. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to subject records.

- Obtaining approval from the IRB/IEC before the start of the study and for any changes to the clinical study Protocol, important Protocol deviations, routine updates, and safety information in accordance with institutional requirements and local law.
  - The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by the IRB/IEC.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling subjects who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws, but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
  - All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

10.2. Accountability, Handling, and Disposal of Study Drug

The investigator is responsible for drug accountability at the study site; however, some of the drug accountability duties may be assigned to an appropriate pharmacist or other designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. The investigator or designee must maintain records that document:

- Delivery of study drug to the study site.
- Inventory of study drug at the site.
- Subject use of the study drug including pill or unit counts from each supply dispensed.
- Return of study drug to the investigator or designee by subjects.

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the subjects were provided the specified

study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study subjects.

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional standard operating procedures. If local procedures mandate on-site destruction of investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

10.3. Data Management

Data management will be performed in a validated database via an Electronic Data Capture (EDC) system. All data entry, verification, and validation will be performed in accordance with the current standard operating procedures of the Data Management Department at the sponsor or its designee. The database provider's information security controls are aligned with ISO 27002. The database will be authorized for lock once all defined procedures are completed.

The investigator will be provided with access to an EDC system so that an eCRF can be completed for each subject. Entries made in the eCRF must be verifiable against source documents; if updates to the database are not possible, any discrepancies should be explained and documented. The investigator will be responsible for reviewing all data and eCRF entries, and will sign and date the designated forms in each subject's eCRF, verifying that the information is true and correct. The investigator is responsible for the review and approval of all query responses.

Protocol deviations will be identified and recorded in the Protocol Deviation form of the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements.

10.4. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data privacy laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that sensitive information is handled in accordance with local requirements (eg, HIPAA). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

Subject names will not be supplied to the sponsor or its designee, if applicable. Only the subject number and subject's initials (subject's initials will only be recorded if allowable by local regulations) will be recorded in the eCRF, where permitted; if the subject's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of

the sponsor or its designee, IRB or IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

In the event of a serious breach, the sponsor should be notified immediately and will notify the licensing authority as per local regulations.

10.5. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies subject to FDA Regulation Title 21 Code of Federal Regulations (CFR) Part 54 – Financial Disclosure by Clinical Investigators (ie, "covered studies") are required to submit a completed Clinical Investigator Financial Disclosure form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, "clinical investigator" is defined as any investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects, including the spouse and each dependent child of the clinical investigator or subinvestigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new clinical investigators added to the covered clinical study during its conduct must also submit a completed Investigator Financial Disclosure Form. During a covered clinical study, any changes to the financial information previously reported by a clinical investigator must be reported to the sponsor or its designee. At the conclusion of the covered clinical study, the clinical investigators will be reminded of their obligations. In the event that the clinical investigator is not reminded, they nevertheless will remain obligated to report to the sponsor or its designee any changes to the financial information previously reported, as well as any changes in their financial information for a period of 1 year after completion of the covered clinical study.

10.6. Publication Policy

By signing the study Protocol, the investigator and his or her institution agree that the results of the study may be used by the sponsor, Incyte Corporation (Incyte), for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. Study results will be published in accordance with applicable local and national regulations. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

The following methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods.

Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - injectable
  - implantable[2]
- Intrauterine device (IUD)[2]
- Intrauterine hormone-releasing system (IUS)[2]
- Bilateral tubal occlusion[2]
- Vasectomised partner[2,3]
- Sexual abstinence[4]

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.
[2] Contraception methods that in the context of this guidance are considered to have low user dependency.
[3] Vasectomised partner is a highly effective method provided of avoiding pregnancy that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
[4] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
Source: CTFG 2014.

APPENDIX B. CYTOCHROME P450 INHIBITORS AND INDUCERS

University of Washington School of Pharmaceutics: Drug Interaction Database Program. 2002. http://www.druginteractioninfo.org. Accessed May 2015. Highlighted rows indicate recent additions to the lists at the time the database search was performed.

In Vivo CYP3A Inhibitors

Inhibitor	Therapeutic Class	Inhibitor dosing (oral)	Object[1] (oral, unless otherwise specified)	AUC_{ratio}	PMID or NDA #	Published
Potent CYP3A Inhibitors (yielding substrate AUCr > 5)						
indinavir /RIT	Protease Inhibitors	800/100 mg BID (1 day)	alfentanil	36.5	19225389	2009 Mar
tipranavir/RIT	Protease Inhibitors	500/200 mg BID (2 days)	midazolam	26.91	20147896	2010 Jun
ritonavir	Protease Inhibitors	3 doses of 100 mg over 24 h	midazolam	26.41	20002087	2009 Dec
cobicistat (GS-9350)	None	200 mg QD (14 days)	midazolam	19.03	20043009	2010 Mar
indinavir	Protease Inhibitors	800 mg TID (7 days)	vardenafil	16.25	NDA # 021400	2003 Aug
ketoconazole	Antifungals	400 mg QD (4 days)	midazolam	15.9	8181191	1994 May
troleandomycin	Antibiotics	500 mg single dose	midazolam	14.8	15536460	2004 Dec
telaprevir	Antivirals	750 mg TID (16 days)	midazolam	13.5	22162542	2012 Oct
danoprevir / RIT	Antivirals	200/100 mg QD (14 days)	midazolam	13.42	23872824	2013 Nov
elvitegravir / RIT	Treatments of AIDS	150/100 mg QD (10 days)	midazolam	12.8	NDA # 203100	2012
saquinavir / RIT	Protease Inhibitors	1000/100 mg BID (14 days)	midazolam	12.48	19792991	2009 Oct
lopinavir / RIT	Protease Inhibitors	400/100 mg BID (2 days)	alfentanil	11.47	24067429	2013 Dec
itraconazole	Antifungals	200 mg QD (4 days)	midazolam	10.8	8181191	1994 May
voriconazole	Antifungals	200 mg BID (9 days)	midazolam	9.63	21937987	2011 Nov
mibefradil	Calcium Channel Blockers	100 mg single dose	midazolam	8.86	14517191	2003 Oct
LCL161	Cancer Treatments	600 mg single dose	midazolam	8.8	23585187	2013 Jun
clarithromycin	Antibiotics	500 mg BID (7 days)	midazolam	8.39	16432272	2006 Feb
posaconazole	Antifungals	400 mg BID (7 days)	midazolam	6.23	19302901	2009 Feb
telithromycin	Antibiotics	800 mg QD (6 days)	midazolam	6.2	NDA# 021144	2004
grapefruit juice DS[2]	Food Products	240 mL TID (2 days) and 90 min, 60 min, 30 min prior to midazolam	midazolam	5.95	12953340	2003 Aug
conivaptan	Diuretics	40 mg BID (5 days)	midazolam	5.76	NDA # 021697	2005
nefazodone	Antidepressants	100-200 mg BID (12 days)	midazolam	5.44	14551182	2003 Nov
nelfinavir	Protease Inhibitors	1250 mg BID (14 days)	midazolam	5.29	21406602	2011 Jun
saquinavir	Protease Inhibitors	1200 mg TID (5 days)	midazolam	5.18	10430107	1999 Jul
idelalisib	Kinase Inhibitors	150 mg BID (8 days)	midazolam	5.15	NDA # 206545	2014
boceprevir	Antivirals	800 mg TID (6 days)	midazolam	5.05	NDA # 202258	2011
Moderate CYP3A Inhibitors (AUCr ≥ 2 and < 5)						
erythromycin	Antibiotics	1000 mg single dose	midazolam	4.99	25139487	2014 Dec
fluconazole	Antifungals	400 mg single dose	midazolam	4.93	16172184	2005 Oct
atazanavir / RIT	Protease Inhibitors	300/100 mg BID	maraviroc	4.9	18333863	2008 Apr
darunavir	Protease Inhibitors	1200 mg BID (14 days)	saquinavir	4.9	NDA # 021976	2006
diltiazem	Calcium Channel Blockers	60 mg TID (2 days)	midazolam	4.06	21209240	2011 Nov
darunavir / RIT	Protease Inhibitors	400/100 mg BID (8 days)	sildenafil	4.0	NDA # 021976	2006
dronedarone	Antiarrhythmics	400 mg BID (14 days)	simvastatin	3.66	NDA # 022425	2009
crizotinib	Kinase Inhibitors	250 mg BID (28 days)	midazolam	3.65	NDA # 202570	2011
atazanavir	Protease Inhibitors	400 mg QD (7 days)	maraviroc	3.57	18333863	2008 Apr
aprepitant	Antiemetics	80-125 mg QD (5 days)	midazolam	3.29	12891225	2003 Aug
casopitant	Antiemetics	120 mg QD (14 days)	midazolam	3.13	20840445	2010 Oct
amprenavir	Protease Inhibitors	1200 mg BID (10 days)	rifabutin	2.93	11158747	2001 Feb
imatinib	Antineoplastic Agents	400 mg QD (7 days)	simvastatin	2.92	14612892	2003 Nov
verapamil	Calcium Channel Blockers	80 mg TID (2 days)	midazolam	2.92	8198928	1994 Mar
ledipasvir	Antivirals	30 mg QD (10 days)	simeprevir	2.69	NDA # 205123	2013
netupitant	Antiemetics	300 mg single dose	midazolam	2.44	23729226	2013 Oct
grapefruit juice	Food Products	240 mL QD (4 days)	midazolam	2.39	10546919	1999 Oct
tofisopam	Benzodiazepines	100 mg TID (9 days)	midazolam	2.36	17989974	2008 Jan
cyclosporine	Immunosuppressants	Not provided (1-5 years)	midazolam	2.21	21753749	2011 Sep
ACT-178882	Renin Inhibitors	300 mg QD (14 days)	midazolam	2.19	22849770	2013 Dec
ciprofloxacin	Antibiotics	500 mg single dose	sildenafil	2.12	16372380	2005 Dec
schisandra sphenanthera	Herbal Medications	3 capsules (= 11.25 mg deoxyschizandrin) BID (7 days)	midazolam	2.05	19552749	2009 May

cimetidine	H-2 Receptor Antagonists	200-400 mg QID (1.5 days)	midazolam	2.02	6152615	1984 Sep
FK1706	Central Nervous System Agents	60 mg QD (14 days)	midazolam	2.01	19889885	2010 Feb
lomitapide	Other Antilipemics	60 mg QD (7 days)	simvastatin	2.0	NDA # 203858	2012
Weak CYP3A Inhibitors (AUCr ≥ 1.25 and < 2)						
tabimorelin	Hormone Replacement	2.86-3.21 mg QD (7 days)	midazolam	1.93	12610745	2003 Feb
ranolazine	Cardiovascular Drugs	1000 mg BID (7 days)	simvastatin	1.89	NDA # 021526	2006
amlodipine	Calcium Channel Blockers	10 mg QD (9 days)	simvastatin	1.8	23965645	2014 Apr
lomitapide	Other Antilipemics	60 mg QD (7 days)	simvastatin	1.77	24734312	2014 Mar
fosaprepitant (IV)	Antiemetics	150 mg single 30-min infusion	midazolam	1.76	21209230	2011 Dec
Seville orange juice	Food Products	240 mL single dose	felodipine	1.76	11180034	2001 Jan
amiodarone	Antiarrhythmics	400 mg QD (4 days)	simvastatin acid	1.76	17301736	2007 May
chlorzoxazone	Muscle Relaxants	250 mg single dose (part of a 6-drug cocktail)	midazolam	1.68	11736864	2001 Nov
M100240	Antihypertensive Agents	50 mg single dose	midazolam	1.66	15051745	2004 Apr
fluvoxamine	Antidepressants	50-00 mg BID (12 days)	midazolam	1.66	14551182	2003 Nov
ranitidine	H-2 Receptor Antagonists	150 mg BID (1.5 days)	midazolam	1.66	6135440	1983 Jun
goldenseal	Herbal Medications	1,323 mg (= 24.1 mg isoquinoline alkaloids) TID (14 days)	midazolam	1.63	17495878	2008 Jan
clotrimazole	Antifungals	10 mg TID (5 days)	midazolam	1.61	20233179	2010 Feb
tacrolimus	Immunosuppressants	Not provided (1-5 years)	midazolam	1.61	21753749	2011 Sep
cilostazol	Antiplatelets	100 mg BID (7 days)	lovastatin	1.56	10702889	1999
ticagrelor	Antiplatelets	180 mg bid (7 days)	simvastatin	1.56	NDA # 022433	2011
peppermint oil	Food Products	600 mg (= 300 uL peppermint oil) single dose	felodipine	1.55	12235445	2002 Sep
ivacaftor	Cystic fibrosis treatments	150 mg BID (6 days)	midazolam	1.54	NDA # 203188	2012
GSK2248761	Transcriptase Inhibitors	100 mg QD (12 days)	midazolam	1.54	22288567	2012 Aug
roxithromycin	Antibiotics	300 mg QD (6 days)	midazolam	1.47	7995324	1994
suvorexant	Hypnotics - Sedatives	80 mg QD (14 days)	midazolam	1.47	NDA # 204569	2014
propiverine	Anticholinergics	15 mg BID (7 days)	midazolam	1.46	16183781	2005 Dec
isoniazid	Antibiotics	90 mg BID (4 days)	triazolam	1.46	6140941	1983 Dec
berberine	Herbal Medications	300 mg TID (14 days)	midazolam	1.45	21870106	2012 Feb
oral contraceptives	Oral contraceptives	OC with low doses of estrogen (< 35 ug ethinylestradiol) (> 3 months)	triazolam	1.44	6149030	1984 Nov
delavirdine	NNRTIs	400 mg TID (9 days)	indinavir	1.44	9665503	1998 Jul
daclatasvir	Antivirals	60 mg QD (7 days)	simeprevir	1.44	NDA # 205123	2013
faldaprevir	Antivirals	240 mg BID (8 days)	ethinyl estradiol	1.44	25385099	2015 Jan
simeprevir	Protease Inhibitors	150 mg QD (11 days)	midazolam	1.43	NDA # 205123	2013
atorvastatin	HMG CoA Reductase Inhibitors (Statins)	10-40 mg/day (chronic treatment)	midazolam IV	1.41	12911366	2003 Sep
tolvaptan	Vasopressin Antagonists	60 mg single dose	lovastatin	1.41	NDA # 022275	2009
almorexant	Hypnotics - Sedatives	200 mg QD (9 days)	midazolam	1.37	22990330	2013 Mar
GSK1292263	Other Antilipemics	300 mg BID (9 days)	simvastatin	1.36	23256625	2013 Jun
linagliptin	Dipeptidyl Peptidase 4 Inhibitors	10 mg QD (6 days)	simvastatin	1.34	20497745	2010 Jun
resveratrol	Food Products	1 g QD (4 weeks)	buspirone	1.33	20716633	2010 Sep
lacidipine	Calcium Channel Blockers	4 mg QD (8 days)	simvastatin	1.33	11259986	2001 Feb
cranberry juice	Food Products	240 mL double strength juice, 1 glass q 15 min x 3	midazolam	1.33	19114462	2009 Mar
pazopanib	Kinase Inhibitors	800 mg QD (17 days)	midazolam	1.32	20881954	2010 Nov
everolimus	Immunosuppressants	10 mg QD (5 days)	midazolam	1.31	23426978	2013 Apr
blueberry juice	Food Products	two doses of 300 mL, separated by 16 hours	buspirone	1.31	22943633	2013 Apr
nilotinib	Kinase Inhibitors	600 mg single dose	midazolam	1.3	NDA # 022068	2007
AMD070	Fusion Inhibitors	200 mg BID (8 days)	midazolam	1.29	18362694	2008 Apr
alprazolam	Benzodiazepines	1 mg TID (7 days)	buspirone	1.29	8300893	1993 Nov
bicalutamide	Antiandrogens	150 mg QD (>3 months)	midazolam	1.27	15509184	2004
sitaxentan	Endothelin Receptor Antagonists	100 mg QD (7 days)	sildenafil	1.27	20078609	2010 Jan
azithromycin	Antibiotics	500 mg QD (3 days)	midazolam	1.27	8720318	1996 Feb
ginkgo	Herbal Medications	120 mg TID (28 days)	midazolam	1.25	17050793	2006 Nov
teriflunomide	Other Immunomodulators	14-70 mg QD (14 days)	midazolam	1.25	NDA # 202992	2012

[1] To allow better comparability, DDI studies with the probe substrate midazolam were selected first.
When no study with midazolam was available, the AUCratio of another probe or sensitive substrate is presented.

[2] 240 mL GFJ double-strength administered TID for 3 days

In Vivo CYP3A Inducers

Inducers	Therapeutic class	Object (oral, unless otherwise specified)	% ↓ AUC	% ↑ oral CL	Precipitant Dose (oral)	PMID or NDA #	Published
Potent Inducers (AUC decreased by ≥ 80% or CL increased by more than 5 fold (400%))							
rifampin	Antibiotics	budesonide	99.7	36904.5	600 mg QD (7 days)	15726657	2005 Mar
mitotane	Other Antineoplastics	midazolam	94.5	Not Provided	maximum of 3.5 g TID (chronic therapy)	21220434	2011 Apr
avasimibe	Other Antilipemics	midazolam	93.5	Not Provided	750 mg/day (7 days)	12766253	2003 Sep
phenytoin	Anticonvulsants	nisoldipine	89.5	Not Provided	200-450 mg/day (chronic treatment)	8917062	1996 Nov
carbamazepine	Anticonvulsants	quetiapine	86.6	643.1	200 mg TID (26 days)	16390352	2006 Jan
enzalutamide	Antiandrogens	midazolam	85.9	Not Provided	160 mg QD (85±3 days)	NDA # 203415	2012
St John's Wort	Herbal Medications	midazolam	80.0	Not Provided	300 mg TID (14 days)	16341856	2006 Jan
rifabutin	Antibiotics	delavirdine	Not Provided	458.0	300 mg QD (14 days)	9224961	1997 Jun
phenobarbital	Anticonvulsants	verapamil	76.6	400.9	100 mg QD (21 days)	3392664	1988 Jul
Moderate Inducers (AUC decreased by 50-80% or CL increased by 2-5 fold (100-400%))							
ritonavir and St. Johns wort	None	midazolam	77.2	Not Provided	ritonavir: 300 mg BID and SJW: 300 mg TID (14 days)	19924124	2010 Feb
semagacestat	Alzheimer's Treatments	midazolam	76.4	324.6	140 mg QD (10 days)	22789530	2012 Oct
efavirenz	NNRTIs	alfentanil	76	369.4	600 mg QD (20 days)	22398970	2012 Apr
tipranavir and ritonavir	Protease Inhibitors	saquinavir	75.6	Not Provided	tipranavir: 500 mg and ritonavir: 200 mg BID (14 days)	18176328	2008 Apr
bosentan	Endothelin Receptor Antagonists	sildenafil	69.0	239.8	62.5-125 mg BID (8 weeks)	15963102	2005 Jul
genistein	Food Products	midazolam	13.7	136.9	1000 mg QD (14 days)	21943317	2012 Feb
thioridazine	Antipsychotics	quetiapine	68.7	104.5	100-300 mg QD (15 days)	22569350	2012 Jun
nafcillin	Antibiotics	nifedipine	62.6	145.1	500 mg 4 times daily (5 days)	12814453	2003 Jun
talviraline	NNRTIs	indinavir	61.7	181.2	500 mg TID (14 days)	10516944	1999 Oct
lopinavir	Protease Inhibitors	amprenavir	59.7	Not Provided	400 mg BID (4 weeks)	15060509	2004 Apr
modafinil	Psychostimulants	triazolam	57.6	35.7	200-400 mg QD (28 days)	11823757	2002 Jan
etravirine	NNRTIs	sildenafil	56.7	Not Provided	800 mg BID (13.5 days)	NDA# 022187	2008
lersivirine	NNRTIs	midazolam	51.4	105.5	1000 mg BID (14 days)	22527351	2012 Nov
Weak Inducers (AUC decreased by 20-50% or CL increased by less than 2 fold (100%))							
eslicarbazepine	Anticonvulsants	simvastatin	49.4	98.4	800 mg QD (14 days)	23726291	2013 Sep
telaprevir	Antivirals	darunavir	48.4	Not Provided	1125 mg BID (4 days)	NDA# 201917	2011
garlic	Food Products	saquinavir	44.7	Not Provided	caplet of GarliPure BID (20 days)	11740713	2002 Jan
bexarotene	Other Antineoplastics	atorvastatin	45.3	Not Provided	400 mg/m2 QD (at least two 4-week cycles)	22057855	2012 Feb
amprenavir	Protease Inhibitors	lopinavir	43.0	Not Provided	700 mg BID (2-4 weeks)	15668539	2005 Jan
raltegravir	HIV-Integrase Strand Transfer Inhibitors	darunavir	42.0	Not Provided	400 mg BID	21958880	2012 Feb
vemurafenib	Kinase Inhibitors	midazolam	39.4	Not Provided	960 mg BID (15 days)	NDA # 202429	2011
troglitazone	Thiazolidinediones	simvastatin	37.7	Not Provided	400 mg QD (24 days)	11361054	2001 May
sorafenib	Kinase Inhibitors	sirolimus	36.9	Not Provided	200 mg BID (11 days)	21045832	2010 Nov
rufinamide	Anticonvulsants	triazolam	36.7	53.4	400 mg BID (11.5 days)	NDA # 021911	2008
pleconaril	Antivirals	midazolam	34.6	52.8	400 mg TID (6 days)	16467135	2006 May
ginseng	Herbal Medications	midazolam	34.2	50.7	500 mg BID (28 days)	21646440	2012 Jun
boceprevir	Antivirals	darunavir	34.2	41.0	800 mg every 8 hrs (6 days)	23155151	2013 Mar
sulfinpyrazone	Antigout and Uricosuric Agents	cyclosporine	33.9 (change in C_{ave})		200 mg/day	11124491	2000 Dec
gingko	Herbal Medications	midazolam	33.7	52.6	120 mg BID (28 days)	18205997	2008 Feb
vinblastine	Vinca Alkaloids	midazolam IV	33.2	48.8	not provided (4 cycles)	20959500	2010 Nov
nevirapine	NNRTIs	indinavir	32.5	Not Provided	200 mg QD (14 days), then BID (19 days)	10191212	1999 May
armodafinil (R-modafinil)	Psychostimulants	midazolam	32.2	54.7	100-250 mg/day (31 days)	18076219	2008
ticagrelor	Anticoagulants and Antiplatelets	midazolam	31.7	46.5	400 mg QD (6 days)	23870610	2013 Jul
LCL161	Cancer Treatments	midazolam	29.8	34.0	600 mg single dose	23585187	2013 Jun
vicriviroc and ritonavir	Treatments of AIDS	ethinyl estradiol	29.4	Not Provided	30 mg vicriviroc and 100 mg ritonavir QD (10 days)	22015327	2011 Oct

ritonavir	Protease Inhibitors	ethinyl estradiol	**29.2**	Not Provided	100 mg QD (10 days)	22015327	2011 Oct
prednisone	Corticosteroids	tacrolimus	**29.0**	Not Provided	1.5 mg/kg/day	15787787	2005 Apr
oxcarbazepine	Anticonvulsants	felodipine	**28.1**	Not Provided	450 mg BID (7 days)	8451779	1993 Feb
danshen	Herbal Medications	midazolam	**27.9**	**32.8**	4 g TID (14 days)	20565457	2010 Jun
clobazam	Benzodiazepines	midazolam	**27.7**	Not Provided	40 mg QD (15 days)	22422635	2012 Apr
echinacea	Herbal Medications	midazolam	**27.3**	**37.5**	500 mg TID (28 days)	20393696	2010 Aug
ticlopidine	Anticoagulants and Antiplatelets	alfentanil	**27.0**	**50.0**	250 mg BID (4 days)	23361846	2013 Mar
brivaracetam	Anticonvulsants	ethinyl estradiol	**26.8**	**37.3**	200 mg BID (21 days)	24386664	2013 Dec
Stribild*	Treatments of AIDS	ethinyl estradiol	**26.2**	**31.3**	150 mg ELV + 150 mg COB + 200 mg EMT+ 300 mg TEN	NDA # 203100	2012
pioglitazone	Thiazolidinediones	midazolam	**26.0**	Not Provided	45 mg QD 7 days	Actos® Product Label	
dexamethasone	Corticosteroids	aprepitant	**25.0**	Not Provided	8 mg/day (5 days)	NDA # 021549	2003
terbinafine	Antifungals	midazolam	**24.5**	Not Provided	250 mg QD (4 days)	8527290	1995 Sep
quercetin	Food Products	midazolam	**23.6**	Not Provided	500 mg QD (13 days)	21680781	2012 Jun
glycyrrhizin	Herbal Medications	midazolam	**23.0**	Not Provided	150 mg BID (15 days)	20393696	2010 Aug
aprepitant	Neurokinin-1 Receptor Antagonists	midazolam IV	**22.1**	**28.5**	125/80 mg QD (3 days)	14973304	2004 Mar
PA-824	Antibiotics	midazolam	**22.1**	**20.7**	400 mg QD (14 days)	23689718	2013 Aug
oritavancin	Antibiotics	midazolam	**18.7**	**23.9**	1200 mg IV single infusion	NDA # 206334	2014
AZD 7325	Anxiolytics	midazolam	**18.7**	**22.6**	10 mg QD (12 days)	22122233	2012 Jul
methylprednisolone	Corticosteroids	cyclosporine	**15.8**	**35.0**	16 mg/day (12 days) then 8 mg/day (6 months)	12164891	2002 Sep
topiramate	Anticonvulsants	ethinyl estradiol	**12.0**	**20.2**	50 mg/day (21 days)	12681003	2003 Apr

1- Ritonavir has dual effects of simultaneous CYP3A inhibition and induction, and the net pharmacokinetic outcome during chronic ritonavir therapy is inhibition of CYP3A activity.
2- All the substrates presented in the table are sensitive CYP3A substrates (see definition in FDA guidance) except verapamil, cyclosporine, ethinyl estradiol, and delavirdine.

* **Stribild** is a combination of elvitegravir, cobicistat, emtricitabine and tenofovir DF

APPENDIX C. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	27 JUN 2016
Amendment (Version) 2:	11 MAY 2017
Amendment (Version) 3:	05 FEB 2018
Amendment (Version) 4:	01 MAR 2018
Amendment (Version) 5:	18 JUN 2020

Amendment 5 (18 JUN 2020)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to remove the Phase 2 secondary endpoint of overall survival.

1. **Synopsis; Section 2.1.2.2, Secondary Objectives; Section 2.2.2.2, Secondary Endpoints; Section 4.5, Overall Study Duration; Section 5.6.2, Withdrawal Procedures; Section 5.9, Study Completion; Section 6, Study Assessments (Table 8: Schedule of Assessments); Section 6.4.1, Safety Follow-Up; Section 6.4.3, Survival Follow-Up; Section 7.9.2, Data Collection for Survival Follow-Up; Section 9.4.2, Secondary Analyses**

   Description of change: Removed all references to survival follow-up from applicable sections.

   Rationale for change: To discontinue the Phase 2 secondary endpoint of overall survival in the Protocol.

2. **Synopsis**

   Description of change: Updated to add [redacted], MD as the principal coordinating investigator for the study.

   Rationale for change: To identify the principal coordinating investigator for the study.

Amendment 4 (01 MAR 2018)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to revise the criteria for study termination; include blood volumes required for safety, [redacted] assessments; and clarify the methods used for estimating the rate of responders for the primary analysis.

1. **Section 4.6, Study Termination**

   Description of change: Revised to remove "etc" in the following sentence:

   "The sponsor may terminate the study electively due to ethical concerns, insufficient subject recruitment, alterations in accepted clinical practice, emerging data, etc, or if required by regulatory decision."

   Rationale for change: To clarify the expected grounds for early termination of the study by the sponsor.

2. **Section 7.4.6, Laboratory Assessments; Section 7.7.1, Blood Sample Collection; [redacted]**

   Description of change: All relevant sections were revised to include the blood volume required for safety, [redacted] assessments.

   Rationale for change: To include blood volumes required for safety, [redacted] assessments.

3. **Section 9.4.1, Primary Analyses; Section 11, References**

   Description of change: Updated to include additional detail regarding the methods for estimating the rate of responders.

   Rationale for change: To provide clarification of the methods used to estimate the rate of responders for the primary analysis.

4. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 3 (05 FEB 2018)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to revise inclusion criteria, include additional rationale for the study population, and to clarify aspects of the study design, study duration, study drugs, data management, statistics, and study termination.

1. **Synopsis; Section 3.1, Subject Inclusion Criteria**

   Description of change: Inclusion criterion 8f was revised to include only those subjects with total bilirubin ≤ 1.5 × ULN if no liver metastases or < 3 × ULN in the presence of liver metastases or presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia).

   Rationale for change: To provide a more appropriate upper limit for total bilirubin at study entry in this population.

2. **Section 1.2.4, Combined Inhibition of JAK and BTK in DLBCL**

   Description of change: The rationale for the DLBCL subpopulations included in both Phase 1 and 2 was added.

   Rationale for change: To clarify the rationale for the difference in DLBCL subpopulations between Phase 1 and Phase 2.

3. **Section 1.3.3, Potential Risks and Benefits for the Combination of INCB039110 and Ibrutinib**

   Description of change: Potential benefits for the combination of INCB039110 and ibrutinib were added to the risks of the combination.

   Rationale for change: To provide a more detailed risk-benefit assessment of the study drug combination.

4. **Section 3.1, Subject Inclusion Criteria**

   Description of change: Inclusion criterion 10 was revised to extend the timeframe to avoid pregnancy or fathering children to 3 months after completion of study treatment.

   Rationale for change: To align the Protocol with the ibrutinib SmPC.

5. **Section 4.5, Overall Study Duration**

   Description of change: Language was added to ensure access to treatment for subjects who continue to benefit from study treatment at the time of study termination.

   Rationale for change: To clarify the sponsor's guarantee to provide study drug after study termination to those subjects continuing to benefit from the study treatment.

6. **Section 4.6, Study Termination**

   Description of change: Examples were added to demonstrate potential reasons for the sponsor to terminate the study electively.

   Rationale for change: To provide examples of the most commonly expected grounds for early termination of the study by the sponsor.

7. **Section 5.2.1, Description and Administration**

   Description of change: The administration instructions for INCB039110 were updated to indicate that the use of strong CYP3A inhibitors/inducers, grapefruit, and pomegranate should be avoided for the duration of the study . The INCB039110 formulation used in the study was also added to this section.

   Rationale for change: To align the Protocol with the most recent Investigator's Brochure and to clarify the formulation used in the study.

8. **Section 5.2.2, Supply, Packaging, and Labeling**

   Description of change: The language describing the product labels of INCB039110 was updated to be accurate for all countries participating in the study.

   Rationale for change: Updated to accommodate the involvement of multiple countries.

9. **Section 9.4.3, Other Analyses**

   Description of change: Revised to clarify the statistical analysis planned for [redacted] analysis.

   Rationale for change: To clarify and ensure consistency in the Protocol regarding the statistical analysis of biomarkers.

10. **Section 10.3, Data Management**

    Description of change: Section was revised to include the information that the database provider's information security controls are aligned with ISO 27002.

    Rationale for change: Clarify database alignment with ISO 27002.

11. **Section 10.4, Data Privacy and Confidentiality of Study Records**

    Description of change: Section was revised to include the process in place in the case of a serious breach in data privacy.

    Rationale for change: To clarify measures that will be implemented in the case of a data security breach.

12. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 2 (11 MAY 2017)

The primary purpose of this amendment is to update several of the inclusion and exclusion criteria, correct inconsistencies with tissue sample requirements, and update restricted medications.

1. **Synopsis; Section 3.1, Subject Inclusion Criteria**

   a. **Description of change:** Inclusion criterion 8e was revised to indicate that aspartate aminotransferase and alanine aminotransferase must be ≤ 2.5 × institutional upper limit of normal (ULN) or ≤ 5 × ULN for subjects with known hepatic metastases.

   Rationale for change: To provide appropriate requirements for subjects with hepatic metastases.

   b. **Description of change:** Inclusion criterion 8f was revised to indicate that subjects can be included in the study if total bilirubin is < 2.0 × ULN if there are no liver metastases or < 3 × ULN in the presence of liver metastases or if bilirubin increase was due to presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia).

   Rationale for change: To provide appropriate requirements for subjects with liver metastases.

2. **Synopsis; Section 3.2, Subject Exclusion Criteria; Section 5.7.1, Restricted Medications**

   Description of change: Exclusion criterion 5 was revised to indicate that subjects can be included in the study if they are receiving corticosteroids at a dose level ≤ 10 mg/day within 7 days of initiating study treatment. Section 5.7.1 was revised to indicate that systemic corticosteroid doses greater than the equivalent of 10 mg prednisolone per day are not permitted from the screening visit through the follow-up visit, except with medical monitor approval.

   Rationale for change: To provide appropriate requirements for subjects receiving corticosteroids.

3. **Synopsis; Section 3.2 Subject Exclusion Criteria**

   a. **Description of change:** Exclusion criterion 6 was revised to remove lenalidomide. Subjects can be included in the study if they received prior or concurrent therapy with lenalidomide.

   Rationale for change: To provide appropriate requirements for eligibility following prior therapy.

   b. **Description of change:** Exclusion criterion 7d was revised to indicate that subjects will be excluded from the study if they received monoclonal antibodies used as anticancer treatment < 4 weeks before starting study treatment.

   Rationale for change: To provide appropriate washout requirements for eligibility following prior therapy with monoclonal antibodies.

   c. **Description of change:** Exclusion criterion 25 was added to indicate that subjects will be excluded from the study if they received prior radiotherapy within 2 weeks

before starting study treatment. A 1-week washout period is permitted for palliative radiation to non–central nervous system disease with medical monitor approval.

Rationale for change: To provide appropriate washout requirements for eligibility following prior radiotherapy.

4. **Section 1.3.1, INCB039110**

   Description of change: Section 1.3.1 was revised to include updated risk language for INCB39110 and to provide recent clinical safety experience and consistency with the INCB39110 Investigator's Brochure.

   Rationale for change: To provide updated INCB039110 data as of December 2016.

5. **Section 5.7.1, Restricted Medications**

   Description of change: Section was revised to indicate that aspirin in doses exceeding 81 mg/day is not permitted during the treatment phase of the study.

   Rationale for change: To provide appropriate and more conservative aspirin dose for concurrent treatment while in the treatment phase of the study.

[redacted]

7. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 1 (27 JUN 2016)

The primary purpose of this amendment is to provide clarifications around [redacted] sample collection requirements, eligibility, and assessment of dose-limiting toxicities.

1. **Synopsis; Section 3.2, Subject Exclusion Criteria**

   Description of change: Exclusion criterion #4 was revised to include autologous stem cell transplant within the previous 3 months.

   Rationale for change: Clarification per external feedback.

   Description of change: Exclusion criteria #7c, 7d, and 7e (receipt of anticancer medications) were revised to indicate c. < 21 days or 5 half-lives (whichever is greater) for all other *cytotoxic* anticancer medications, *d. < 8 weeks for monoclonal antibodies used as anticancer treatment*, and e. < 10 weeks *or 5 half-lives* from completion of any radio- or toxin-immunoconjugates.

   Rationale for change: Clarification per external feedback, as certain monoclonal antibodies have longer half-lives.

2. **Synopsis; Section 4.1.1, Phase 1 (Table 1)**

   Description of change: In Table 1 (Phase 1 Dose Cohorts), column header was revised from "DLTs" to "Subjects With DLT."

   Rationale for change: Clarification that DLT assessments are made based on the number of subjects with a DLT, not the number of DLTs, as 1 subject could have multiple DLTs.

3. **Section 6, Study Assessments (Table 8, Table 9, and Table 10)**

   Description of change: In Table 8 (Schedule of Assessments), a note was added for the 12-lead ECG assessment to indicate that triplicate ECGs will be performed predose and 2 hours (± 15 minutes) after receiving INCB039110 on Day 8.

   Rationale for change: To indicate the timing for Day 8 ECG assessments and to align with the text in Section 7.4.5 (Twelve-Lead Electrocardiograms).

   Description of changes: Table 9 (Laboratory Assessments) was revised to include 2 ambient correlative blood samples (for BTK receptor occupancy and cell population analysis) and 1 frozen correlative blood sample, and to include correlative plasma samples. The optional on-study tumor biopsy sample was revised to span from Day 1 through end of treatment (instead of the Day 28/Q28D column only).

   Rationale for changes: Clarification of sample collection requirements

4. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.