Official Title:	**A Phase 1/2, Open-Label, Dose Escalation, Safety and Tolerability Study of INCB050465 and Iitacitinib in Subjects With Previously Treated B-Cell Malignancies (CITADEL-101)**
NCT Number:	NCT02018861
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Clinical Study Protocol

INCB 50465-101

A Phase 1/2, Open-Label, Dose-Escalation, Safety and Tolerability Study of INCB050465 and INCB039110 in Subjects With Previously Treated B-Cell Malignancies (CITADEL-101)

Product:	**INCB050465 and INCB039110**
IND Number:	**121,474** **124,540 (INCB050465 in combination with INCB039110)**
Phase of Study:	**1/2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol:	**13 DEC 2013**
Amendment (Version) 1:	**03 FEB 2014**
Amendment (Version) 2:	**13 NOV 2014**
Amendment (Version) 3:	**06 MAR 2015**
Amendment (Version) 4:	**12 NOV 2015**
Amendment (Version) 5:	**30 NOV 2015**
Amendment (Version) 6:	**19 MAY 2016**
Amendment (Version) 7:	**28 JUN 2016**
Amendment (Version) 8:	**29 NOV 2016**
Amendment (Version) 9:	**02 AUG 2017**
Amendment (Version) 10:	**07 AUG 2019**

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochures for INCB050465 and INCB039110. I have read the INCB 50465-101 Protocol Amendment 10 (dated 07 AUG 2019) 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: INCB050465 and INCB039110

Title of Study: A Phase 1/2, Open-Label, Dose-Escalation, Safety and Tolerability Study of INCB050465 and INCB039110 in Subjects With Previously Treated B-Cell Malignancies

Protocol Number: INCB 50465-101	**Study Phase:** 1/2

Primary Objective:

- To assess the safety and tolerability of the planned study treatments and select doses for further evaluation.

Secondary Objectives:

- To assess preliminary efficacy by assessing the overall response rate (ORR) of the planned study treatments
- To assess the pharmacokinetics (PK) of planned study treatments and assess the effect of food on the PK of INCB050465 monotherapy

[redacted]

Overall Study Design:

The study consists of 4 parts. Monotherapy dose escalation (Part 1) will determine the maximum tolerated dose (MTD) and the recommended dose(s) of INCB050465 to be evaluated further. The recommended dose(s) will be defined as dose(s) at least equivalent to the pharmacologically active dose (PAD; a dose that produces substantial pharmacologic target inhibition) and no higher than the MTD.

Combination regimen dose escalation (Part 2) will evaluate the combination of INCB050465 and INCB039110 to determine the recommended dose(s) of the combination.

Expansion (Part 3), which consists of 5 cohorts, will evaluate the recommended dose(s) of INCB050465 as monotherapy and in combination with INCB039110. The monotherapy dose-expansion cohorts will evaluate INCB050465 in subjects with B-cell malignancies, indolent lymphoma (eg, follicular and marginal zone lymphoma), diffuse large B-cell lymphoma (DLBCL), and Hodgkin's lymphoma (HL). The combination expansion cohorts will evaluate the chosen combination dose of INCB050465 and INCB039110 in subjects with B-cell malignancies. Note that expansion cohorts for INCB050465 monotherapy may explore more than 1 recommended dose and schedule to obtain long-term safety data on multiple dose levels and schedules.

Part 6 will include a safety assessment of INCB050465 in combination with the chemotherapy regimen R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) in subjects with B-cell malignancies, followed by an expansion cohort in DLBCL.

Timing for the initiation of Part 6 will be determined by the sponsor based on emerging data from Parts 1 and 3 of the study. Note, for purposes of consistency and database completion, this will remain Part 6.

Note: With Amendment 10, Protocol-required procedures have been reduced for ongoing subjects.

Part 1 – Monotherapy Dose Escalation of INCB050465

Dose escalation will be conducted with a 3 + 3 design, with the exception that the first cohort (dose level of 5 mg QD) will be a single subject cohort. There will be an observation period of 21 days before enrollment of the next cohort and administration of the next dose level. For each subsequent dose level, dose escalation will be conducted with a 3 + 3 dose titration design.

- The initial cohort will consist of a single subject (the cohort may include an additional subject to ensure completion of 1 evaluable subject through Day 21); the initial dose will be 5 mg QD.
  - If a Grade 2 or greater adverse event (AE) is observed, the cohort will be expanded to 3 subjects. If the initial cohort is expanded to 3 subjects, the safety assessment will follow the 3 + 3 design. Subsequent cohorts will have increases in the dose of INCB050465 limited to no more than 50%.
  - If a Grade 2 or greater AE is not observed, the dose of INCB050465 will be increased to 10 mg QD (or 5 mg twice daily [BID] depending on PK data) in the subsequent cohort, and dose escalation will be conducted using a 3 + 3 dose titration design. After the 10 mg QD (or 5 mg BID) dose level cohort, subsequent increases in the dose of INCB050465 will be limited to no more than 50%.
  - If the MTD has been exceeded or the PAD has been achieved in the initial cohort, this cohort may be expanded to at least 3 subjects and a lower dose of INCB050465 (eg, 2.5 mg QD) may be explored.
- With the 3 + 3 design, each cohort will enroll a minimum of 3 subjects. If no dose-limiting toxicities (DLTs) are observed in the initial 3 subjects, the next cohort will begin enrollment. If 1 DLT is observed in the first 3 subjects, 3 additional subjects will be enrolled in the cohort. If DLTs occur in > 1 of the first 3 subjects or the total cohort of 6 subjects, then the MTD will be deemed to have been exceeded and the next lower tolerable dose level will be deemed to be the MTD.
- If the dose increment has been 100% and deemed exceeding the MTD, an intermediate dose level may be explored (eg, from 10 mg QD to 7.5 mg QD).

If a dose level is reached that provides a suitable profile of pharmacologic target inhibition before reaching the MTD (PAD), then this dose may be deemed a recommended dose(s) and used to move to Part 3 monotherapy dose-expansion, as well as taken to Part 2 for testing in the combination. Dose escalation of the monotherapy may continue at doses above the PAD until the MTD is reached or dose escalation is stopped.

Part 2 – Dose Escalation With the Combination of INCB050465 and INCB039110

Dose escalation will proceed using a 3 + 3 design with a starting dose of INCB050465 approximately 25% (rounded down to the nearest tablet size combination) below the recommended dose determined in Part 1 followed by escalation of INCB050465 in combination with INCB039110 at 300 mg QD. Escalation of the dose of INCB050465 will continue in combination with INCB039110 300 mg QD until the recommended dose is determined. If the starting dose of INCB050465 cannot be combined safely with INCB039110 300 mg QD, INCB039110 at 200 mg QD will be tested. If that combination is tolerated, escalation of INCB050465 will proceed with INCB039110 200 mg QD. Additional dose de-escalation may occur with INCB050465 if DLTs occur with a causality that can be reasonably assigned to INCB050465. Additional dose escalation or de-escalation of INCB039110 may be considered if supported by emerging safety, PK, [redacted] data in this combination.

Part 3 – Expansion

Expanded cohorts for both monotherapy and combination therapy will be treated with the selected doses of INCB050465 as a single agent, INCB039110 as a single agent, and both agents in combination, to further determine safety, tolerability, efficacy, PK, [redacted] in this population. The subjects with B-cell malignancies in the INCB050465 monotherapy expansion cohort (Part 3 Cohort A) will also be used for an optional evaluation of food effect. Expansion Cohorts A through D may proceed with recommended dose(s) identified in Part 1. Note that expansion cohorts for INCB050465 monotherapy may explore more than 1 recommended dose and schedule to obtain long-term safety data on multiple dose levels and schedules.

When the recommended dose for combination therapy has been determined from Part 2, enrollment will proceed simultaneously for Expansion Cohort E. Details regarding the dose expansion cohorts are described in the table below.

If ≥ 5 subjects in the first 15 subjects of any cohort, cumulatively, (or more than 33% of subjects in cohorts larger than 15 subjects) experience DLTs during Cycle 1, further enrollment to the cohort will be stopped, and a lower dose level may be explored. Based on emerging data, the sponsor may decide on the number of subjects with a specific subtype of an indication to be enrolled into each expansion cohort (eg, non–germinal center B-cell like [non-GCB] or GCB in DLBCL).

Part	Cohort	Population	# of Subjects	Treatment
3	A	B-cell malignancies	15-30	INCB050465 monotherapy
	B	HL	≤ 15	
	C	DLBCL[a]	≤ 15	
	D	Indolent lymphoma	≤ 30	
	E	B-cell malignancies	≤ 15	INCB050465 + INCB039110

[a] Based on emerging data, the sponsor may decide on the number of subjects with a specific subtype of an indication to be enrolled (eg, non-GCB or GCB).

Part 6 – Dose Evaluation and Expansion With the Combination of INCB050465 and R-ICE

Initiation of Part 6 dose evaluation will be dependent on preliminary data from Parts 1 and 3 of the study. Dose evaluation would proceed in subjects with DLBCL using a 3 + 3 design with a starting dose of INCB050465 approximately 25% (rounded down to the nearest tablet size combination) below the recommended dose determined in Part 1 in combination with the chemotherapy components at the following doses in a 21-day cycle for a total of 3 cycles:

- Rituximab 375 mg/m^2 given on Day 1 and Day 2 of Cycle 1, and on Day 1 of Cycles 2 and 3.
- Ifosfamide 5000 mg/m^2 continuous IV infusion over 24 hours on Day 3
  - Mesna should be added to ifosfamide infusion.
- Carboplatin area under the curve (AUC) = 5 mg/mL (maximum dose 800 mg) IV infusion on Day 3
- Etoposide 100 mg/m^2 IV on Days 3 to 5.

If tolerated, the dose of INCB050465 will be escalated to the recommended dose in combination with R-ICE. INCB050465 will be given daily and may be continued until a criterion is met for treatment discontinuation. If the starting dose of INCB050465 cannot be combined safely with R-ICE at the schedule described above, the dose of INCB050465 will be reduced to 25% below the dose first administered in combination with R-ICE. Additional dose de-escalation may occur with INCB050465 if DLTs occur with a causality that can be reasonably assigned to INCB050465. Additional dose de-escalation of INCB050465 may be considered if supported by emerging safety, PK, [redacted] data in this combination. Following the identification of a tolerable dose of the combination of INCB050465 and R-ICE (a dose less than or equal to the MTD), expanded Cohort L will be opened to further evaluate the safety, efficacy, PK, [redacted]:

Part	Cohort	Population	# of Subjects	Treatment
6	L	DLBCL[a]	~15	INCB050465 + R-ICE

[a] Based on emerging data, the sponsor may decide on the number of subjects with a specific subtype of an indication to be enrolled (eg, non-GCB or GCB).

If ≥ 5 subjects in Cohort L experience DLTs during Cycle 1, further enrollment to the cohort will be stopped, and a lower dose level may be explored.

Study Drug, Dosage, and Mode of Administration for INCB050465:

INCB050465 tablets (2.5 mg and 5 mg strengths) will be administered without regard to food (except on Cycle 2 Day 1 in the optional monotherapy expansion cohort [Expansion Cohort A] for food effect) orally QD or BID as determined by emerging PK [redacted] data. Tablet strength of 20 mg may also be used depending on the dose escalation of INCB050465. For QD administration, if a dose is missed by more than 12 hours, the subject should skip the dose and take the next scheduled dose at the usual time. For BID administration, if the morning or evening dose is missed by more than 4 hours, the subject should skip that dose and take next scheduled dose at the usual time. For once-weekly dosing, if the dose is missed by more than 2 days, the subject should skip the dose and take the next scheduled dose. One cycle will be defined as 21 days of treatment (eg, 21 continuous days of QD treatment, 21 days of once-weekly treatment).

The initial dose in Part 1 will be 5 mg QD with dose escalation to 10 mg QD (or 5 mg BID depending on emerging PK [redacted] data) if a Grade 2 or greater AE is not reported. Subsequent cohort expansion will proceed with dose escalation limited to approximately 50% increments in the total daily dose. If a Grade 2 or greater AE is reported in the initial cohort, it will be expanded to 3 subjects, and subsequent cohort expansion will proceed with dose escalation limited to approximately 50% increments in the total daily dose.

INCB050465 should be administered in the clinic on days when PK [redacted] sampling is scheduled.

The sponsor may implement alternative dose regimens such as intermediate doses, BID doses, or alternative formulations, depending on PK, [redacted] and safety results.

Study Drug, Dosage, and Mode of Administration for INCB039110:

INCB039110 tablets (100 mg strength) should be taken on an empty stomach if possible (refrain from food consumption during the period 2 hours before and 1 hour after INCB039110 administration) and can be administered at the same time as INCB050465 where applicable.

In Part 2, INCB050465 will be given in combination with INCB039110. The starting dose of INCB039110 will be 300 mg orally given QD (tablet strength 100 mg) and will de-escalate to 200 mg QD if 300 mg QD cannot be tolerated in combination with INCB050465. Subjects may have dose reductions of INCB039110 during the course of treatment, based upon safety and laboratory assessments; guidelines for dose adjustments and restart are provided in the body of the Protocol.

INCB039110 should be administered in the clinic on Days 1, 8, and 15 of Cycle 1. INCB039110 will be given after all INCB050465 PK sampling is complete on Day 1.

The dose of INCB039110 in combination with INCB050465 selected after Part 2 will be administered in Part 3 Cohort E.

All subjects receiving INBC050465, either as monotherapy or in combination therapy, must receive prophylaxis against *Pneumocystis jirovecii* pneumonia from the start of study treatment to at least 2 to 6 months after the last dose of study drug.

Dosage and Mode of Administration for Components of R-ICE Regimen:

Rituximab, ifosfamide, carboplatin, and etoposide will be administered as open-label commercial product to subjects in Part 6 for 3 cycles.

Rituximab 375 mg/m^2 will be given on Day 1 and Day 2 of Cycle 1 and Day 1 of Cycles 2 and 3. Ifosfamide will be administered via continuous infusion over 24 hours at a dose of 5000 mg/m^2 on Day 3 of each cycle. Carboplatin will be administered on Day 3 as a dose of AUC = 5 mg/mL. Etoposide 100 mg/m^2 will be given IV on Days 3 to 5.

As an alternate to the Protocol-specified dose and dose schedule, R-ICE may be administered according to institutional practice with medical monitor approval.

Duration of Participation:

Subjects will be treated until withdrawn from the study. This may occur due to toxicity, disease progression, refusal to continue, the subject becomes eligible for a stem cell transplant or investigator, sponsor, or regulatory authority decision to terminate the study or institute a clinical hold. Subjects who have evidence of objective clinical benefit, regardless of dose level, may continue to be treated at that dose level.

Subjects enrolled onto INCB050465 monotherapy have the option of crossing over to combination therapy upon progressive disease at the discretion of the investigator if a combination cohort is currently enrolling.

The average duration of participation is expected to be approximately 6 months.

Study Population:

Individuals diagnosed with B-cell malignancies (except Burkitt's lymphoma and precursor B-lymphoblastic leukemia/lymphoma) or HL who have failed or are refractory to available treatments.

Key Inclusion Criteria:

- Aged 18 years or older with lymphoid malignancies of B-cell origin including the following:
  - Indolent / aggressive B-cell non-Hodgkin's lymphoma (NHL)
    - EXCLUDING: Burkitt's lymphoma and precursor B-lymphoblastic leukemia/lymphoma
    - INCLUDING: any non-Hodgkin's B-cell malignancy such as chronic lymphocytic leukemia (CLL) and rare non-Hodgkin's B-cell subtypes such as hairy cell leukemia, Waldenström macroglobulinemia (WM), mantle cell lymphoma, and transformed NHL histologies
  - Hodgkin's lymphoma
- For Part 3 Expansion, Cohort B, subjects must have relapsed/refractory HL.
- For Part 3 Expansion, Cohort C, and Part 6, Cohort L, subjects must have relapsed/refractory DLBCL. Note: DLBCL subtype (eg, GCB) should be known at study entry.
- For Part 3 Expansion, Cohort D, subjects must have relapsed/refractory indolent lymphoma. Indolent lymphoma is defined as histologically confirmed follicular lymphoma Grade 1, 2, or 3a, or histologically confirmed marginal zone lymphoma.
- Life expectancy of 12 weeks or longer.
- Subject must have received ≥ 1 prior treatment regimen(s).
- The subject must not be a candidate for potentially curative therapy, including hematopoietic stem-cell transplantation, except where one of the standard therapy regimen combinations (such as R-ICE) may be used prior to transplantation per standard medical practice.
- For Part 6, subjects must be CD20-positive (assessed at the site) and must be currently eligible to receive rituximab.

Key Exclusion Criteria:

- Received an investigational study drug within 28 days or 5 half-lives (whichever is longer) before receiving the first dose of study drug or with medical monitor approval.
- Received any approved anticancer medications within 21 days or 5 half-lives (whichever is longer) before receiving the first dose of study drug(s) (42 days for nitrosoureas) EXCEPT steroids at ≤ 10 mg prednisone daily (or equivalent), or with medical monitor approval.
- Any unresolved toxicity ≥ Grade 2 from previous anticancer therapy except for stable chronic toxicities (≤ Grade 2) not expected to resolve, such as stable Grade 2 peripheral neurotoxicity.
- History of brain metastasis or spinal cord compression (unless treated, asymptomatic, and stable on most recent imaging and enrolling in expansion cohort), or lymphoma involving the central nervous system (permitted in Expansion Cohorts A and E).

- ECOG performance status of ≥ 3 (≥ 2 during dose escalation).
- Received allogeneic hematopoietic stem-cell transplant within the last 6 months, has active graft-versus-host disease following allogeneic transplant, or is currently receiving immunosuppressive therapy following allogeneic transplant.
- Received autologous hematopoietic stem-cell transplant within the last 3 months.
- Any of the following laboratory results at screening unless directly resulting from the bone marrow infiltration of the underlying malignancy. Screening values must be independent of blood product or hematopoietic growth factor support. All of the following laboratory tests should be performed within 14 days of treatment initiation.

Laboratory Parameter	For Monotherapy Cohorts (No Bone Marrow Involvement)	For Combination Therapy Cohorts (No Bone Marrow Involvement)	Bone Marrow Infiltration of Underlying Malignancy (for Any Cohort)
Hemoglobin	≤ 8.0 g/dL	≤ 9.0 g/dL	≤ 8.0 g/dL
Platelet count	≤ 50×10^9/L	≤ 100×10^9/L	≤ 50×10^9/L
Absolute neutrophil count	≤ 1.0×10^9/L	≤ 1.5×10^9/L	≤ 1.0×10^9/L

- Any of the following laboratory results at screening irrespective of causality:
  - Total bilirubin ≥ 1.2 × upper limit of normal (ULN) (if total bilirubin is ≥ 1.2 × ULN then the direct bilirubin must be < 1.2 × ULN).
  - Alkaline phosphatase ≥ 2.5 × ULN (or ≥ 5 × ULN if bone metastases are present and hepatic parenchymal metastases are absent).
  - Aspartate aminotransferase or alanine aminotransferase ≥ 2.0 × ULN.
  - Creatinine clearance ≤ 50 mL/min measured or calculated by Cockroft-Gault equation or estimated glomerular filtration rate ≤ 50 mL/min/1.73 m^2 using the modification of diet in renal disease formula.
- Known human immunodeficiency virus infection, or hepatitis B virus (HBV) or hepatitis C virus (HCV) viremia or at risk for HBV or HCV reactivation. HBV DNA and testing for HCV RNA must be undetectable. At risk for HBV reactivation is defined as hepatitis B surface antigen positive or anti–hepatitis B core antigen antibody positive. At risk for HCV reactivation is defined as HCV antibody positive.
- Prior treatment with a PI3Kδ inhibitor or pan-PI3K inhibitors (excluded in Part 1 and Part 3 Expansion Cohorts A, B, C, and D only, or with medical monitor approval).
- Radiation treatment within the previous 4 weeks. Palliative radiation treatment to nonindex or bone lesions may be considered with medical monitor approval.
- Prior treatment with a JAK inhibitor (excluded in Part 2 and Part 3 Cohorts E only).
- For Part 2 and Part 3 (Cohort E) subjects only: Any ≤ Grade 2 immune-related AEs from prior immunotherapy must have complete resolution and must have resolved at least 2 weeks before Cycle 1 Day 1. Subjects with a history of a Grade 3 or 4 immune-related AE or any grade ocular immune-related AE from prior immunotherapy are excluded.

Study Schedule/Procedures:

Subjects will have scheduled study visits as follows:

- Screening
- Cycle 1: Day 1, Day 8 (applicable only to certain parts of the study), Day 15
- Subsequent Cycles: Day 1
- End of treatment
- Follow-up

Local laboratory tests:

Study visits will include sample collection for hematology, chemistry, coagulation, and urinalysis testing to be conducted at a local laboratory. Additionally, the screening visit will include hepatitis screening and fertility/pregnancy testing conducted at a local laboratory.

Central laboratory tests:

[redacted] PK samples will be collected at designated visits and shipped to the sponsor or designee for analysis.

Clinical assessments:

Electrocardiograms (ECGs), physical examinations, ECOG performance status, tumor assessments, and other assessments will be performed by the investigative site.

An objective assessment of disease status will be performed at screening, appropriate to the malignancy type. For example:

- Computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET)/CT (as applicable by subtype) for subjects with HL or NHL.
- Bone marrow biopsy and immunophenotyping.

Subsequently, disease measurable by CT, MRI, or PET/CT will be assessed every 9 weeks or at a frequency consistent with the standard of care for the subject's disease. For disease status assessed in bone marrow, on-treatment biopsies will occur only if needed to confirm complete response (CR). Immunophenotyping will be performed after 1 cycle and if confirming CR for subjects with CLL.

Note: With Amendment 10, Protocol-required procedures have been reduced for ongoing subjects.

Primary Endpoint:

- Safety and tolerability of the planned study treatments as assessed by summary of AEs, clinical laboratory assessments, physical examination results, and 12-lead ECGs.

Secondary Endpoints:

- Efficacy as measured by ORR, defined as the sum of subjects achieving a minor response (only among subjects with WM), partial response, very good partial response (only among subjects with WM), and a CR to the planned study treatments based on:
  - International Workshop on Chronic Lymphocytic Leukemia criteria for chronic lymphocytic leukemia.
  - VIth International Workshop on Waldenström Macroglobulinemia response assessment for subjects with WM.
  - Revised response criteria for lymphoma for HL and NHL.
- C_{max}, T_{max}, C_{min}, AUC_{0-t}, and $AUC_{0-\tau}$ at Cycle 1 Day 15 of INCB039110 in combination with INCB050465.
- C_{max}, T_{max}, C_{min}, AUC_{0-t}, and $AUC_{0-\tau}$ of INCB050465 as monotherapy and in combination with INCB039110.

[redacted]

Planned Number of Subjects: Up to approximately 150 subjects
Planned Number of Study Sites: Approximately 15 sites
Principal Coordinating Investigator: [redacted], MD, [redacted].
Estimated Study Duration: 36 months
Statistical Methods: [redacted] The clinical safety data (vital signs, ECGs, routine laboratory tests, physical examinations, and AEs) will be summarized descriptively. The ORR will be estimated with 95% exact confidence interval (CI). [redacted]

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LIST OF ABBREVIATIONS

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

Term	Explanation
ABC	activated B cell
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
anti-HBc	antibody against hepatitis B core antigen
anti-HBsAg	antibody against hepatitis B surface antigen
AST	aspartate aminotransferase
BCR	B-cell receptor
BID	twice daily
BTK	Bruton's tyrosine kinase
CFR	Code of Federal Regulations
CI	confidence interval
CLL	chronic lymphocytic leukemia
CMV	cytomegalovirus
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
[redacted]	[redacted]
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FSH	follicle-stimulating hormone
GCB	germinal center B-cell like
GCP	Good Clinical Practice

Term	Explanation
HBV	hepatitis B virus
HCV	hepatitis C virus
HL	Hodgkin's lymphoma
IB	Investigator's Brochure
IC50	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IL	interleukin
IN	Investigator notification
IRB	institutional review board
ITT	intent to treat
IV	intravenous
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
JAK	Janus kinase
LDH	lactate dehydrogenase
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MR	minor response
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NHL	non-Hodgkin's lymphoma
NOAEL	no-observed-adverse-effect level
ORR	overall response rate
PD	pharmacodynamics
PAD	pharmacologically active dose
PET	positron emission tomography
[redacted]	[redacted]
P-gp	P-glycoprotein
PI3K	phosphatidylinositol 3-kinase
PIP3	phosphatidylinositol-3,4,5-trisphosphate
PJP	*Pneumocystis jirovecii* pneumonia
PK	pharmacokinetics
PP	per Protocol
PR	partial response
QD	once daily

Term	Explanation
R-ICE	rituximab, ifosfamide, carboplatin, and etoposide
RNA	ribonucleic acid
SAE	serious adverse event
SCM	stromal conditioned media
SD	stable disease
SPD	sum of product of diameters
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TYK2	tyrosine kinase 2
ULN	upper limit of normal
VGPR	very good partial response
WM	Waldenström macroglobulinemia

1. INTRODUCTION

1.1. Background

Phosphatidylinositol 3-kinases (PI 3-kinases or PI3Ks) belong to a family of lipid signaling kinases that phosphorylate phosphoinositides at the D3 position of the inositol ring (Cantley 2002). PI3Ks are divided into 3 classes (Class I, II, and III) according to their structure, regulation, and substrate specificity. Class I PI3Ks, which include PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ, are dual-specificity lipid and protein kinases that catalyze the phosphorylation of phosphatidylinositol-4,5-bisphosphate, giving rise to phosphatidylinositol-3,4,5-trisphosphate (PIP3). PIP3 functions as a second messenger that controls a number of cellular processes, including growth, survival, adhesion, and migration. The recognition that aberrant signal transduction occurs in malignant B-lymphocytes via the PI3K pathways resulting in disease progression has led to a focus on agents that modulate these signaling pathways.

INCB039110 is an inhibitor of the Janus kinase (JAK) family of protein tyrosine kinases with selectivity for JAK1. Janus kinases play an important role in signal transduction following cytokine and growth factor binding to their receptors. Aberrant production of cytokines and growth factors has been associated with neoplasms, therefore inhibition of this pathway may be beneficial in the treatment of these conditions.

Incyte is proposing to study INCB050465, an inhibitor of PI3Kδ, as monotherapy and in combination with INCB039110 for the treatment of relapsed/refractory diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma (HL), and other lymphoid malignancies, including indolent lymphoma. In addition, INCB050465 will be studied in combination with agents considered as part of the standard of care in this population, including bendamustine, rituximab, and the chemotherapy regimen R-ICE (rituximab, ifosfamide, carboplatin, and etoposide).

1.1.1. PI3Kδ in Oncology

The B-cell receptor (BCR) is present on both normal and most malignant B cells. Engagement of the BCR provides important survival signals, and interruption of the B-cell survival signal can lead to B-cell death (Kraus et al 2004). Elegant studies performed with siRNA to inhibit BCR expression have shown that constitutive signaling by BCR is critical for the survival and proliferation of human B-cell lymphomas (Gururajan et al 2006). The primary role of BCR signaling in these cells seems to be activation of spleen tyrosine kinase (Benschop and Chambier 1999), which in turn leads to several downstream events that promote cell survival, including activation of Bruton's tyrosine kinase (BTK), PI3K, and protein kinase B (Akt). Aberrant activation of PI3Kδ specifically has been associated with increased malignant B-cell proliferation and survival. Although no mutations have been identified in PI3Kδ, it has been shown to be oncogenic in cell culture (Kang et al 2005). Consistent overexpression of PI3Kδ has also been observed in acute myeloblastic leukemia, and inhibitors of PI3Kδ can prevent the growth of leukemic cells *in vitro*. Phosphatidylinositol 3-kinase δ was also shown to be expressed in Hodgkin's and Reed-Sternberg cells. Inhibition of PI3Kδ with idelalisib blocked phosphorylation of Akt and induced apoptosis in the HL cell line (Meadows et al 2012). The role of the PI3K pathway in BCR signaling is beginning to be clarified for non-Hodgkin's

lymphoma (NHL) subtypes. It has been shown that the activated B-cell (ABC) subtype of DLBCL through chronic active BCR signaling engages PI3K, augmenting anti-apoptotic nuclear factor-κB (NF-κB) signaling and survival signals and that inhibition of the PI3K/Akt pathway synergizes with NF-κB inhibition in killing ABC DLBCL cell lines *in vitro* (Monti et al 2005). BCR signaling has also been shown to activate the PI3K/Akt pathway in Burkitt's lymphoma and in other types of NHL.

Several PI3Kδ selective inhibitors, including idelalisib, INCB040093, and duvelisib (formerly IPI-145), have been advanced into the clinic for the treatment of hematological malignancies. The orally available PI3Kδ selective inhibitor, idelalisib, was shown to specifically inhibit the growth of cell lines representative of B-cell malignancies and multiple myeloma in preclinical models (Kahl et al 2014). Based on this and other clinical studies, idelalisib was approved by the FDA as monotherapy for patients with relapsed follicular lymphoma and small lymphocytic lymphoma and as combination therapy with rituximab for patients with chronic lymphocytic lymphoma. In addition, the approval of ibrutinib, the BTK inhibitor for the treatment of subjects with relapsed or refractory mantle cell lymphoma (MCL), demonstrated a 66% overall response rate (ORR), with 17% of subjects achieving a complete response (CR). The median response duration was 17.5 months. Responses to ibrutinib increase with longer time on study treatment (Wang et al 2012). Ibrutinib and idelalisib have demonstrated a high ORR and durable remissions in most subjects with chronic lymphocytic leukemia (CLL) and many subjects with MCL and indolent NHL. These data suggest the importance of the BCR pathway for survival in these diseases. [redacted]

1.1.2. JAK1 Inhibition in Oncology and Lymphoma

Aberrant activation of JAKs, through production of cytokines and growth factors, has been associated with increased malignant cell proliferation and survival in a number of tumor types. Janus kinases activate a number of downstream pathways implicated in the proliferation and survival of malignant cells including the signal transducers and activators of transcription (STATs), a family of important latent transcription factors. In DLBCL, JAK pathway activation occurs through both autocrine and paracrine mechanisms. In the tumor cells, BCR signaling leads to increased interleukin (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).

Of clinical relevance, levels of serum IL-10 and IL-6, which signal through the JAKs, have been found to be elevated in subjects with DLBCL compared with normal controls (Gupta et al 2012). Further, subjects 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 2 (TYK2) and to play a dominant role in mediating the signaling of a number of inflammatory cytokines including IL-6 and IL-10.

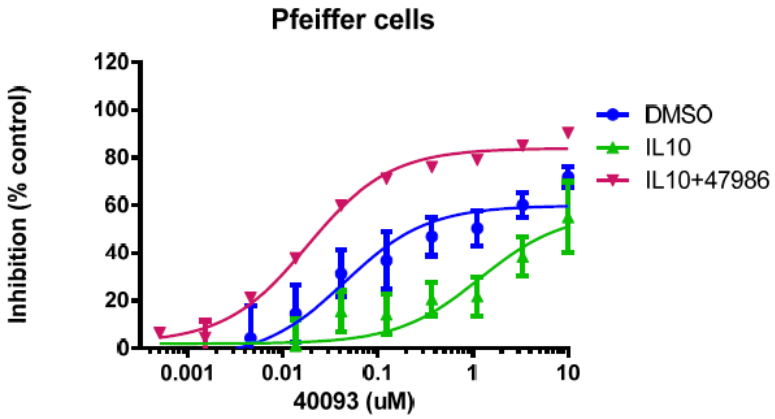
1.1.3. Targeting JAK1 in DLBCL and Rationale for Combining PI3Kδ and JAK Inhibition

[redacted] Phase 1 studies with the PI3Kδ inhibitor idelalisib and the PI3Kδ γ inhibitor duvelisib demonstrated no responses in DLBCL, although 4 of 10 subjects treated with duvelisib showed stable disease (Flinn et al 2014, Horowitz et al 2013). Similarly, early studies with the JAK2 inhibitor SB1518 showed 0 out of 3 responses in relapsed/refractory DLBCL (Younes et al 2012).

To test this hypothesis preclinically, a panel of DLBCL cell lines was grown in conditions to activate the JAK pathway. These cells lines were exposed to the PI3Kδ inhibitor INCB040093, either alone or in combination with a panel of compounds that were shown to selectively inhibit JAK1 to examine their effects on cell proliferation and signaling. The JAK pathway was not constitutively activated when grown in the absence of stromal conditioned media (SCM), IL-6, or IL-10 as assessed by the levels of phosphorylated STAT3 (pSTAT3), a direct downstream target of JAK proteins. In addition, IL-6 or SCM, which contains predominantly IL-6, IL-8, and G-CSF, failed to activate the pathway in the majority of cell lines. In contrast, IL-10 activated the JAK/STAT pathway in the majority of cell lines tested, consistent with previous reports (Gupta et al 2012).

To test the effects of IL-10 on cell growth and sensitivity to BCR pathway inhibition, the Pfeiffer cell line was used as a model system of DLBCL. Pfeiffer cells are of the germinal center B-cell like (GCB) subtype of DLBCL, have been shown to express PI3Kδ, are sensitive to PI3Kδ inhibition, and activate the JAK/STAT pathway in response to multiple cytokines as shown above. Pfeiffer cells were treated for 3 days with various concentrations of a novel, selective inhibitor of the PI3Kδ kinase isoform, INCB040093, in the presence or absence of IL-10 and 1 μM of a JAK1 inhibitor (INCB047986), and cell growth was measured using an ATP readout. As shown in Figure 1, the presence of IL-10 shifted the potency of INCB040093 by approximately 10-fold (half-maximal inhibitory concentration [IC_{50}] = 0.67 μM, - IL-10; IC_{50} = 6.36 μM, + IL-10). Addition of the JAK1 inhibitor reversed this effect so that the combination was approximately 50-fold more potent. In this system, the JAK1 inhibitor compound alone had no effect (IC_{50} > 1 μM).

Figure 1: Synergistic Anti-Proliferative Activity of PI3Kδ and JAK Inhibition



This model also showed that inhibition of PI3Kδ together with JAK signaling led to increased apoptosis whereas neither agent alone had a significant effect.

Finally, to assess the effects on downstream signaling pathways, Pfeiffer cells were treated with INCB040093 +/- a JAK1 selective inhibitor and then stimulated with IL-10. In this model, the combination of both compounds was required to block both pathways.

Similar effects have been observed in other cell lines, including HBL-1 cells, which are of the ABC subtype of DLBCL, and with other JAK1 selective compounds.

In summary, these data demonstrate that the presence of IL-10, a cytokine shown to be elevated in DLBCL subjects and to correlate with decreased survival, reduces the potency of a PI3Kδ inhibitor 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. Consistent with these findings, the early clinical data from studies of monotherapy BCR and JAK pathway inhibitors suggest only limited evidence of activity in relapsed/refractory DLBCL. [redacted]

Clinically the combination of PI3Kδ inhibition and JAK1 inhibition has been tested in Study INCB 40093-102. Preliminary activity has been observed in subjects with NHL and HL receiving INCB040093 monotherapy and combination treatment (data on file).

1.1.4. Rationale for Combining INCB050465 With the Chemotherapy Regimen R-ICE in DLBCL

The combination chemotherapy regimen ICE (ifosfamide, carboplatin, and etoposide) was developed for use in relapsed aggressive NHL to induce a response while minimizing treatment toxicity with the goal of stem cell transplant, which may be a curative treatment. Kewalramani et al (2004) explored whether adding rituximab to the ICE regimen would improve the CRR and therefore improve outcomes from stem cell transplant. The CRRs of subjects with DLBCL who received R-ICE was 53%, which was an improvement from the 27% CRR historically observed (Kewalramani et al 2004). The CORAL trial studied the salvage chemotherapy regimens R-ICE

and R-DHAP. No difference was seen between these 2 regimens, and the ORR and CRR for the R-ICE regimen was 63% and 24%, respectively (Gisselbrecht et al 2010). As R-ICE has become frequently used as salvage chemotherapy in this population, additional research has been performed to add noncytotoxic agents. Lenalidomide was added to R-ICE in a study by Feldman et al (2014) with promising response rates in DLBCL subjects (60% CRR) after first relapse or with primary refractory disease. Therefore, there is interest in combining the targeted agent INCB050465 with this salvage chemotherapy regimen to hopefully improve response rates seen with R-ICE alone and allow more subjects to become eligible for a potentially curative stem cell transplant.

1.2. Overview of INCB050465

Refer to the INCB050465 IB for current information on INCB050465.

1.2.1. Pharmacology of INCB050465

INCB050465 represents a novel, potent, and selective inhibitor of the Class IA PI3K enzymes, with selectivity for the delta isoform, which is proposed for development for treatment of hematological malignancies. Because aberrant activation of PI3Kδ has been associated with increased malignant B-cell proliferation and survival, its inhibition may be therapeutic for the treatment of such conditions. INCB050465 potently inhibits the PI3Kδ kinase (IC_{50} = 1.0 ± 0.5 nM), with ~ 20,000-fold selectivity for the other PI3K family members and > 300-fold selectivity against a broad panel of 192 other kinases. INCB050465 also showed no significant cross-reactivity (defined as > 50% inhibition of specific binding) when screened *in vitro* at 0.1 and 1.0 µM against approximately 70 receptors, ion channels, transporters, and enzymes. Moreover, INCB050465 is potent (IC_{50} values of ≤ 10 nM) in cell-based assays relevant to the pathogenesis of B-cell malignancies, such as PI3Kδ-mediated signaling and growth of human B-cell lines. This effect is not due to general cytotoxicity, because 10 µM INCB050465 had no significant effect on the growth of nonlymphoid cell lines. Compared to inhibition of B-cell proliferation, INCB050465 is similarly potent in blocking helper T-cell differentiation but is > 100 times less potent in assays that measure effects on human T-cell and natural killer cell proliferation or monocyte function. These data suggest that the impact of INCB050465 on the human immune system will largely be restricted to B-cell and helper T-cell differentiation. Similar results have been reported with the PI3Kδ inhibitor idelalisib (CAL-101, GS-1101) and duvelisib, although INCB050465 is significantly more potent in all of the assays examined (refer to the INCB050465 IB), suggesting that it may have more marked effects in the clinic due to more significant target inhibition throughout the dosing interval. *In vivo*, the effects of oral INCB050465 were evaluated in mice in the Pfeiffer human tumor xenograft model of B-cell malignancy. In the Pfeiffer model of NHL, INCB050465 administration inhibited PI3Kδ signaling and tumor growth as a single agent in a dose-dependent manner.

In a core battery of safety pharmacology studies, a single oral dose of INCB050465 produced no adverse effects on central nervous system or respiratory function in the rat, or cardiovascular function in telemeterized conscious dogs. The IC_{50} for inhibition of human ether-à-go-go-related gene potassium current in stably transfected HEK293 cells was 188.0 µM (Hill coefficient = 1.0), which is > 8000-fold higher than the projected steady-state C_{max} (0.023 µM unbound) after a 10 mg human dose.

INCB050465 had no effect on central nervous system function in rats; the no-observed-effect level was 100 mg/kg, the highest dose tested.

Lower respiratory frequency and/or lower minute volume were observed in rats after administration of 30 and 100 mg/kg INCB050465. These changes were not considered adverse based on relatively small magnitude (≤ 20% below controls) and short duration of the effects (resolved within 1-3 hours postdose). The no-observed-adverse-effect level (NOAEL) for effects on respiratory function was 100 mg/kg, the highest dose tested.

Slightly higher pulse pressure occurred in male dogs after administration of 15 mg/kg INCB050465 but was not considered to be adverse based on small magnitude (< 10% above controls) and short duration (resolved within 6 hours postdose). The NOAEL for effects on cardiovascular function in this study was 15 mg/kg, the highest dose tested.

The NOAELs for respiratory and cardiovascular function are well above the intended starting dose for this study and the anticipated therapeutic dose in humans. Therefore, together with the planned monitoring of vital signs, the risk to subjects is expected to be low.

[redacted]

[redacted]

1.2.3. Potential Risks of INCB050465

1.2.3.1. Potential Risks of INCB050465 Based on Preclinical Safety

Based on findings in repeat-dose toxicity studies of INCB050465 in rats and dogs, lymphoid depletion and resulting immunosuppression represents a potential risk for humans.

[redacted]

INCB050465 was not mutagenic or genotoxic in a bacterial reverse mutation assay, *in vitro* chromosomal aberrations study in human peripheral blood lymphocytes, or rat *in vivo* micronucleus assay.

1.2.3.2. Potential Risks of PI3Kδ Inhibition Based on Other Agents in Class

Idelalisib was approved by the FDA in July 2014 for treatment of relapsed/refractory follicular lymphoma and relapsed small lymphocytic lymphoma and for treatment of CLL in combination with rituximab. Severe toxicities seen with the use of this agent include hepatotoxicity (fatal or serious occurring in 14%), fatal and/or serious diarrhea or colitis (14%), intestinal perforation, *Pneumocystis jirovecii* pneumonia (PJP), and pneumonitis. Hepatotoxicity, colitis, and pneumonitis have also been reported in subjects treated with the PI3Kδ-inhibitor INCB040093. Subjects will be monitored closely for the development of these conditions and will have

treatment held and dose reduced as appropriate. A standard PJP prophylaxis regimen will be required for all subjects receiving INCB050465 (see Section 5.8.2) either as monotherapy or in combination.

Based on experience with idelalisib and INCB040093, hepatotoxicity is a risk with this class of agents. Preclinically, hepatotoxicity with INCB050465 was only seen at plasma exposures > 65-fold higher than the projected clinical exposure at 10 mg QD. The pharmacophore of INCB050465 is different from both idelalisib and INCB040093, which are similar to each other. Other PI3Kδ inhibitors with a different pharmacophore have not shown hepatotoxicity in early studies (Savona et al 2013).

1.2.4. Clinical Summary of INCB050465

As of 02 SEP 2016, data were available for 46 subjects who received INCB050465 administered orally at QD doses of 5 mg (n = 1), 10 mg (n = 3), 15 mg (n = 3), 20 mg (n = 15), 30 mg (n = 20), and 45 mg (n = 4). The median duration of treatment was 104 days. Adverse events observed in ≥ 20% of subjects were nausea, diarrhea, vomiting, neutropenia, fatigue, hypokalemia, and fever. No ≥ Grade 3 treatment-related AEs were reported in ≥ 10% of subjects. Serious AEs (SAEs) that occurred in ≥ 2 subjects included colitis (n = 3), diarrhea (n = 3), and pyrexia, pneumonia, dehydration, exfoliative dermatitis, and hypotension (n = 2 each). Eleven of the 46 subjects (24%) discontinued study treatment due to the following AEs: colitis, diarrhea, pneumonitis, rash, exfoliative dermatitis, psoriasis, neutropenia, pneumonia, and hypercalcemia. All but 1 of these events occurred after the 9-week disease assessment. No liver function test abnormalities > Grade 1 were reported while subjects were receiving study treatment. No dose-limiting toxicities were identified, and the maximum tolerated dose was not reached.

As of 02 SEP 2016, 20 objective responses as reported by investigators were observed at doses ≥ 10 mg QD in 41 evaluable subjects. Objective responses were observed in 5 subjects with DLBCL (n = 14), 6 subjects with follicular lymphoma (n = 6), 4 subjects with marginal zone lymphoma (n = 4); 3 subjects with mantle cell lymphoma (n = 4), 1 subject with Hodgkin lymphoma (n = 8), and 1 subject with CLL (n = 5). The objective response rate in evaluable subjects with NHL (n = 28) was 64%. Among the 18 objective responses observed in subjects with NHL, 17 (94%) were observed by the time of the first disease assessment. Pharmacokinetics analysis showed the T_{max} is 0.5 to 1 hour, the terminal half-life is approximately 8 to 12 hours, and exposure appeared to be dose-proportional between 5 mg QD and 45 mg QD at steady state. The pharmacodynamic analyses demonstrated robust and sustained pathway inhibition at all dose levels tested. Refer to the INCB050465 IB for further details.

Food effect was assessed in Part 3 Cohort A. Although coadministration of INCB050465 with a high-fat meal decreased 42% of dose-normalized C_{max} compared with the fasted state, it had mild effect on dose-normalized AUC (10% decrease) based on data from 12 subjects. The geometric mean ratio of AUC (fed vs fasted) and 90% confidence interval (CI) are 0.90 (0.68, 1.18), and INCB050465 may be administered without regard to meals (refer to the INCB050465 IB).

1.3. Overview of INCB039110

INCB039110 is an inhibitor of the JAK family of protein tyrosine kinases with selectivity for JAK1. Refer to the INCB039110 IB for current information on INCB039110.

1.3.1. Pharmacology Summary

INCB039110 represents a novel, potent, and selective inhibitor of the JAK family of protein kinases with selectivity for JAK1. Because JAKs serve to transduce extracellular signals from a number of cytokines and growth factors that are upregulated and thought to be involved in the pathogenesis of cancer cachexia and cancer progression, inhibition of their signaling may be therapeutic for the treatment of such conditions. JAK1 has been shown to cooperate with other JAKs to mediate the signaling of a number of inflammatory cytokines. 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. It does not significantly inhibit (< 30% inhibition) a broad panel of approximately 60 other kinases. 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 also inhibits the growth of the cytokine-dependent cell line INA-6. This effect is not due to general cytotoxicity. 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. In contrast, INCB039110 shows less inhibition in cell-based assays dependent on JAK2 (eg, thrombopoietin or prolactin-stimulated STAT phosphorylation) with IC_{50} values of approximately 1 μM or greater, suggesting that INCB039110 is JAK2-sparing in cells. In *in vivo* models of JAK-dependent malignancy, INCB039110 impedes subcutaneous tumor growth of INA-6 cells expressing wild-type JAKs when administered by continuous infusion, achieving plasma concentrations well below those required to inhibit JAK2.

INCB039110 did not demonstrate off-target activity nor was it active in a panel of approximately 60 non-JAK family kinases. Adverse findings in rat safety pharmacology studies, noted only at 1000 mg/kg, included a transient decrease in locomotor activity, a slight decrease in body temperature, and suppression of respiratory function. The IC_{50} for inhibition of the human-ether-a-go-go related gene channel was determined to be 65.3 μM. In a cardiovascular evaluation of INCB039110 in dogs, ≥ 60 mg/kg produced a potentially adverse lowering of arterial pressure, compensatory higher heart rate, and an increase in core body temperature. The NOAEL for the cardiovascular study was 30 mg/kg for both sexes.

In summary, pharmacological data obtained in both *in vitro* and *in vivo* model systems support the potential utility of orally administered INCB039110 in the treatment of cancer and associated cachexia.

1.3.2. Drug Disposition Summary

The preclinical PK of INCB039110 was evaluated in rats, dogs, and monkeys. INCB039110 exhibits low-to-moderate systemic clearance, a low volume of distribution, and a short terminal elimination half-life. The oral bioavailability was low in monkeys (< 20%), moderate in dogs (43%), and high in rats (82%). INCB039110 is mainly cleared by metabolism and is a substrate

of CYP3A4 but does not significantly inhibit the activity of the major CYP enzymes, suggesting that the potential for INCB039110 to cause clinical drug-drug interactions through CYP inhibition is low.

1.3.3. Nonclinical Toxicology Summary

The toxicologic profile of INCB039110 was characterized in single- and multiple-dose oral studies of up to 3 months in duration in rats and dogs.

[redacted] Pharmacology-related clinical pathology and anatomical alterations in multiple-dose rat studies included a reversible lowering of white blood cell count, primarily because of a lower circulating lymphocyte count, and reversible lymphoid depletion in lymphoid tissues and reduction in bone marrow cellularity. [redacted]

In repeat-dose studies in dogs, gastrointestinal inflammation was determined to be the DLT. [redacted] Clinical and histological evidence of JAK inhibition included decreased reticulocyte and/or lymphocyte counts, lymphoid depletion of lymphoid tissues, and/or reduction of bone marrow cellularity. [redacted]

INCB039110 was not genotoxic in the bacterial mutagenicity assay, the *in vitro* chromosome aberration assay in human lymphocytes, or the *in vivo* micronucleus assay in rats.

INCB039110 also did not demonstrate off-target activity nor was it active in a panel of approximately 60 non-JAK family kinases. Additional information on pharmacology, drug disposition, and nonclinical toxicology is available in the INCB039110 IB.

1.3.4. Clinical Summary of INCB039110

INCB039110 has been administered as monotherapy in clinical studies to healthy subjects and subjects with rheumatoid arthritis, chronic plaque psoriasis, and myelofibrosis. INCB039110 is being administered in combination with gemcitabine and *nab*-paclitaxel to subjects with advanced solid tumors in an ongoing study (INCB 39110-116). INCB039110 has also been administered in combination with INCB040093 in subjects with B-cell malignancies. Additional information is available in the INCB039110 IB.

1.3.5. Potential Risks of INCB039110

INCB039110 is known to affect the immune system; therefore an increased incidence of infections could occur. Strict clinical monitoring is indicated to identify and treat infections in study subjects should they occur, and a standard PJP prophylaxis regimen will be required for all

subjects receiving combination treatment with INCB050465 and INCB039110. Refer to the INCB039110 IB for further details.

INCB039110 has been shown to affect hematologic parameters. In a study of INCB039110 in subjects with myelofibrosis, anemia, and thrombocytopenia occurred in > 30% of the 87 subjects enrolled (refer to the INCB039110 IB). Subjects will have hematologic parameters closely monitored during this study.

Hyperlipidemia has previously been noted in subjects receiving JAK inhibitors (Kontzias et al 2012). Ten subjects (18.2%) were observed to have an increase in blood cholesterol greater than the upper limit of normal (ULN) after receiving combination treatment with INCB040093 and INCB039110 while enrolled in the INCB 40093-102 study. In the oncology population, monitoring and treatment of hyperlipidemia should be tailored as appropriate to individual subject characteristics, while exercising caution on study with cholesterol-lowering agents such as HMG-CoA reductase inhibitors that are associated with liver function abnormalities.

1.4. Overview of the Combination of INCB050465 and INCB039110

1.4.1. Nonclinical Pharmacokinetics and Drug Metabolism of the Combination

Both INCB050465 and INCB039110 are metabolized predominately by CYP3A4, but neither appears to be an inducer or inhibitor of CYP3A4 at clinically relevant concentrations. Also, INCB050465 is a P-gp inhibitor, while INCB039110 is a weak P-gp inhibitor. While both INCB050465 and INCB039110 are P-gp substrates, their efflux transport via P-gp is likely to be saturated at the doses proposed for clinical evaluation and thus further inhibition of P-gp should have no effect on INCB050465 or INCB039110 absorption. Therefore, a drug interaction between these compounds is unlikely in the setting of the proposed clinical study. Pharmacokinetics will be evaluated in this study to evaluate potential effect of INCB040093 on INCB039110 PK, with evaluation of INCB050465 PK in combination with INCB039110 compared with INCB050465 monotherapy.

1.4.2. Clinical Summary of Combination Treatment with INCB050465 and INCB039110

As of 02 SEP 2016, 3 subjects had received the INCB050465 and INCB039110 combination therapy. No SAEs were reported for these 3 subjects, and no AEs led to study treatment discontinuation. Non–treatment-related AEs of spinal cord compression and pain led to study treatment interruption in 1 subject. Among these 3 subjects, 2 partial responses (PRs) were reported in Hodgkin lymphoma and mantle cell lymphoma (n = 1 each).

1.4.3. Clinical Summary of Combination Treatment With PI3Kδ Inhibition (INCB040093) and JAK Inhibition (INCB039110)

Study INCB 40093-102 is an ongoing, open-label, dose escalation, safety and tolerability study of the PI3Kδ inhibitor INCB040093 as monotherapy and in combination with INCB039110. As of 13 DEC 2015, 67 subjects had received treatment with the combination. No evidence of any impact on the PK of the INCB040093 from coadministration of INCB039110 was apparent (INCB040093 IB).

1.4.4. Potential Risks of Combination Therapy of INCB050465 and INCB039110

Incyte is proposing to study 2 investigational drugs INCB050465 and INCB039110 in combination for the treatment of relapsed/refractory B-cell malignancies. The principle toxicity of inhibiting both PI3Kδ and JAK pathways is expected to be reversible effects on immune function. Combined inhibition may adversely affect both B cell and T cell immune function with resultant increased risk of a variety of infections. Subjects will be closely monitored for bacterial infections, viral reactivation, and opportunistic infections, and treatment will be interrupted for infections that can be easily managed with antibiotic therapy and discontinued for infections that are serious or require prolonged antibiotic therapy. Study INCB 40093-102 is combining another PI3Kδ inhibitor, INCB040093 with INCB039110. The most frequently reported SAE in this study was PJP (5 subjects, 7.5%). The use of a standard Pneumocystis prophylaxis regimen is now mandated in subjects receiving combination therapy with INCB040093 and INCB039110. Since implementing this requirement, no additional cases of PJP have been observed in subjects receiving prophylaxis. Therefore, all subjects receiving combination therapy with INCB050465 and INCB039110 in this study must receive PJP prophylaxis. Viral reactivation (ie, shingles) was observed in subjects receiving INCB040093 monotherapy and combination therapy with INCB039110.

Effects on white blood cell, red blood cell, and platelet counts could result from JAK inhibition and result in infections, anemia, or thrombocytopenia requiring transfusions, which may be more likely in subjects with NHL that is refractory to recent therapy or transplantation.

INCB039110 has been shown to affect hematologic parameters; however, cytopenias are not expected to be worse with combination PI3Kδ and JAK inhibition. In the study combining INCB039110 with INCB040093 as of 13 DEC 2015, anemia has occurred in 14.9% of subjects receiving combination therapy. Neutropenia has occurred in 28.4% of subjects receiving combination therapy; thrombocytopenia was reported in 31.3% of subjects receiving combination therapy (refer to the INCB039110 IB).

Combined inhibition is not expected to increase the risk of hepatic toxicity and liver function testing will be monitored regularly. Any hepatic toxicity is expected to be reversible. These potential risks are considered acceptable in a population with relapsed/refractory lymphoid malignancies.

1.5. Overview of Standard Therapies

1.5.1. Rituximab

1.5.1.1. Pharmacology Summary

Rituximab (RITUXAN®) is a CD-20 cytolytic antibody that has been approved in the United States for the treatment of NHL, CLL, rheumatoid arthritis, and granulomatosis with polyangiitis and microscopic polyangiitis (Rituxan 2014). Rituximab is used both as monotherapy and in combination with other agents in NHL.

1.5.1.2. Potential Risks

Boxed warnings for rituximab include fatal infusion reactions, severe mucocutaneous reactions, hepatitis B reactivations, and progressive multifocal leukoencephalopathy (PML). Subjects

should be premedicated and will be monitored closely during rituximab infusion, and medical treatment should be performed as necessary for infusion reactions as described in the package insert. Mucocutaneous reactions observed in patients receiving rituximab include Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. Subjects who experience a severe mucocutaneous reaction should be discontinued. Hepatitis B virus reactivation can occur in patients receiving drugs classified as anti-CD20 antibodies. Subjects in this Protocol are screened for evidence of prior hepatitis B infection, which will mitigate the risk. Progressive multifocal leukoencephalopathy should be considered in any subject with new-onset neurologic manifestations. Evaluation should be performed as described in the package insert.

Additional risks and precautions according to the package insert include tumor lysis syndrome infection (bacterial, fungal, and viral), cardiac events including arrhythmias, renal toxicities, and bowel obstruction and perforation. Adverse reactions experienced by ≥ 30% of NHL subjects receiving monotherapy treatment with rituximab include fever, chills, infection, and lymphopenia. A complete discussion of risks associated with rituximab can be found at http://dailymed.nlm.nih.gov/.

1.5.2. R-ICE

Rituximab is described in detail in Section 1.5.1.

1.5.2.1. Ifosfamide

1.5.2.1.1. Pharmacology Summary

Ifosfamide is an alkylating agent that crosslinks DNA and results in cell death. Ifosfamide requires breakdown of the parent compound to metabolites in the liver before it becomes active.

1.5.2.1.2. Potential Risks

The DLTs of ifosfamide are myelosuppression and urotoxicity. Dose fractionation, vigorous hydration, and a protector such as mesna can significantly reduce the incidence of hematuria. Subjects enrolled into this study will receive mesna with the infusion of ifosfamide to protect against urotoxicity. Adverse reactions occurring in > 10% of patients receiving ifosfamide include alopecia, nausea, vomiting, hematuria, gross hematuria, and CNS toxicity (IFEX 2015). A complete discussion of risks associated with ifosfamide can be found at http://dailymed.nlm.nih.gov/.

1.5.2.2. Carboplatin

1.5.2.2.1. Pharmacology Summary

Carboplatin is a platinum compound that produced interstrand DNA cross-links in a manner that is cell-cycle nonspecific. Carboplatin is generally felt to be less toxic than the earlier platinum agent, cisplatin.

1.5.2.2.2. Potential Risks

Labeled warnings for carboplatin include bone marrow suppression, vomiting, and anaphylactic-like reactions. Carboplatin should be administered under the supervision of a qualified physician for appropriate management of therapy and complications. Bone marrow suppression is the DLT, and blood counts will be monitored before each dose of carboplatin in this study. Supportive care including transfusions and G-CSF may be administered per the site's institutional policy. Vomiting may be severe and the use of antiemetics prior to dose administration may reduce this risk and is allowed on study (Carboplatin 2015). A complete discussion of risks associated with ifosfamide can be found at http://dailymed.nlm.nih.gov/.

1.5.2.3. Etoposide

1.5.2.3.1. Pharmacology Summary

Etoposide is a topoisomerase II inhibitor that causes DNA strand breaks, which works to kill dividing cells by inhibiting DNA synthesis in the S phase.

1.5.2.3.2. Potential Risks

Etoposide is to be administered under the supervision of a qualified physician. Etoposide can cause severe myelosuppression with resulting infection or bleeding. Blood counts will be monitored closely per Protocol, and dose administration should be held if necessary to allow counts to sufficiently recover. Other toxicities to be aware of include nausea and vomiting, which is generally mild to moderate and can be controlled with antiemetic therapy, hypotension following infusion, anaphylactic-like allergic reactions, and alopecia (Toposar 1998). A complete discussion of risks associated with ifosfamide can be found at http://dailymed.nlm.nih.gov/.

1.6. Study Rationale

Lymphoid malignancies are the seventh leading cause of death in the United States, and their incidence has been increasing, with an estimated incidence of approximately 79,190 cases in 2012, with 70,130 cases of NHL and 9,060 cases of HL (Siegel et al 2012). Among these malignancies, the majority are derived from B-lymphocytes. Although several therapeutic approaches such as combination chemotherapy, external beam irradiation, hematopoietic stem-cell transplantation, and molecular targeted agents, including B-lymphocyte–specific antibodies used alone or conjugated with radiopharmaceuticals or toxins, have significantly improved the prognosis of these patients, the annual mortality rate remains high, with 20,130 patients dying from these malignancies in 2012.

The recognition that aberrant signal transduction occurs in malignant B-lymphocytes via the PI3K pathways, resulting in disease progression, has led to a focus on agents that modulate these signaling pathways. On 13 NOV 2013, the FDA granted accelerated approval to ibrutinib for the treatment of patients with MCL who have received at least 1 prior therapy. The approval was based on the results of a multicenter, single-group study demonstrating a 66% ORR (95% CI: 56.2, 74.5). Idelalisib (a PI3K inhibitor) has been recently approved for the treatment of CLL in combination with rituximab, and as monotherapy for follicular lymphoma and small lymphocytic lymphoma. The Phase 3 dose of idelalisib (150 mg twice daily [BID]) was shown to have a C_{min}

of approximately 1 μM (Flinn et al 2014) and is therefore not expected to cover the IC_{90} for inhibiting Akt phosphorylation in whole blood (IC_{90} = 1.8 μM; refer to the INCB050465 IB) throughout the treatment interval. As described in Section 1.2.1, INCB050465 is significantly more potent in all of the assays examined (refer to the INCB050465 IB), and based on its projected PK would be expected to cover > IC_{90} at C_{min}, suggesting that it may have more marked effects than idelalisib in the clinic.

Incyte is proposing to study 2 new investigational drugs (INCB050465 and INCB039110) in combination for the treatment of relapsed/refractory B-cell malignancies. Both the JAK/STAT and PI3K pathways may contribute to driving tumor growth and survival in DLBCL as described above, 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.

In addition, Incyte is proposing to study INCB050465 in combination with a standard therapy in subjects with B-cell malignancies. The therapy proposed is routinely used in subjects with DLBCL, and the addition of a PI3Kδ inhibitor may improve the activity of this therapy with limited additive toxicity from this targeted agent.

1.7. Justification of Route, Dose Regimen, and Treatment Period

1.7.1. INCB050465

INCB050465 is being developed as a new investigational drug for oral administration. Oral drug administration is generally the most convenient and cost-effective method of drug delivery for medications requiring continuous exposure. INCB050465 tablets will be administered orally (QD, BID, or intermittently), as determined by emerging PK, pharmacodynamic (PD), and safety data. INCB039110 will be administered orally QD. One cycle of INCB050465 monotherapy will be defined as 21 days of treatment (eg, 21 continuous days of QD treatment, 21 days of once-weekly treatment); treatment for subjects in this study will consist of repeating 21-day cycles. Combination regimens with standard agents may have different cycle lengths to accommodate standard regimens.

Preclinical data suggest that the whole blood IC_{90} for INCB050465 is approximately 77 nM. Based on the preclinical PK profile of INCB050465, the clinical dose estimated to achieve IC_{90} at trough is approximately 10 mg every 24 hours; unbound C_{max} after this dose is projected to be approximately 0.023 μM, and unbound AUC is projected to be 0.37 μM·h. Thus, it is reasonable to expect that full pharmacologic inhibition can be achieved with INCB050465 at a feasible clinical dose.

Based on preclinical toxicology, the highest nonseverely toxic dose in the most sensitive species is 1 mg/kg per day in the dog. This produces a human equivalent dose of 32 mg, and one-sixth of this dose indicates the estimated safe starting dose in oncology as 5.4 mg QD. The NOAEL in the female dogs from the 28-day study (the most sensitive species) is 34.2 μM·h (1.20 μM·h unbound; refer to the INCB050465 IB). The dose-related toxicities included changes in the lymphoid system consistent with pharmacological PI3Kδ inhibition (decrease in B-lymphocyte populations) by INCB050465. The increase in incidence and/or severity of inflammatory changes was considered to be secondary to expected immunosuppression following PI3Kδ inhibition as inflammatory changes were noted in multiple tissues, secondary to putative loss in

antibody protection. Upon cessation of administration of INCB050465, all of the inflammatory changes were reversed, with no histologic evidence of residual damage to the affected tissues.

Based on this information, the initial dose will be 5 mg QD. Based on preclinical models, INCB50465 has an IC_{50} of approximately 9 nM and IC_{90} of 77 nM. The estimated plasma concentration in humans for a 5 mg QD dose exceeds the IC_{50} for 24 hours and the IC_{90} for approximately 12 hours.

Dose escalation will be conducted with a 3 + 3 design, with the exception that the first cohort (dose level of 5 mg QD) will be a single subject cohort. For each subsequent dose level, dose escalation will be conducted with a 3 + 3 dose titration design. The initial cohort will consist of a single subject; and the initial dose will be 5 mg QD. If a Grade 2 or greater AE is observed in the initial single subject cohort, the cohort will be expanded to 3 subjects. Subsequent cohorts will have increases in the dose of INCB050465 limited to no more than 50%. If a Grade 2 or greater AE is not observed, the dose of INCB050465 will be increased to 10 mg QD (or 5 mg BID depending on PK data) in the subsequent cohort, and dose escalation will be conducted using a 3 + 3 dose titration design. After the 10 mg QD (or 5 mg BID) dose level cohort, subsequent increases in the dose of INCB050465 will be limited to no more than 50%. Doses less than 5 mg QD may also be explored.

Expansion cohorts of 15 to 30 subjects will be treated with the selected dose, either the maximum tolerated dose (MTD) or the PAD of INCB050465, as a single agent to further determine safety, tolerability, efficacy, PK, and PD in this population. Part 3 Cohort A will study INCB050465 in subjects with refractory B-cell malignancies. The subjects in Part 3 Cohort A will also be used for an optional evaluation of food effect. (Note that the food-effect study may be terminated based on emerging data before completing enrollment of Cohort A.) If the dose selected for the expansion cohort was the MTD in the dose-escalation part of the study, on Cycle 1 Day 15 and Cycle 2 Day 1, the dose administered ONLY for these 2 doses will be 1 dose level below the MTD (if the PAD is selected for the expansion cohort, there will be no alteration to the doses on Cycle 1 Day 15 or Cycle 2 Day 1).

The sponsor may implement alternative regimens such as intermediate doses, intermittent dosing schedules, BID doses, or alternative formulations, depending on PK, PD, and safety results. Based on emerging efficacy and safety data from study INCB 50465-101 as of 02 SEP 2016, 1 recommended regimen that will be evaluated in Parts 2, 3, and 6 is 20 mg QD for 9 weeks, followed by 20 mg once weekly. The 20 mg QD dose provides exposure that is approximately 2-fold greater than the IC_{90} (based on an *in vitro* whole-blood assay) at trough. Furthermore, all 11 NHL subjects who received 20 mg QD have achieved an objective response. However, 24% of all 46 subjects in study INCB 50465-101 as of 02 SEP 2016 discontinued study treatment due to an AE. Among the subjects with an objective response (n = 20), 7 (35%) discontinued study treatment due to an AE. Consequently, after administration of 20 mg QD for 9 weeks, the dosing regimen will be reduced to 20 mg once weekly. This once-weekly regimen is proposed to maintain response while providing time off from pathway inhibition, which may reduce the frequency of AEs. Pharmacodynamic data from INCB 50465-101 showed that a single dose of 20 mg exhibited maximal inhibition of AKT in an *ex vivo* pharmacodynamic assay, and PK modeling suggests that 20 mg once weekly will 1) achieve maximal inhibition equivalent to approximately $10 \times IC_{90}$, 2) exceed the IC_{90} for approximately 36 hours, and 3) have minimal to no inhibition for approximately half the dosing interval. This once-weekly regimen is similar to

that of another PI3K inhibitor (copanlisib), which is administered intravenously on Days 1, 8, and 15 of a 28-day cycle, and which achieved 7 objective responses in 9 subjects with non-Hodgkin lymphoma (Patnaik et al 2016). Among the 51 subjects who received study drug, 4 discontinued treatment due to an AE. There were 2 events of Grade 3 noninfectious pneumonitis, 1 event of Grade 3 diarrhea, and no events of colitis.

1.7.2. INCB039110

For Part 2, the initial starting dose for the other investigational agent, INCB039110, to be administered in combination with INCB050465, will be 300 mg QD. Pharmacokinetic and safety data from prior studies in nononcologic indications support QD administration of INCB039110 in this study. In the combination Phase 1 study INCB 40093-102, the MTD of INCB039110 was not reached when given at doses up to 600 mg QD in combination with another PI3Kδ inhibitor, INCB040093. However, based on an increased incidence of thrombocytopenia and neutropenia in subjects receiving a dose of 600 mg QD, the dose of INCB039110 was reduced to 400 mg in combination with INCB040093 for use in the expansion cohort. Although this combination is tolerated, emerging PK and PD data indicate that inhibition of the JAK/STAT pathway at this dose exceeds the target (approximately 50%-60%). As the probability of some AEs, such as cytopenias and infections, may correspond to the level of inhibition of INCB039110, 300 mg QD is considered an appropriate dose level for chronic administration and will be the starting dose of INCB039110 in combination with INCB050465. Alternative dose regimen strategies may be explored based on the aggregate safety, PK, PD, and clinical activity data. For instance, if INCB039110 300 mg QD is not tolerated, then INCB039110 200 mg QD will be combined with INCB050465 (see Section 1.3.4).

1.7.3. R-ICE in Combination With INCB050465

In Part 6 of the study, INCB050465 will be administered at a starting dose approximately 25% (rounded down to the nearest tablet size combination) below the recommended dose determined in Part 1 in combination with the R-ICE chemotherapy regimen at the following doses for three 21-day cycles:

- Rituximab 375 mg/m^2 given on Day 1 and Day 2 of Cycle 1 and on Day 1 of Cycles 2 and 3.
- Ifosfamide 5000 mg/m^2 continuous IV infusion over 24 hours on Day 3.
  - Mesna should be added to ifosfamide infusion.
- Carboplatin area under the curve (AUC) = 5 mg/mL (maximum dose 800 mg) IV infusion on Day 3.
- Etoposide 100 mg/m^2 IV on Days 3 to 5.

Note: As an alternative to the Protocol-specified dose and schedule, R-ICE may also be administered per institutional practice with medical monitor approval.

If tolerated, the dose of INCB050465 will be escalated to the recommended dose in combination with R-ICE. The selected doses of the components of R-ICE have been administered to subjects with DLBCL in a number of clinical studies (Zelenetz et al 2003, Kewalramani et al 2004, Gisselbrecht 2010, Feldman et al 2014, Matasar et al 2013). The 21-day cycle was used by

Gisselbrecht et al (2010) in the CORAL study as well as by Matasar et al (2013) and was chosen here to allow subjects the maximum time to recover from any toxicities including myelosuppression. INCB050465 may be administered continuously or intermittently.

2. STUDY OBJECTIVES AND PURPOSE

2.1. Primary Objective

- To assess the safety and tolerability of the planned study treatments and select doses for further evaluation.

2.2. Secondary Objectives

- To assess preliminary efficacy by assessing the ORR of the planned study treatments.
- To assess the PK of the planned study treatments and assess the effect of food on the PK of INCB050465 monotherapy.

3. SUBJECT ELIGIBILITY

3.1. Study Population

The study will include individuals diagnosed with B-cell malignancies (excluding Burkitt's lymphoma and precursor B-lymphoblastic leukemia/lymphoma) who have failed or are refractory to available treatments.

3.2. Subject Inclusion Criteria

The following criteria are required for inclusion in the study:

1. Aged 18 years or older with lymphoid malignancies of B-cell origin including the following:
   a. Indolent/aggressive B-cell NHL
      – EXCLUDING: Burkitt's lymphoma and precursor B-lymphoblastic leukemia/lymphoma
      – INCLUDING: any non-Hodgkin's B-cell malignancy such as CLL and rare non-Hodgkin's B-cell subtypes such as hairy cell leukemia, Waldenström macroglobulinemia (WM), MCL, and transformed NHL histologies.
   b. Hodgkin's lymphoma
2. For Part 3, Expansion Cohort B, subjects must have relapsed/refractory HL.
3. For Part 3, Expansion Cohort C, and Part 6, Cohort L, subjects must have relapsed/refractory DLBCL. Note: DLBCL subtype (eg, GCB) should be known at study entry.
4. Life expectancy of ≥ 12 weeks.
5. Subject must have received ≥ 1 prior treatment regimen(s).
6. The subject must not be a candidate for potentially curative therapy, including hematopoietic stem-cell transplantation, except where one of the standard therapy regimen combinations (such as R-ICE) may be used prior to transplantation per standard medical practice.
7. Women who are either postmenopausal for at least 1 year with documented follicle-stimulating hormone (FSH) > 30 IU/L or are surgically sterile for at least 3 months, or who agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through follow-up if of childbearing potential. (Note: Permitted methods that are at least 99% effective in preventing pregnancy [Appendix A] should be communicated to the subjects and their understanding confirmed). For all women, the pregnancy test result must be negative at screening.
8. Men must agree to take appropriate precautions to avoid fathering a child (with at least 99% certainty) from screening through follow-up. (Note: Permitted methods that are at least 99% effective in preventing pregnancy [Appendix A] should be communicated to the subjects and their understanding confirmed).

9. Ability to comprehend and willingness to sign an informed consent form (ICF).
10. For Part 3 Expansion, Cohort D, subjects must have relapsed/refractory indolent lymphoma. Indolent lymphoma is defined as histologically confirmed follicular lymphoma Grade 1, 2, or 3a, or histologically confirmed marginal zone lymphoma.
11. For Part 6, subjects must be CD20-positive (assessed at the site) and must be currently eligible to receive rituximab.

3.3. Subject Exclusion Criteria

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

1. Pregnant or breastfeeding women.
2. Received an investigational study drug within 28 days or 5 half-lives (whichever is longer) before receiving the first dose of study drug or with medical monitor approval.
3. Received any approved anticancer medications within 21 days or 5 half-lives (whichever is longer) before receiving the first dose of study drug(s) (42 days for nitrosoureas) EXCEPT steroids at ≤ 10 mg prednisone daily (or equivalent), or with medical monitor approval.
4. Any unresolved toxicity ≥ Grade 2 from previous anticancer therapy except for stable chronic toxicities (≤ Grade 2) not expected to resolve, such as stable Grade 2 peripheral neurotoxicity.
5. History of brain metastases or spinal cord compression (unless treated, asymptomatic, and stable on most recent imaging and enrolling in an expansion cohort), or lymphoma involving the central nervous system (permitted in Expansion Cohorts A and E).
6. ECOG performance status of ≥ 3 (≥ 2 during dose escalation) (Appendix C).
7. Received allogeneic hematopoietic stem-cell transplant within the last 6 months, or has active graft-versus-host disease following allogeneic transplant, or is currently receiving immunosuppressive therapy following allogeneic transplant.
8. Received autologous hematopoietic stem-cell transplant within the last 3 months.
9. Laboratory parameters:
   a. Any of the following laboratory values at screening, unless directly resulting from the bone marrow infiltration of the underlying malignancy. Screening values must be independent of blood product or hematopoietic growth factor support. All of the following laboratory tests should be performed within 14 days of treatment initiation.

Laboratory Parameter	For Monotherapy Cohorts (No Bone Marrow Involvement)	For Combination Therapy Cohorts (No Bone Marrow Involvement)	Bone Marrow Infiltration of the Underlying Malignancy (for Any Cohort)
Hemoglobin	≤ 8.0 g/dL	≤ 9.0 g/dL	≤ 8.0 g/dL
Platelet count	≤ 50 × 10^9/L	≤ 100 × 10^9/L	≤ 50 × 10^9/L
Absolute neutrophil count (ANC)	≤ 1.0 × 10^9/L	≤ 1.5 × 10^9/L	≤ 1.0 × 10^9/L

b. Any of the following laboratory results at screening irrespective of causality:
   - Total bilirubin ≥ 1.2 × ULN (if total bilirubin is ≥ 1.2 × ULN then direct bilirubin must by < 1.2 × ULN)
   - Alkaline phosphatase (ALP) ≥ 2.5 × ULN (or ≥ 5 × ULN if bone metastases are present and hepatic parenchymal metastases are absent)
   - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 2.0 × ULN.
   - Creatinine clearance ≤ 50 mL/min measured or calculated by Cockroft-Gault equation or estimated glomerular filtration rate ≤ 50 mL/min/1.73 m^2 using the modification of diet in renal disease formula.

10. Current or recent history (< 30 days before screening and/or < 45 days before study drug administration) of a clinically meaningful bacterial, fungal, parasitic, or mycobacterial infection.
11. Current, clinically active viral infection.
12. Known human immunodeficiency virus infection, or hepatitis B virus (HBV) or hepatitis C virus (HCV) viremia or at risk for HBV or HCV reactivation. Hepatitis B virus DNA and testing for HCV RNA must be undetectable. At risk for HBV reactivation is defined as HBSAg positive or anti-HBc antibody positive. At risk for HCV reactivation is defined as HCV antibody positive.
13. History or presence of an abnormal electrocardiogram (ECG) that, in the investigator's opinion, is clinically meaningful. Screening QTc interval > 450 milliseconds is excluded (corrected by Fridericia). In the event that a single QTc is > 450 milliseconds, the subject may enroll if the average QTc for the 3 ECGs is < 450 milliseconds. For subjects with an intraventricular conduction delay (QRS interval > 120 milliseconds), the JTc interval may be used in place of the QTc with sponsor approval. The JTc must be < 340 milliseconds if JTc is used in place of the QTc. Subjects with left bundle branch block are excluded.
14. Clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study drug administration, New York Heart Association Class III or IV congestive heart failure, and arrhythmia requiring therapy.
15. History of major stomach or intestinal surgery, or malabsorption syndrome (eg, Crohn's disease or chronic pancreatitis) that would, by clinical judgment, affect the absorption of study drug.
16. Use of any potent CYP3A4 inhibitor (Appendix G) or inducer within 14 days or 5 half-lives (whichever is longer) of the first dose of study drug.
17. Prior treatment with a PI3Kδ inhibitor or pan-PI3K inhibitors (excluded in Part 1 and Part 3 Expansion Cohorts A, B, C, and D only, or with medical monitor approval).
18. Radiation treatment within the previous 4 weeks. Palliative radiation treatment to nonindex or bone lesions may be considered with medical monitor approval.

19. Subjects who, in the opinion of the investigator, are unable or unlikely to comply with the administration schedule and study evaluations.
20. Any serious medical condition that, in the opinion of the investigator, would pose a significant risk to the subject or interfere with the interpretation of study data.
21. Prior treatment with a JAK inhibitor (excluded in Part 2 and Part 3 Cohort E only).
22. Known hypersensitivity to any of the active substances or any of their excipients, including INCB050465 or INCB039110.
23. For Part 2 and Part 3 (Cohort E) subjects only: Any ≤ Grade 2 immune-related AEs from prior immunotherapy must have complete resolution and must have resolved at least 2 weeks before Cycle 1 Day 1. Subjects with a history of a Grade 3 or 4 immune-related AE or any grade ocular immune-related AE from prior immunotherapy are excluded.

4. INVESTIGATIONAL PLAN

4.1. Study Drugs

The investigational drugs in this study include INCB050465 and INCB039110. All study subjects will receive these study drugs in an open-label manner, as oral, self-administered agents. INCB050465 will be administered in all parts of the study. INCB039110 will only be administered in Part 2 and Part 3 Expansion Cohorts E.

4.2. Overall Study Design

The study consists of 4 parts. The overall study design is shown in Figure 2. Monotherapy dose escalation (Part 1) will determine recommended dose(s) to be explored further. The recommended dose(s) will be defined as dose(s) at least equivalent to the PAD (a dose that produced substantial pharmacologic target inhibition) and no higher than the MTD.

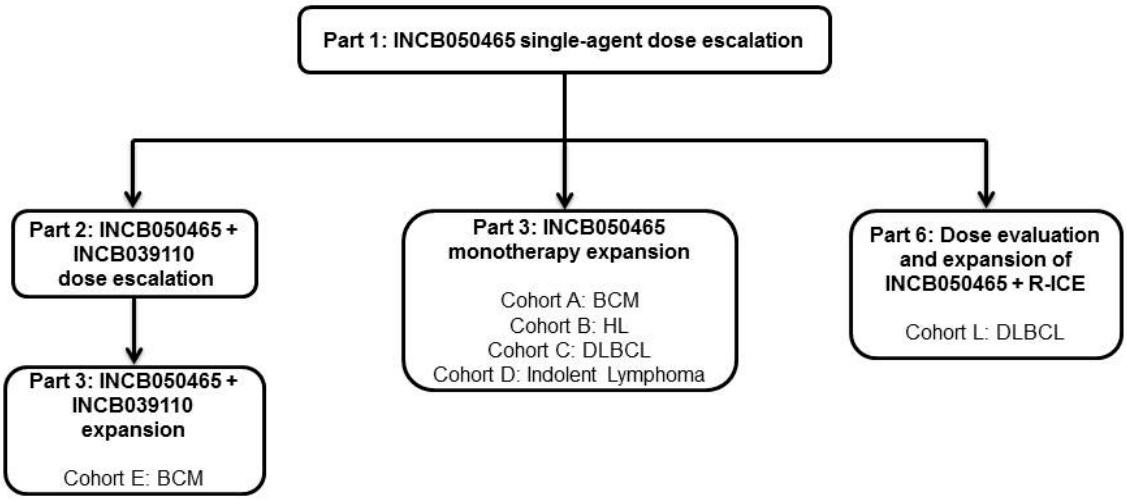
Part 2 will evaluate the combination of INCB050465 and INCB039110 to determine the recommended dose(s) of the combination.

Expansion (Part 3), which consists of 5 cohorts, will evaluate the recommended dose(s) of INCB050465 as monotherapy and in combination with INCB039110. The monotherapy dose-expansion cohorts will evaluate INCB050465 in subjects with B-cell malignancies, indolent lymphoma, DLBCL, and HL. Note that expansion cohorts for INCB050465 monotherapy may explore more than 1 recommended dose and schedule to obtain long-term safety data on multiple dose levels and schedules. The combination expansion cohorts will evaluate the chosen combination dose of INCB050465 and INCB039110 in subjects with B-cell malignancies.

Part 6 will include a safety assessment of INCB050465 in combination with the chemotherapy regimen R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) in subjects with B-cell malignancies, followed by an expansion cohort in DLBCL. Timing for the initiation of Part 6 will be determined by the sponsor based on emerging data from Parts 1 and 3 of the study. Note, for purposes of consistency and database completion, this will remain Part 6.

Note: With Amendment 10, Protocol-required procedures have been reduced for ongoing subjects.

Figure 2: Study Design



4.2.1. Part 1 – Monotherapy Dose Escalation of INCB050465

Dose escalation will be conducted with a 3 + 3 design, with the exception that the first cohort (dose level of 5 mg QD) will be a single subject cohort. There will be an observation period of 21 days before enrollment of the next cohort and administration of the next dose level. Subjects who receive at least 17 days of INCB050465 at the level assigned to that cohort will be considered evaluable for determining tolerability of dose. Subjects enrolling but not meeting these criteria may be replaced in order to fill the cohort.

- The initial cohort will consist of a single subject (the cohort may include an additional subject to ensure completion of 1 evaluable subject through Day 21); the initial dose will be 5 mg QD.
  - If a Grade 2 or greater AE is observed, the cohort will be expanded to 3 subjects. If the initial cohort is expanded to 3 subjects, the safety assessment will follow the 3 + 3 design. Subsequent cohorts will have increases in the dose of INCB050465 limited to no more than 50%.
  - If a Grade 2 or greater AE is not observed, the dose of INCB050465 will be increased to 10 mg QD (or 5 mg BID depending on PK data) in the subsequent cohort, and dose escalation will be conducted using a 3 + 3 dose titration design. After the 10 mg QD (or 5 mg BID) dose level cohort, subsequent increases in the dose of INCB050465 will be limited to no more than 50%.
  - If the MTD has been exceeded or the PAD has been achieved in the initial cohort, this cohort may be expanded to at least 3 subjects and a lower dose of INCB050465 (eg, 2.5 mg QD) may be explored.

- With the 3 + 3 design, each cohort will enroll a minimum of 3 subjects. If no DLTs are observed in the initial 3 subjects, the next cohort will begin enrollment. If 1 DLT is observed in the first 3 subjects, 3 additional subjects will be enrolled in the cohort. If DLTs occur in > 1 of the first 3 subjects or the total cohort of 6 subjects, then the MTD will be deemed to have been exceeded and the next lower tolerable dose level will be deemed to be the MTD.
- If the dose increment has been 100% and deemed exceeding the MTD, an intermediate dose level may be explored (eg, from 10 mg QD to 7.5 mg QD).
- Dose increases will occur using 1 of 2 options: 1) increasing the number of tablets taken at each QD administration, or 2) increasing the dose frequency to BID. For example, based on safety in a cohort receiving 5 mg QD, the total daily dose might be increased 2-fold in the next cohort by using a 5 mg BID regimen or by using a 10 mg QD regimen, depending on emerging PK data. The dose regimen will be designed to maintain a suitable peak-to-trough ratio and minimize accumulation.

If a dose level is reached that provides a suitable profile of pharmacologic target inhibition (PAD) before reaching the MTD, then this dose may be deemed a recommended dose(s) and used to move to Part 3 monotherapy dose expansion, as well as taken to Part 2 for testing in the combination. Dose escalation of the monotherapy may continue at doses above the PAD until the MTD is reached or dose escalation is stopped. In the event that the half-life suggests alternative schedules will provide optimum target inhibition, additional cohorts may be evaluated (eg, BID administration).

4.2.2. Part 2 – Dose Escalation With the Combination of INCB0504065 and INCB039110

Dose escalation will proceed using a 3 + 3 design with a starting dose of INCB050465 approximately 25% (rounded down to the nearest tablet size combination) below the recommended dose determined in Part 1 followed by escalation of INCB050465 in combination with INCB039110 300 mg QD. Escalation of the dose of INCB050465 will continue in combination with INCB039110 300 mg QD until the recommended dose is determined. If the starting dose of INCB050465 cannot be combined safely with INCB039110 300 mg QD, INCB039110 at 200 mg QD will be tested. If that combination is tolerated, escalation of INCB050465 will proceed with INCB039110 200 mg QD. Additional dose de-escalation may occur with INCB050465 if DLTs occur with a causality that can be reasonably assigned to INCB050465. Additional dose escalation or de-escalation of INCB039110 and/or INCB050465 may be considered if supported by emerging safety, PK, [redacted] data in this combination.

4.2.3. Part 3 – Expansion

Monotherapy Expansion Cohorts A, B, C, and D will open when the recommended dose(s) is chosen from Part 1, independently from Part 2. Recommended dose(s) will be at least equivalent to the PAD and no higher than the MTD (or the highest dose tested). Expansion Cohort A will enroll subjects with B-cell malignancies, Cohort B will enroll subjects with HL, Cohort C will enroll subjects with DLBCL, and Cohort D will enroll subjects with indolent lymphoma. Note that expansion cohorts for INCB050465 monotherapy may explore more than 1 recommended dose and schedule to obtain long-term safety data on multiple dose levels and schedules.

When the recommended dose for Phase 2 combination therapy has been determined from Part 2, enrollment will proceed simultaneously for Expansion Cohort E, which will enroll subjects with B-cell malignancies. Details regarding the dose expansion cohorts are described in Table 1.

If ≥ 5 subjects in the first 15 subjects of any cohort, cumulatively, (or more than 33% of subjects in cohorts larger than 15 subjects) experience DLTs during Cycle 1, then further enrollment to the cohort will be stopped, and a lower dose level may be explored. Based on emerging data, the sponsor may decide on the number of subjects with a specific subtype of an indication to be enrolled into each expansion cohort (eg, non-GCB or GCB in DLBCL) or specific tumor types to be enrolled in Cohorts A and E (eg, mantle cell lymphoma).

Table 1: Part 3 Expansion Cohorts

Part	Cohort	Population	# of Subjects	Treatment
3	A	B-cell malignancies	15-30	INCB050465 monotherapy
	B	HL	≤ 15	
	C	DLBCL[a]	≤ 15	
	D	Indolent lymphoma	≤ 30	
	E	B-cell malignancies	≤ 15	INCB050465 + INCB039110

[a] Based on emerging data, the sponsor may decide on the number of subjects with a specific subtype of an indication to be enrolled (eg, non-GCB or GCB).

4.2.4. Part 6 – Dose Evaluation and Expansion With the Combination of INCB050465 and R-ICE

Initiation of Part 6 dose evaluation will be dependent on preliminary data from Parts 1 and 3 of the study. Dose evaluation would proceed in subjects with DLBCL using a 3 + 3 design with a starting dose of INCB050465 approximately 25% (rounded down to the nearest tablet size combination) below the recommended dose determined in Part 1 in combination with the chemotherapy components at the following doses in a 21-day cycle for a total of 3 cycles:

- Rituximab 375 mg/m^2 given on Day 1 and Day 2 of Cycle 1, and on Day 1 of Cycles 2 and 3.
- Ifosfamide 5000 mg/m^2 continuous IV infusion over 24 hours on Day 3.
  - Mesna should be added to ifosfamide infusion.
- Carboplatin AUC = 5 mg/mL (maximum dose 800 mg) IV infusion on Day 3.
- Etoposide 100 mg/m^2 IV on Days 3 to 5.

Note: As an alternative to the Protocol-specified dose and schedule, R-ICE may be administered according to institutional practice with medical monitor approval.

If tolerated, the dose of INCB050465 will be escalated to the recommended dose in combination with R-ICE. INCB050465 will be given daily or intermittently and may be continued until a criterion is met for treatment discontinuation. If the starting dose of INCB050465 cannot be combined safely with R-ICE at the schedule described above, the dose of INCB050465 will be reduced to 25% below the dose first administered in combination with R-ICE. Additional dose de-escalation may occur with INCB050465 if DLTs occur with a causality that can be reasonably

assigned to INCB050465. Additional dose de-escalation of INCB050465 and intermittent schedules may be considered if supported by emerging safety, PK, [redacted] data in this combination. Following the identification of a tolerable dose of the combination of INCB050465 and R-ICE (a dose less than or equal to the MTD), expanded Cohort L will be opened to further evaluate the safety, efficacy, PK, [redacted] as described in Table 2.

Table 2: Part 6 Expansion Cohort

Part	Cohort	Population	# of Subjects	Treatment
6	L	DLBCL[a]	~15	INCB050465 + R-ICE

[a] Based on emerging data, the sponsor may decide on the number of subjects with a specific subtype of an indication to be enrolled (eg, non-GCB or GCB).

If ≥ 5 subjects in Cohort L experience DLTs during Cycle 1, further enrollment to the cohort will be stopped, and a lower dose level may be explored.

4.2.5. Crossover to Combination Therapy After Monotherapy Treatment

For subjects who discontinue INCB050465 monotherapy for a reason described in Section 5.7.1, the investigator may feel that the best option for the subject is to enroll in a combination therapy offered in this Protocol. Prior use of a PI3K inhibitor is not prohibited per the inclusion/exclusion criteria for combination cohorts. Therefore, subjects who discontinue INCB050465 may be allowed to cross over to combination therapy. In these cases, the subject must meet the eligibility criteria for the cohort they will cross over to, and the sponsor must approve the crossover.

4.3. Study Endpoints

4.3.1. Primary Endpoint

- Safety and tolerability of the planned study treatments as assessed by summary of AEs, clinical laboratory assessments, physical examination results, and 12-lead ECGs.

4.3.2. Secondary Endpoints

- Efficacy as measured by ORR, defined as the sum of subjects achieving a minor response (MR, only among subjects with WM), PR, very good partial response (VGPR, only among subjects with WM), and CR to the planned study treatments based on:
  - International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria for CLL (Hallek et al 2008, Cheson et al 2012).
  - VIth International Workshop on Waldenström macroglobulinemia response assessment for subjects with Waldenström macroglobulinemia (Owen et al 2013)
  - Revised response criteria for lymphoma for HL and NHL (Cheson et al 2014).
- C_{max}, T_{max}, C_{min}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\tau}$ at Cycle 1 Day 15 of INCB039110 in combination with INCB050465.

- C_{max}, T_{max}, C_{min}, AUC_{0-t}, and $AUC_{0-\tau}$ of INCB050465 as monotherapy and in combination with INCB039110.

[redacted]

4.4. Measures Taken to Avoid Bias

This is an open-label study; no comparisons will be made between subjects or against historical controls. Measurements of safety and efficacy are objective measurements and only comparisons to pretreatment conditions will be made.

4.5. Number of Subjects

Up to approximately 150 subjects are planned for enrollment at approximately 15 sites. The number of subjects may vary due to the number of cohorts required to determine the tolerated or recommended dose.

4.6. Study Termination

If a PAD (eg, trough plasma concentration of $\geq IC_{90}$) cannot be reached in a cohort with less than one-third of the subjects experiencing a DLT as monotherapy or combination therapy, the study will be terminated.

The sponsor may terminate the study electively or if required by regulatory decision. If the study is terminated prematurely, the sponsor will notify the investigators, the institutional review boards and independent ethics committees (IRBs/IECs), and regulatory bodies of the decision and the reason for termination of the study.

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 IRB or IEC in writing of the study's completion or early termination, and send a copy of the notification to the sponsor or sponsor's designee and retain 1 copy for the site study regulatory file.

5. TREATMENT OF SUBJECTS

5.1. Treatment Groups and Administration of Study Drug

5.1.1. INCB050465 Monotherapy

Subjects will self-administer INCB050465 using an oral daily QD, BID, or intermittent regimen, as instructed by the investigator. INCB050465 should be administered in the clinic on Days 1, 8, and 15 of Cycle 1. Subjects enrolled in Part 3 Cohort A participating in the food-effect study will also have INCB050465 administered in clinic on Cycle 2 Day 1. INCB050465 will be taken orally with water without regard to food. If QD or once-weekly intervals are used, INCB050465 should be taken at approximately the same time each day.

5.1.2. INCB050465 and INCB039110 Combination Therapy

In Part 2 and Part 3 (Cohort E), subjects will concomitantly receive INCB039110 (administered QD) with INCB050465. INCB050465 and INCB039110 should be administered in the clinic on Days 1, 8, and 15 of Cycle 1. INCB039110 will be given after all INCB050465 PK sampling is complete on Day 1. At other designated visits where INCB039110 is administered at the site, it can be given with INCB050465. For either drug, if a dose of is missed, the subject should skip the dose and take the next scheduled dose at the usual time.

If BID doses are used, INCB050465 should be taken morning and evening, at approximately 12-hour intervals. For QD administration, if a dose is missed by more than 12 hours, the subject should skip the dose and take the next scheduled dose at the usual time. For BID administration, if the morning or evening dose is missed by more than 4 hours, the subject should skip that dose and take next scheduled dose at the usual time. For once-weekly dosing, if the dose is missed by more than 2 days, the subject should skip the dose and take the next scheduled dose.

One cycle will be defined as 21 days of treatment; subjects will receive treatment in continuous cycles. All subjects will attend study visits weekly during the first cycle, and at the beginning of each 21-day cycle thereafter.

5.1.3. INCB050465 and R-ICE Combination Therapy

Subjects enrolled into Part 6 of the study will receive INCB050465 continuously in 21-day cycles. INCB050465 should be administered in the clinic on Days 1 and 15 of Cycle 1. The R-ICE chemotherapy regimen will be administered as described below for 3 cycles, which will be 21 days each. INCB050465 may be continued until a criterion is met for treatment discontinuation.

- Rituximab 375 mg/m^2 given on Day 1 and Day 2 of Cycle 1 and on Day 1 of Cycles 2 and 3.
- Ifosfamide 5000 mg/m^2 continuous IV infusion over 24 hours on Day 3 of each cycle.
  - Mesna will be infused with ifosfamide.

- Carboplatin area under the curve = 5 (maximum dose 800 mg) IV infusion on Day 3 of each cycle.
- Etoposide 100 mg/m^2 IV on Days 3 to 5 of each cycle.

Note: As an alternative to the Protocol-specified dose and schedule, R-ICE may be administered per institutional practice with medical monitor approval.

5.2. Treatment Compliance

Subjects should be counseled by the investigator to maintain strict adherence to the study regimen as prescribed and to keep a record of any missed doses. Subject diaries will be provided for the purposes of keeping accurate documentation of study drug administration and treatment compliance. The subject will be instructed to bring all unopened, empty, and opened/partially used bottles of study drug to each study visit, at which time compliance will be assessed.

5.3. Randomization and Blinding

Not applicable.

5.4. Duration of Treatment and Subject Participation

Subjects in Parts 1, 2, and 3 will be treated in continuous 21-day cycles indefinitely; this may include temporary interruptions described in Section 5.6. Subjects in Part 6 will be treated in 21-day cycles. INCB050465 may continue indefinitely, but R-ICE will only be given for 3 cycles.

Subjects who have evidence of objective clinical benefit, regardless of dose level, may continue to be treated at that dose level. Dose and schedule changes may be implemented for ongoing subjects based on emerging tolerability data. If study drug is permanently discontinued (for reasons, see Section 5.6.2.1) the subject will be withdrawn from the study. Treatment duration will vary among subjects, but is expected to average approximately 6 months.

5.5. Rationale for Dose Modification

Selections and modifications to the dosage of study drug are planned for dose-escalation cohorts. Also, dose interruptions and modifications may occur for individual study subjects. The identification of DLTs will define the doses used in planned cohorts. Further, the occurrence of DLTs and other toxicities will guide decisions for treatment interruptions and discontinuation for individual subjects.

Subjects enrolled in lower doses in the dose-escalation portion of the study will have the option of escalating to a dose found to be tolerated in a subsequent cohort provided the criteria specified in Section 5.6.1 are met.

5.5.1. Dose-Limiting Toxicity

A DLT is any AE noted in Table 3. DLTs include all AEs of the specified grades, regardless of investigator attribution of relatedness. AEs occurring during Cycle 1 of the dose-escalation portion of the study will be considered to be DLTs if they are not clearly related to the underlying disease, its progression, a comorbidity, concomitant medication, or transient

(≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination. Events not meeting these precise criteria may be considered DLTs as determined during review by the Incyte medical monitor and principal investigators.

Individual subject dose reductions may be made based on events observed at any time during treatment with INCB050465; however, for the purposes of dose cohort escalation/de-escalation, expanding a dose cohort, and determining the MTD or recommended dose of INCB050465, decisions will be made based on events deemed to be DLTs that are observed from the first day of INCB050465 administration through and including the final day of Cycle 1 (Day 21 or Day 28 depending on the part of the study that the subject has been enrolled to); in addition, all safety data available to date will be considered.

Each dose cohort in this study will be reviewed before dose escalation by the Incyte medical monitor and principal investigators. Telephone conferences will be scheduled by the sponsor with all investigators in order to review cohort-specific data and overall safety data from prior cohorts (if applicable), and to agree on dose escalation and the recommended dose for Phase 2 per DLT rules defined in this section.

Dose-limiting toxicities will be assessed by the investigator using the current CTCAE version 4.03 criteria. All toxicities will be graded based on the highest grade that is actually reached, rather than the level that might have been reached if left untreated. A DLT will be defined as any AE that is new in onset or worsening in severity and meets any of the criteria listed in Table 3.

Table 3: Definition of Dose-Limiting Toxicity

Nonhematologic:
• ≥ Grade 3 nonhematologic toxicity, excluding nausea, vomiting, diarrhea. • ≥ Grade 3 nausea, vomiting, or diarrhea uncontrolled by maximal antiemetic/antidiarrheal therapy lasting > 48 hours. • Any toxicity considered a DLT in the opinion of the investigator and medical monitor.
Hematologic:
• Grade 4 neutropenia lasting ≥ 7 days. NOTE: INCB039110 is suspected to cause transient decreases in white blood cells due to margination, therefore, DLT rules require neutropenia to persist after holding INCBC039110 for 2 to 3 days. Where the clinical status of the subject allows, investigators are encouraged to wait 24 hours before starting growth factors, to determine if white blood cell margination is contributing to the degree of neutropenia. • Febrile neutropenia (ANC < 1.0×10^9/L with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour). • Grade 3 thrombocytopenia associated with clinically significant bleeding (clinically significant as determined by the investigator or resulting in the need for a transfusion of red blood cells). • Grade 4 thrombocytopenia lasting > 7 days. • Grade 4 anemia.
General:
• Any specific AE that results in a dose delay or reduction in > one-third of subjects.

5.5.2. Follow-Up of Dose-Limiting Toxicities

Any DLT should be followed until it resolves to baseline 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.

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

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

5.6. Dose Adjustment of Study Drug

5.6.1. Planned Dose Adjustments

Cohort dose escalation is described in Section 4.1. Intrasubject dose escalation of INCB050465 will be allowed during dose escalation, provided that the following criteria are met:

- The Protocol inclusion criteria are met.
- The subject has received 4 cycles of study drug and has not had a related or possibly related toxicity ≥ Grade 2.
- The next dose level has been determined to be safe based on DLT rules (eg, no DLTs during Cycle 1).
- The subject is willing to submit to all visits and procedures as in Cycle 1 per the Protocol, except the PK [redacted] sampling will only be done as on Cycle 1 Day 15 (Day 1 and Day 8 PK [redacted] sampling will not be done).
- In the opinion of the investigator, the subject does not have any concurrent condition or circumstance that would complicate the dose escalation or PK sampling, or pose increased risk to the subject.
- The intrasubject dose escalation has been approved by the sponsor.

5.6.2. Criteria and Procedures for Dose Interruptions and Dose Reductions of INCB050465 and INCB039110

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of adverse experiences that may have an unclear relationship to study drug. Treatment with INCB050465, the combination with INCB039110, or the combination with standard therapies may be delayed up to 2 weeks to allow for resolution of toxicity. If treatment needs to be interrupted in subjects receiving the combination of INCB050465 and INCB039110 for toxicities with unknown causality, both study medications should be held. However, based on the evolving experience with the study treatments, the suspected causal agent only may be held (while the other study treatment continues) until resolution of toxicity following consultation and approval with the medical monitor. 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's medical monitor to discuss the case of any subject whose treatment has been delayed for more than 14 days before treatment with INCB050465 or the combination of INCB050465

and INCB039110 may be restarted (see Table 4). Dose reductions of 1 or both (as applicable for subjects on combination therapy) study treatments may be necessary as described in Table 4. For subjects who start on the 300 mg QD dose of INCB039110, the first dose reduction would be to 200 mg QD. If subjects start at a 200 mg QD dose of INCB039110, the combination of INCB050465 with INCB039110 at a lower dose (eg, 100 mg QD) will be subject to discussion with the sponsor. Alternatively, INCB039110 may be discontinued if dose reduction is indicated, and subjects may continue on INCB050465 monotherapy if they continue to receive benefit.

Because subjects may enter the study with extensive pretreatment and/or severe bone marrow infiltration by the primary disease, these dose-reduction rules are provided as guidelines. 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. Subjects receiving dose reductions (but not meeting DLT criteria) during the first cycle will not be considered evaluable for the purposes of determining the MTD.

Table 4: Guidelines for Interruption and Restart of Study Drug

TOXICITY/NCI CTCAE GRADE	ACTION TAKEN
Chemistries:	
• Total bilirubin > 3.0 × ULN • AST and/or ALT > 3.0 × ULN • ALP ≥ 2.5 × ULN Note: For ALP increases in subjects with bone metastasis-related ALP elevation at baseline, contact sponsor to discuss clinical management and possible dose reductions.	**Step 1:** Interrupt study drug(s) up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1 except ALT/AST elevations, which may require 4 weeks (28 days) to resolve. **Step 2:** Restart study drug(s) at next lower dose (or INCB050465 at 25% reduction if in expansion cohorts, rounded down to the nearest pill strength); monitor as clinically indicated.[a] Dose reductions may be made solely to the suspected agent if the causality can be reasonably assigned to that agent based on existing data (refer to the INCB050465 IB and INCB039110 IB) with approval of the medical monitor.
Hematologic:	
• ANC < 1.0 × 10^9/L for subjects who enrolled with ANC > 1.5 × 10^9/L • ANC < 0.5 × 10^9/L for subjects who enrolled with ANC ≤ 1.5 × 10^9/L • Platelet count is 50 to < 75 × 10^9/L for subjects who enrolled with platelets > 100 × 10^9/L • Platelet count is < 50 × 10^9/L for subjects who enrolled with platelets ≤ 100 × 10^9/L	**Step 1:** Interrupt study drug(s) up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1 or pretherapy baseline. **Step 2:** Restart study drug(s) and monitor as clinically indicated. Dosing interruption may be made solely to the suspected agent if the causality can be reasonably assigned to that agent based on existing data (refer to the INCB050465 IB and INCB039110 IB) with approval of the medical monitor.
• Grade 4 ANC (< 0.5 × 10^9/L) lasting 7 days • ≥ Grade 3 ANC with an oral temperature of at least 38.5°C OR with ≥ Grade 3 infection • Platelet count is < 50 × 10^9/L for subjects who enrolled with platelets > 100 × 10^9/L • Platelet count is < 25 × 10^9/L for subjects who enrolled with platelets ≤ 100 × 10^9/L	**Step 1:** Interrupt study drug(s) up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1. **Step 2:** Restart study drug(s) at next lower dose (or INCB050465 at 25% reduction if in expansion cohorts) and monitor as clinically indicated.[a] Dose reductions may be made solely to the suspected agent if the causality can be reasonably assigned to that agent based on existing data (refer to the INCB050465 IB and INCB039110 IB) with approval of the medical monitor.

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

TOXICITY/NCI CTCAE GRADE	ACTION TAKEN
Other drug-related toxicities or toxicities not attributable to other causes:	
Diarrhea/colitis (Grade 1)	**Step 1:** Treat with antimotility agents (eg, 4 mg loperamide followed by 2 mg every 4 hours or after every unformed stool) and initiate supportive care (see Section 5.6.2.1). If not improved after 48 hours, treat per guidance for ≥ Grade 2.
Diarrhea/colitis (≥ Grade 2)	**Step1:** Interrupt INCB050465. Perform work-up for infection (including CMV, *C. difficile*, etc). Initiate or continue supportive care (see Section 5.6.2.1). Consider colonoscopy with biopsy for ≥ Grade 3. **Step 2:** If infection is ruled out, start oral steroids, or consider IV steroids if subject is being given IV fluids. If no improvement with oral steroids, switch to IV steroids. When diarrhea resolves to ≤ Grade 1, continue supportive care and taper steroids over 4 weeks. When taper is complete and diarrhea is ≤ Grade 1, restart INCB050465 at next lower dose in consultation with the medical monitor. If ≥ Grade 2 diarrhea reoccurs, permanently discontinue INCB050465.
Pneumonitis (Grade 1)	**Step 1:** Interrupt INCB050465 until the toxicity has resolved. **Step 2:** Restart INCB050465 at next lower dose. Monitor as clinically indicated.
Pneumonitis (Grade ≥ 2)	Permanently discontinue INCB050465.
Skin toxicity (eg, rash, pruritus, etc, unless otherwise specified) (Grade 2-3)	**Step 1:** Interrupt INCB050465 until the toxicity has resolved to ≤ Grade 1. **Step 2:** Restart INCB050465 at same dose. If assessed as related to INCB050465, restart at next lower dose in consultation with the medical monitor.
Exfoliative dermatitis (Grade 1)	**Step 1:** Interrupt INCB050465 until the toxicity has resolved. **Step 2:** Restart INCB050465 at next lower dose. Monitor as clinically indicated.
Exfoliative dermatitis (≥ Grade 2)	Permanently discontinue INCB050465.
Intestinal perforation (any grade)	Permanently discontinue INCB050465.
Pneumocystis jiroveci pneumonia infection	Interrupt INCB050465. Permanently discontinue INCB050465 if *Pneumocystis jiroveci* pneumonia infection is confirmed.
CMV infection	Subjects with CMV viremia without associated clinical signs of CMV infection should be carefully monitored. Consider interrupting INCB050465 for subjects with CMV viremia and clinical signs of infection until the infection has resolved. Restart INCB050465 reduced by 1 dose level if approved by the medical monitor.
Varicella zoster infection	Interrupt INCB050465. Restart INCB050465 only by approval of the medical monitor.
Any Grade 1 or 2 toxicity unless otherwise specified	Continue study drug treatment(s); monitor as clinically indicated.

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

TOXICITY/NCI CTCAE GRADE	ACTION TAKEN
Any Grade 2 or 3 toxicity, if clinically significant and not manageable by supportive care unless otherwise specified	**Step 1:** Interrupt study drug(s) up to 2 weeks (14 days) until toxicity resolves to ≤ Grade 1 or medical monitor approval. **Step 2:** Restart study drug(s) at next lower dose for events considered to be drug-related (or 25% reduction if in expansion cohort, rounded down to the nearest pill strength); monitor as clinically indicated.[a] Dose reductions may be made solely to the suspected agent if the causality can be reasonably assigned to that agent based on existing data (refer to the INCB050465 IB and INCB039110 IB) with approval of the medical monitor.
Any recurrent Grade 2 or 3 toxicity after 2 dose reductions	Discontinue study drug treatment(s) and follow-up per Protocol.
Any other Grade 4 toxicity	Discontinue study drug(s) and follow-up per Protocol. However, if toxicity resolves to ≤ Grade 1 within 2 weeks, may restart treatment at 1 dose level lower with medical monitor approval.

CMV = cytomegalovirus; IV = intravenous.
[a] Note: Only 2 dose reductions due to AEs are permitted.

5.6.2.1. Supportive Care Guidelines for Diarrhea/Colitis

Subjects should be informed to immediately report to the investigator any event of diarrhea. Subjects should receive appropriate supportive care measures as deemed necessary by the investigator. For any Grade ≥ 1 diarrhea, subjects should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. Subjects should try to eat 5 to 6 small meals per day; low-fat, high-protein foods; and cooked instead of raw vegetables. Subjects may supplement their diet with bananas, rice, applesauce, and toast to reduce the number of bowel movements, and may also try crackers, gelatin, noodles, or oatmeal. Subjects should avoid fried, fatty, greasy, or spicy foods; milk, milk products, and acidic drinks; high-fiber foods and foods that cause gas; and alcohol, caffeine, and herbal supplements (Coutré et al 2015).

For each occurrence, attempts should be made to rule out other causes, such as metastatic disease or bacterial or viral infection (including CMV), which might require additional supportive care.

It may be necessary to perform conditional procedures such as colonoscopy with biopsy as part of evaluation of the event. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain or cramping, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

5.6.2.2. Dose Interruptions for Standard Therapies

Dose interruptions and adjustments for standard therapy in Part 6 of the study will be at the discretion of the investigator, in accordance with the individual product package insert and applicable treatment guidelines (eg, NCCN Guidelines).

5.6.3. Criteria for Permanent Discontinuation of Study Drug

The occurrence of unacceptable toxicity will require that the study drug be permanently discontinued. Unacceptable toxicity is defined as:

- Occurrence of an AE that is related to treatment with the study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest.
- Toxicity requiring more than 2 dose reductions of INCB050465 or the combination of INCB050465 and INCB039110 or the standard therapy. Subjects enrolled in Part 6 who require > 2 reductions of the standard therapy may remain on INCB050465 monotherapy with medical monitor approval.
- Persistent toxicity requiring a delay of therapy for more than 2 weeks (14 days), except ALT/AST elevation, which may require 4 weeks (28 days) to resolve, unless approved by the medical monitor.
- Prolongation of QTc by > 60 milliseconds or to > 500 milliseconds confirmed by repeat ECG.
- Recurrent toxicity despite 2 dose reductions.

If study drug is permanently discontinued, the subject will be withdrawn from the study.

5.7. Withdrawal of Subjects From the Study

5.7.1. Withdrawal Criteria

Subjects **must** be withdrawn from the study for the following reasons:

- 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.
- Unacceptable toxicity has occurred (see Section 5.6.2.1).
- Disease progression has occurred (see Appendix D, Appendix E, or Appendix F for definition) except
  - in the circumstance where, in the setting of otherwise stable disease, a medical procedure or radiation therapy is required to a single lesion, with medical monitor approval, or
  - if progression is observed on a once-weekly schedule after an objective response was observed on a QD schedule, a subject may be returned to the QD schedule if it is determined to be in the subject's best interest by the investigator (eg, no better

alternative) and agreed by both the subject and the medical monitor. The subject should be withdrawn when a subsequent radiological assessment demonstrates further deterioration or sooner based on clinical signs and symptoms.

– Note: Subjects receiving INCB039110 monotherapy study treatment may receive combination therapy with INCB039110 and INCB050465 as described in Section 4.2.

A subject **may** be withdrawn from the study as follows:

- If, during the course of the study, a subject is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the subject should be withdrawn from the study. Refer to Section 11.3, Protocol Adherence.
- If a subject is noncompliant with study procedures or study drug administration in the opinion of the investigator, the sponsor should be consulted for instruction on handling the subject.

5.7.2. Withdrawal Procedures

In the event that the decision is made to permanently discontinue the study drug, 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. These visits are described in Section 5.10. The last date of the last dose of study drug will be recorded in the case report form (CRF), and the reason for subject withdrawal will be recorded.

If a subject is withdrawn from the study:

- 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 CRF.
- 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.

5.8. Concomitant Medications and Measures

All concomitant medications and treatments must be recorded in the CRF. Any prior medication received up to 30 days before enrollment (Cycle 1 Day 1) will be recorded in the CRF. Concomitant treatments and/or procedures that are required to manage a subject's medical condition during the study will also be recorded in the CRF.

5.8.1. Supportive Care Measures

Supportive care should be administered to subjects as per the institutional policy at the site for the standard therapy that the subject will receive. Additional information may be available in the appropriate package inserts. This includes the use of prophylactic growth factors should be

based on American Society of Clinical Oncology guidelines for the use of white blood cell growth factors (Smith et al 2006) and the investigator's clinical judgment.

5.8.2. *Pneumocystis jirovecii* Pneumonia Prophylaxis

All subjects in this study are required to receive a standard PJP prophylaxis regimen determined by the investigator. Examples of standard PJP prophylaxis therapies for this population include trimethoprim-sulfamethoxazole, atovaquone, dapsone with or without pyrimethamine, and pentamidine (NCCN 2014). Due to reports of cross-sensitivity between sulfonamides and dapsone, all subjects who have a known or suspected allergy to sulfonamides must receive either inhaled pentamidine or atovaquone (Mepron®) for PJP prophylaxis. Prophylaxis should be given while subjects are receiving study treatment and continue for at least 2 to 6 months after the last dose of study drug.

5.9. Restricted Medications and Measures

- Use of systemic corticosteroid doses ≤ 10 mg/day prednisone (or equivalent) is permitted but discouraged from the screening visit through the EOT visit.
- Use of weak or moderate inducers or inhibitors of CYP3A4 (Appendix G) is discouraged, and investigators should seek other options where possible.
- P-glycoprotein substrates of clinical relevance should be used with caution
- Aspirin in doses exceeding 81 mg/day is not permitted. Low-dose aspirin (≤ 81 mg/day) is permitted. Acetaminophen and nonsteroidal anti-inflammatory agents (NSAIDs, eg, ibuprofen) may be used. Due to the risk of liver injury with the use of high doses of acetaminophen, subjects should be advised to stay within the recommend daily dose of acetaminophen.
- If concomitant administration of an anticoagulant/antiplatelet medication is indicated, caution and enhanced monitoring are required. History of thrombocytopenia and any concurrent INCB039110-related thrombocytopenia should be a factor in the choice of anticoagulant and dose. Aspirin use should be carefully considered because of the potential for gastric irritation in subjects with concomitant bleeding risk.

5.10. Prohibited Medications and Measures

- Use of potent inducers and inhibitors of CYP3A4 are prohibited (Appendix G). Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole.
- Use of any anticancer medications other than the study medications from 21 days before Day 1 through the 30-day follow-up is prohibited.
- Use of systemic corticosteroid doses > 10 mg/day prednisone (or equivalent) is not permitted from the screening visit through the EOT visit.
- Any concomitant use of another JAK inhibitor (Part 2 and Part 3 Cohort E only).
- Administration of live virus vaccines within 30 days of rituximab treatment (applicable to Part 6 of the study only).

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedules of assessments (Table 5 and Table 7) and schedules of laboratory assessments (Table 6 and Table 8). Required analytes for laboratory assessments are provided in Table 11. The order of assessments is suggested by the order of mention within the schedules. For instructions on each assessment, see Section 7.

Note: Upon implementation of Protocol Amendment 10, only study assessments indicated in Table 9 and Table 10 will be performed.

Table 5: Schedule of Assessments for Parts 1, 2, and 3

Note: Upon implementation of Protocol Amendment 10, the schedules of assessments in Table 9 and Table 10 should be followed.

Procedure	Protocol Section	Screening Phase	Cycle 1			Other Cycles	EOT	Follow-Up	Notes
		Days -30 to -1	Day 1	Day 8 (± 3 Days)	Day 15 (± 3 Days)	Day 1 (± 3 Days)		EOT + 30-37 Days	
Informed consent	7.1	X							
Review inclusion and exclusion criteria	3	X	X						
Demography and medical history	7.3	X							
Prior/concomitant medications	7.3.2	X	X	X	X	X	X	X	
Physical examination/body weight, height	7.4.2	X*	X	X	X	X	X	X	* Comprehensive examination at screening, targeted physical examination thereafter. Height at screening only.
Vital signs	7.4.4	X	X	X	X	X	X	X	
12-lead ECG	7.4.5	X	X*		X*	X	X	X	* Timed triplicate ECGs (separated by 5 minutes) at predose and 2 and 4 hours postdose.
Laboratory tests	7.4.6	X	X	X	X	X	X	X	
ECOG status	7.6	X	X	X	X	X	X	X	
CT or MRI	7.5.1	X				X*	X		* Every 9 weeks (3 cycles) or at a frequency consistent with the standard of care for the subject's disease. Performed only if measurable disease is present.
FDG-PET scan	7.5.2	X				X*	X		If performed per standard of care. Applicable for lymphomas only (see Section 7.5.2). * Every 9 weeks (3 cycles) or at a frequency consistent with the standard of care for the subject's disease.

Table 5: Schedule of Assessments for Parts 1, 2, and 3 (Continued)

Note: Upon implementation of Protocol Amendment 10, only the schedules of assessments in Table 9 and Table 10 should be followed.

Procedure	Protocol Section	Screening Phase	Cycle 1			Other Cycles	EOT	Follow-Up	Notes
		Days -30 to -1	Day 1	Day 8 (± 3 Days)	Day 15 (± 3 Days)	Day 1 (± 3 Days)		EOT + 30-37 Days	
Bone marrow examination	7.5.3	X*				X*			* At baseline and if confirming CR. For exceptions to this requirement, see Section 7.5.3.
Review AEs	7.4.1	X	X	X	X	X	X	X	
Study drug dispensing	7.10.1.2		X			X			
Administer INCB050465 at site	7.10.1.1		X	X	X*	X*			Subject to withhold AM dose of study drug on days it will be administered at the site. * For subjects in Part 3 Cohort A, study drug will be administered at the site on Cycle 1 Day 15 and Cycle 2 Day 1 as part of the food-effect study. If the dose selected for the expansion cohort was the MTD in the dose-escalation part of the study, on Cycle 1 Day 15 and Cycle 2 Day 1, the dose administered ONLY for these 2 doses will be 1 dose level below the MTD (if the PAD is selected for the expansion cohort, there will be no alteration to the doses on Cycle 1 Day 15 or Cycle 2 Day 1).
Administer INCB039110 at site	7.10.1.4		X*	X	X				Part 2 and Part 3 Cohort E only. * INCB039110 is administered after INCB050465 PK sampling is complete on Cycle 1 Day 1.
Assess compliance	7.10.1.3					X	X		
Distribute reminders	7.10.2	X	X	X	X	X	X		

CT = computed tomography; PET = positron emission tomography.

Table 6: Schedule of Laboratory Assessments for Parts 1, 2, and 3

Note: Upon implementation of Protocol Amendment 10, only the schedules of assessments in Table 9 and Table 10 should be followed.

Local Laboratory Tests	Protocol Section	Screening	C1 D1	C1 D8	C1 D15	C2 D1	D1 All Other Cycles	EOT	Follow-Up	Details
Serum chemistries	7.4.6.1	X*	X**	X	X	X	X	X	X	* Required within 14 days of treatment initiation. ** May be performed within 3 days of the first dose.
Hematology	7.4.6.2	X*	X**	X	X	X	X	X	X	* Required within 14 days of treatment initiation. ** May be performed within 3 days of the first dose.
Coagulation panel	7.4.6.4	X*				X	X^	X		* Required within 14 days of treatment initiation. ^ Only at Cycles 4, 7, 10, etc.
Hepatitis screening	7.4.6.7	X								
Urinalysis	7.4.6.3	X				X	X*			* Only at Cycles 4, 7, 10, etc.
Serum pregnancy	7.4.6.6	X							X	All female subjects of childbearing potential.
FSH	7.4.6.5	X								To document hormonal menopause.
Immunophenotyping	7.5.4	X				X*				*CLL: Cycle 2 and to confirm CR.
IgM (subjects with WM only)	7.5.5		X**				X*			* To be performed at least every 9 weeks or more frequently as clinically indicated. ** May be performed within 3 days of the first dose.

Table 6: Schedule of Laboratory Assessments for Parts 1, 2, and 3 (Continued)

Note: Upon implementation of Protocol Amendment 10, only the schedules of assessments in Table 9 and Table 10 should be followed.

Central Laboratory Samples	Protocol Section	Screening	C1 D1	C1 D8	C1 D15	C2 D1	D1 All Other Cycles	EOT	Follow-Up	Details
PK plasma (predose)	7.7.1		X	X	X	X*				Collect before morning dose of study drug. *Cycle 2 Day 1 PK is only required for subjects in the monotherapy expansion Cohort A.
PK plasma TIMED (postdose)	7.7.1		X*		X*,**	X*,**				* Collect at 0.5, 1, 2, 4, 6, 8, and, if possible, 12 hours postdose of INCB050465 on Cycle 1 Days 1 and 15. ** Subjects in the monotherapy **expansion cohort** (Part 3 Cohort A) who participate in the food-effect study will be required to undergo PK sampling to test food effect on **Cycle 1 Day 15 after fasted administration** and **on Cycle 2 Day 1 after fed administration of INCB050465**. The sampling on Cycle 2 Day 1 will be identical to the PK testing on Cycle 1 Day 15, except dose administration will be within 5 minutes of completing a high-fat meal. Subjects may be excused from the food-effect portion of the study if they are unable to consume the meal.
Urine PK (postdose)	7.7.2				X					Provide a complete urine output collection from hour 0 (after morning dose) through 8 hours; or 12 hours postdose if 12-hour postdose PK sample is being collected.
[redacted]										

Table 6: Schedule of Laboratory Assessments for Parts 1, 2, and 3 (Continued)

Note: Upon implementation of Protocol Amendment 10, only the schedules of assessments in Table 9 and Table 10 should be followed.

Central Laboratory Samples	Protocol Section	Screening	C1 D1	C1 D8	C1 D15	C2 D1	D1 All Other Cycles	EOT	Follow-Up	Details
[redacted]										

Table 7: Schedule of Assessments for Part 6

Note: Upon implementation of Protocol Amendment 10, only the schedules of assessments in Table 9 and Table 10 should be followed.

Procedure	Protocol Section	Screening Phase	Cycle 1					Other Cycles		EOT	Follow-Up	Notes
		Days -30 to -1	Day 1	Day 2	Day 3	Days 4-5	Day 15	Day 1 (± 3 Days)	Days 3-5[a]		EOT + 30-37 Days	
Informed consent	7.1	X										
Review inclusion and exclusion criteria	3	X	X									
Demography and medical history	7.3	X										
Prior/concomitant medications	7.3.2	X	X	X	X	X	X	X	X	X	X	
Physical examination/ body weight, height	7.4.2	X*	X	X	X	X	X	X	X	X	X	* Comprehensive examination at screening, targeted physical examination thereafter. Height at screening only.
Vital signs	7.4.4	X	X	X	X	X	X	X	X	X	X	
12-lead ECG	7.4.5	X	X*	X	X	X	X*	X	X	X	X	* Timed triplicate ECGs (separated by 5 minutes) at predose and 2 and 4 hours postdose.
Laboratory tests	7.4.6	X	X	X	X	X	X	X	X	X	X	
ECOG status	7.6	X	X	X	X	X	X	X	X	X	X	
CT or MRI	7.5.1	X						X*		X		* Every 9 weeks (3 cycles) or at a frequency consistent with the standard of care for the subject's disease. Performed only if measurable disease is present.
FDG-PET scan	7.5.2	X						X*		X		If performed per standard of care. Applicable for lymphomas only (see Section 7.5.2). * Every 9 weeks (3 cycles) or at a frequency consistent with the standard of care for the subject's disease. Performed only if measurable disease is present.

Table 7: Schedule of Assessments for Part 6 (Continued)

Note: Upon implementation of Protocol Amendment 10, only the schedules of assessments in Table 9 and Table 10 should be followed.

Procedure	Protocol Section	Screening Phase	Cycle 1					Other Cycles		EOT	Follow-Up	Notes
		Days -30 to -1	Day 1	Day 2	Day 3	Days 4-5	Day 15	Day 1 (± 3 Days)	Days 3-5[a]		EOT + 30-37 Days	
Bone marrow examination	7.5.3	X*										* At baseline and if confirming CR. For exceptions to this requirement, see Section 7.5.3.
Review AEs	7.4.1	X	X	X	X	X	X	X	X	X	X	
INCB050465 dispensing	7.10.1.2		X					X				
Administer INCB050465 at site	7.10.1.1		X				X					Subject to withhold AM dose of study drug on days it will be administered at the site.
Administer standard therapy	7.10.1.7		X	X	X	X		X	X			Rituximab will be given on Day 1 and Day 2 of Cycle 1 and Day 1 of Cycles 2 and 3 Ifosfamide and carboplatin will be administered on Day 3 of each cycle. Etoposide will be administered on Days 3 to 5 of each cycle. Note: As an alternative to the Protocol-specified dose and dose schedule, R-ICE may be administered according to institutional practice with medical monitor approval.
Assess compliance	7.10.1.3							X		X		
Distribute reminders	7.10.2	X	X	X	X	X	X	X	X	X		

[a] Subjects who continue to receive INCB050465 after the 3 cycles of R-ICE plus INCB050465 are not required to have Protocol-specified assessments performed on Days 3 to 5 of Cycle 4 and subsequent cycles unless clinically indicated.

Table 8: Laboratory Assessments for Part 6

Note: Upon implementation of Protocol Amendment 10, only the schedules of assessments in Table 9 and Table 10 should be followed.

Procedure	Protocol Section	Screening Phase	Cycle 1					Other Cycles		EOT	Follow-Up	Notes
		Days -30 to -1	Day 1	Day 2	Day 3	Days 4-5	Day 15	Day 1 (± 3 Days)	Days 3-5[a]		EOT + 30-37 Days	
Local Laboratory Tests												
Serum chemistries	7.4.6.1	X*	X**	X	X	X	X	X	X	X	X	* Required within 14 days of treatment initiation. ** May be performed within 3 days of the first dose.
Hematology	7.4.6.2	X*	X**	X	X	X	X	X	X	X	X	* Required within 14 days of treatment initiation. ** May be performed within 3 days of the first dose.
Coagulation panel	7.4.6.4	X*						X^		X		* Required within 14 days of treatment initiation. ^ Only at Cycles 2, 4, 7, 10, etc.
Hepatitis screening	7.4.6.7	X										* Comprehensive examination at screening, targeted physical examination thereafter. Height at screening only.
Urinalysis	7.4.6.3	X						X^				^ Only at Cycles 2, 4, 7, 10, etc.
Serum pregnancy	7.4.6.6	X									X	All female subjects of childbearing potential.
FSH	7.4.6.5	X										
Immunophenotyping	7.5.4	X										

Table 8: Laboratory Assessments for Part 6 (Continued)

Note: Upon implementation of Protocol Amendment 10, only the schedules of assessments in Table 9 and Table 10 should be followed.

Procedure	Protocol Section	Screening Phase	Cycle 1					Other Cycles		EOT	Follow-Up	Notes
		Days -30 to -1	Day 1	Day 2	Day 3	Days 4-5	Day 15	Day 1 (± 3 Days)	Days 3-5[a]		EOT + 30-37 Days	
Central Laboratory Samples												
PK plasma (predose)	7.7.1		X				X					Collect before morning dose of study drug.
PK plasma TIMED (postdose)	7.7.1		X				X					Collect at 0.5, 1, 2, 4, 6, 8, and, if possible, 12 hours postdose of INCB050465 on Cycle 1 Days 1 and 15.
Urine PK (postdose)	7.7.2						X					Provide a complete urine output collection from hour 0 (after morning dose) through 8 hours; or 12 hours postdose in 12-hour postdose PK sample is being collected.
[redacted]												

Table 8: Laboratory Assessments for Part 6 (Continued)

Note: Upon implementation of Protocol Amendment 10, only the schedules of assessments in Table 9 and Table 10 should be followed.

Procedure	Protocol Section	Screening Phase	Cycle 1					Other Cycles		EOT	Follow-Up	Notes
		Days -30 to -1	Day 1	Day 2	Day 3	Days 4-5	Day 15	Day 1 (± 3 Days)	Days 3-5[a]		EOT + 30-37 Days	
[redacted]												

[a] Subjects who continue to receive INCB050465 after the 3 cycles of R-ICE plus INCB050465 are not required to have Protocol-specified assessments performed on Days 3 to 5 of Cycle 4 and subsequent cycles unless clinically indicated.

Table 9: Schedule of Assessments for Ongoing Subjects in All Cohorts Upon Implementation of Protocol Amendment 10

Procedure	Section	At Least Every 12 Weeks in Clinic[a]	EOT	Follow-Up	Notes
				EOT + 30-37 Days	
Prior/concomitant medications	7.3.2	X	X	X	Review to ensure no prohibited medications are being used. Provide data to sponsor in regard to SAEs only.
Study drug dispensing	7.10.1	X			
Assess compliance	7.10.1.3 7.10.1.6	X	X		
Distribute reminders	7.10.2	X	X		
Laboratory tests	Table 10	X	X	X	Performed at each site as per standard of care and monitored per investigator discretion.
AEs/SAEs	7.4.1	X	X	X	AEs that lead to the discontinuation of study treatment and all SAEs must be recorded in the CRFs, regardless of the causal relationship.
Radiographic tumor assessments	7.5.1				Performed per standard-of-care guidelines.

[a] Information related to concomitant medications and adverse events may also be collected between the required clinic visits (eg, by phone or email).

Table 10: Schedule of Laboratory Assessments for Ongoing Subjects in All Cohorts Upon Implementation of Protocol Amendment 10

Local Laboratory Tests	Section	At Least Every 12 Weeks in Clinic	EOT	Follow-Up	Details
				EOT + 30-37 Days	
Serum chemistries	N/A	X	X	X	Performed at each site as per standard of care and monitored per investigator discretion.
Hematology	N/A	X	X	X	Performed at each site as per standard of care and monitored per investigator discretion.

Table 11: Local Laboratory Tests: Required Analytes (Not Applicable After Implementation of Protocol Amendment 10)

Serum Chemistries	Hepatitis Screening	Hematology	Urinalysis	Coagulation
Albumin Alkaline phosphatase ALT AST Blood urea nitrogen Calcium Bicarbonate Chloride Creatinine Glucose CRP (normal range) LDH Magnesium Phosphate Potassium Sodium Total bilirubin Direct (conjugated) bilirubin (required only if total bilirubin is abnormal)	HBs Ag Anti-HB core total HCV antibody HCV-RNA HBV-DNA **Serum Chemistries** Total serum protein Total cholesterol Pre-albumin	Hemoglobin Hematocrit Platelet count Red blood cell count White blood cell count Differential cell count: • Basophils • Eosinophils • Lymphocytes[a] • Monocytes • Neutrophils[a]	Color/appearance pH Specific gravity Bilirubin Glucose Ketones Leukocytes Blood Protein Microscopic analysis	PT PTT INR **Females Only** FSH Serum pregnancy **Immunophenotyping** Immunophenotyping (see Section 7.5.4)

Note: Additional tests may be required, as agreed by investigator and sponsor, based upon emerging safety data.
[a] Absolute values must be provided for lymphocytes and neutrophils.

6.1. Screening Phase

The screening phase is the interval between the signing of the ICF and the day the subject is enrolled in the study (Cycle 1 Day 1). Informed consent must be obtained before performing any study-specific procedures. Assessments that are required to demonstrate eligibility may be performed over 1 or more days during this phase. The maximum screening period is 30 days.

Results from the screening visit evaluations will be reviewed to confirm subject eligibility before enrollment/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 or not representative. 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, after recovery from an infection). Subjects will be assigned a new subject ID.

Additionally, the screening phase will be used to determine the baseline assessments of clinical condition and disease status. Tumor assessments appropriate to the type of malignancy will be performed and recorded in the CRF.

6.2. Treatment Phase

The treatment phase begins on the day the subject is enrolled in the study and receives the first dose of study drug; this is defined as Cycle 1 Day 1. Dates for subsequent study visits will be determined based on this day and should occur within 3 days (±) of the scheduled date unless delayed for safety reasons. At Cycle 1 Day 1, results from screening visit evaluations should be reviewed to determine if the subject continues to meet the eligibility requirements as specified in the Protocol.

During the treatment phase, regular study visits (physician visits) will occur as described in the schedule of assessments for the appropriate part of the study.

At certain study visits as indicated in the laboratory assessment tables above, subjects will attend the study visit having fasted overnight, having recorded the time of the prior study drug administration, and having withheld the morning dose of the study drug. At these visits, PK [redacted] sampling will be conducted.

6.3. End of Treatment

If a decision is made that the subject will withdraw from study participation, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the CRF. The subject should be encouraged to return for the follow-up visit.

6.4. Follow-Up Phase

The follow-up phase is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 to 37 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, until the date of the follow-up visit, or until study drug-related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer.

Reasonable efforts should be made to have the subject return for the follow-up visit, and report any AEs that may occur during this phase.

Subjects are required to remain on PJP prophylaxis for at least 2 to 6 months after the last dose of study drug (see Section 5.8.2) and should be reminded of this at the safety follow-up visit. Sites should follow up with subjects to confirm that they have been compliant with the prophylactic treatment for the duration of this period.

6.5. Unscheduled Visits

Unscheduled visits may occur at any time as medically warranted. Visits where study drug is held are considered unscheduled visits. Any assessments performed at those visits should be recorded in the CRF.

6.6. Early Termination

Not applicable.

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

Required assessments/procedures listed here will be captured on the CRF. Subjects ongoing after implementation of Protocol Amendment 10 will only have assessments performed as indicated in Table 9 and Table 10 and at a frequency determined by the investigator as guided by the standard of care. **Unless noted below, procedures listed in this section are not required to be performed or collected on the CRF after implementation of Amendment 10.**

7.1. Administration of Informed Consent Form

Valid informed consent must be obtained from the study subject before conducting any study-specific procedures. The granting of informed consent for study participation must be documented in writing using an ICF that contains all of the 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; a copy of the signed ICF must be provided to the study subject. Subjects of childbearing potential must agree to take appropriate measures to avoid pregnancy in order to participate in the study (Appendix A).

7.2. Interactive Response Technology Procedure

Not applicable.

7.3. Demography, Medical History, Medication Usage

7.3.1. Demographics and Medical History

Demographic data and a complete medical and medication history will be collected at screening. This will include complete documentation of the history of medical or surgical treatment for the malignancy under study. Note: For subjects with DLBCL, the DLBCL subtype (eg, GCB) should be known at study entry and will be collected at screening.

7.3.2. Prior/Concomitant Medications

Prior and/or ongoing medications will be reviewed during screening to determine study eligibility and will continue to be recorded throughout the duration of the study. The medication record will be maintained after enrollment as a documentation of concomitant medications, including any changes to the dose or regimen. Prior/concomitant medications include any prescription, over-the-counter, or natural/herbal preparations taken or administered during 30 days before Cycle 1 Day 1 and throughout the study period.

Upon implementation of Amendment 10, use of concomitant medications should be monitored to verify that subjects are not taking any concomitant medication prohibited per Protocol (Section 5.10).

7.4. Safety Assessments

Upon implementation of Amendment 10, only safety assessments (including laboratory analytes) that are consistent with standard of care and monitoring should be performed per the investigator's discretion. Subjects must be taken off study treatment if, in the opinion of the investigator, an unacceptable toxicity develops.

7.4.1. Adverse Events

Adverse events will be monitored from the time the subject signs informed consent. Subjects will be instructed to report all AEs during the study and subjects 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 CRFs 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.

Upon implementation of Amendment 10, AEs that lead to the discontinuation of study treatment and all SAEs must be recorded in the CRFs, regardless of the assumption of a causal relationship with the study drug(s).

7.4.2. Comprehensive Physical Examination

Physical examinations must be performed by a medically qualified individual such as a licensed physician, Physician's Assistants, 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; abdomen (liver, spleen); extremities, lymph nodes, and a brief neurological examination. The screening physical examination should also include a measurement of height and body weight.

7.4.3. Targeted Physical Examination

A targeted physical examination must include a measurement of the subject's body weight, examination of the abdomen (liver, spleen), and evaluation of any AEs or any previously reported symptoms or prior physical examination findings.

7.4.4. Vital Signs

Vital sign measurements (blood pressure, heart rate, and body temperature) will be taken with the subject in the recumbent, semirecumbent, or sitting position after 5 minutes of rest.

7.4.5. Electrocardiograms

All 12-lead ECGs will be performed with the subject in a recumbent or semirecumbent position after 5 minutes of rest. The 12-lead ECGs will be interpreted by the investigator at the site and will be used for immediate subject management. The decision to include or exclude a subject or withdraw a subject from the study based on an ECG flagged as "Abnormal, Clinically Meaningful" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate.

7.4.5.1. Timed Electrocardiograms

Timed triplicate (separated by 5 minutes) ECGs will be performed at Cycle 1 Day 1 and Cycle 1 Day 15. ECGs will be conducted predose and will be conducted in conjunction with the 2-hour and 4-hour PK timepoints (Section 7.7.1). ECGs should be conducted before but within 30 minutes of the PK blood draw at the corresponding timepoint. The specified postdose timepoint may be adjusted based on emerging PK data.

7.4.6. Laboratory Assessments

A laboratory local to the study site and subject will perform all clinical laboratory assessments for safety. The investigative site will enter the laboratory results and laboratory normal ranges into the CRF. Hematology, serum chemistry, and urinalysis should be performed using standard procedures on the days indicated in Table 6 and Table 8 where required tests are shown.

Upon implementation of Amendment 10, laboratory assessments (Table 10) only need to be performed in accordance with standard of care at each investigational site and monitored as per the investigator's discretion. Laboratory results do not need to be reported in the CRF, but all laboratory results corresponding with an SAE must be reported on the SAE form.

7.4.6.1. Chemistry

A panel of serum chemistries will be performed as indicated in Table 6 and Table 8; analytes required for this panel are listed in Table 11.

7.4.6.2. Hematology

Hematology will be performed as indicated in Table 6 and Table 8; required analytes are listed in Table 11.

7.4.6.3. Urinalysis

Complete urinalysis will be performed at screening and as indicated in Table 6 and Table 8; required analyses are listed in Table 11.

7.4.6.4. Coagulation Panel

A coagulation panel will be run as indicated in Table 6 and Table 8. Required analytes are listed in Table 11.

7.4.6.5. Fertility Testing

Female subjects who report being amenorrheic for ≥ 1 year will have FSH tested to confirm hormonal menopause; a result of > 30 IU/L will be considered confirmatory. Female subjects must be either confirmed postmenopausal or surgically sterile, OR must be advised on acceptable methods that have been determined to be more than 99% effective in avoiding pregnancy (Appendix A).

7.4.6.6. Pregnancy Testing

A serum pregnancy test will be required for all female subjects of childbearing potential at screening and follow-up. Pregnancy tests will be conducted only as medically indicated during study treatment.

7.4.6.7. Hepatitis Screening

Hepatitis screening assessments will be performed at the screening visit (Table 6 and Table 8) to rule out hepatitis infection; required analytes are shown in Table 11. Additional tests may be performed if clinically indicated.

7.5. Efficacy Assessments

An objective assessment of disease status is required at baseline (screening) using a method that is appropriate for disease subtype, per established and modified guidelines (Hallek et al 2008, Cheson et al 2014, Cheson et al 2012, Owen et al 2013). Disease status will be assessed by the site every 9 weeks (3 cycles) after Cycle 1 Day 1 or at a frequency consistent with the standard of care for the subject's disease. For subjects in Part 3 Expansion Cohorts, the sponsor may also have disease status assessed by a central imaging vendor.

7.5.1. CT Scan or MRI

Subjects with applicable disease types will undergo CT or magnetic resonance imaging (MRI) to evaluate measurable disease during the screening phase. If CT/MRI assessment was performed under standard of care before signing of the ICF but within 30 days of Cycle 1 Day 1, the result of that assessment may be recorded in the CRF in lieu of a study-specific assessment. On-treatment assessments (for subjects with disease measurable by CT or MRI) should be performed at least every 9 weeks (3 cycles) after Cycle 1 Day 1 or at a frequency consistent with the standard of care for the subject's disease. Investigators may have subjects assessed for response earlier than the every-9-week frequency if clinically indicated in discussion with the sponsor.

Upon implementation of Amendment 10, CT/MRI assessments are only required to be performed as per standard of care guidelines and monitored. Subjects must be taken off study if, in the opinion of the investigator, the disease has progressed and the subject is no longer having clinical benefit from the study treatment.

7.5.2. FDG-PET or Combined PET-CT

If positron emission tomography (PET) using [^{18}F] fluorodeoxyglucose (FDG) or combined PET-CT is used as a functional imaging tool for staging or response assessment of lymphoma as a part of the standard of care (eg, in subjects with HL or DLBCL), the results obtained during any study phase will be captured in the CRF.

7.5.3. Bone Marrow Examination

Bone marrow examination is required as a baseline assessment for subjects with disease subtypes that utilize bone marrow histology as part of the objective criteria for disease staging except in the following circumstances or with approval of the medical monitor:

- Subject had a bone marrow examination performed as per standard of care prior to 60 days of the first dose of study drug.
- Subject had a bone marrow examination performed after the last treatment for the lymphoid malignancy and the results showed involvement of the bone marrow.
- Baseline PET scan shows that the subject does have FDG-avid disease in the bone marrow (PET + bone marrow).

Subsequently, bone marrow biopsy will be performed only to confirm CR or as clinically indicated. If the bone marrow does not have lymphoma involvement at baseline, a repeat bone marrow examination is not required to confirm indication of CR on imaging.

Data from the pathology report result from the bone marrow examination will be captured in the CRF. Results of assessments performed under standard of care before the signing of the ICF may be used as the baseline assessment in lieu of a study-specific procedure IF performed within 60 days of the first dose of study drug (Cycle 1 Day 1).

All bone marrow examinations should include a unilateral aspiration and biopsy, when feasible. Subjects may be enrolled based on a biopsy only, when a "packed marrow" precludes aspiration. An aspiration only may be performed at the discretion of the investigator.

7.5.4. Immunophenotyping

Immunophenotyping results for all subjects will be collected at baseline. For subjects with CLL or other B-cell malignancy with circulating tumor cells, lymphocyte immunophenotyping (Table 6) will be conducted by flow cytometry at the local laboratory at screening and Cycle 2 Day 1, and at subsequent times only as part of confirmation of CR. Results will be captured in the CRF.

7.5.5. Immunoglobulin M Monitoring

Subjects with WM should have their disease assessed by IgM monitoring of blood serum at baseline (C1D1) and at least every 9 weeks for response assessment per the response criteria defined by Owen et al (2013). This assessment should be performed locally.

7.6. Performance Status

Eastern Cooperative Oncology Group performance status (Appendix C) must be assessed by a medically qualified individual and recorded in the CRF at visits indicated in Table 5.

7.7. Pharmacokinetic Assessments

7.7.1. Blood Sample Collection

Pharmacokinetic samples will be obtained at the visits indicated in Table 6 and Table 8 (Laboratory Assessments) for all subjects enrolled in this study; collection times and windows are described below. The exact date and time of the PK blood draws will be recorded in the CRF along with the date and time of the last dose of study drug preceding the blood draw and the time of the most recent meal. Instructions for sample preparation and shipping will be provided in the Laboratory Manual. Subjects will receive reminder cards in advance of the study visit providing instruction to hold the morning dose of study drug on the day of the visit, and a place to record the time of the prior dose of study drug, and time of the most recent meal or snack consumed.

On Cycle 1 Day 1, study subjects should have fasted overnight; the clinic visit should be scheduled in the morning. For subjects receiving INCB050465 monotherapy only, a predose PK sample will be taken, followed by administration of the INCB050465 only. For subjects receiving the combination with INCB050465, administration of INCB039110 should be started on Day 1 after INCB050465 PK sampling is complete in Part 2 and Part 3 Cohort E. On Cycle 1 Day 1, subjects should arrive at the clinical after an overnight fast; the clinic visit should be scheduled in the morning. Pharmacokinetic blood samples will be obtained at the times shown in Table 12.

On Cycle 1 Day 8 (only for Parts 1, 2, and 3), subjects will refrain from taking study drug in the morning before arriving at the research unit. A trough (predose) PK sample will be taken, followed by administration of the study drug. Overnight fasting is not required.

On Cycle 1 Day 15, subjects will refrain from taking the study drug in the morning before arriving at the research unit. Subjects should have fasted overnight; the clinic visit should be scheduled in the morning, and a trough PK sample should be drawn early in the study visit. The initial schedule for timed postdose samples is shown in Table 12.

In the 15-subject expansion Cohort A, if the dose selected was the MTD in the dose-escalation part of the study, on Cycle 1 Day 15 and Cycle 2 Day 1, the dose administered ONLY for these 2 doses will be 1 dose level below the MTD. If the PAD is selected for the expansion cohort, there will be no alteration to the doses on Cycle 1 Day 15 or Cycle 2 Day 1.

Table 12: Pharmacokinetic Blood Sampling Schedule

		Postdose						
	Predose	**0.5 hr**	**1 hr ± 15 min**	**2 hr ± 15 min**	**4 hr ± 15 min**	**6 hr ± 30 min**	**8 hr ± 30 min**	**12 hr ± 30 min (if possible)**
C1D1	X	X	X	X	X	X	X	X
C1D8[a]	X							
C1D15	X	X	X	X	X	X	X	X
C2D1[b]	X	X	X	X	X	X	X	X

[a] Cycle 1 Day 8 only required for subjects enrolled in Parts 1, 2, and 3.
[b] **Cycle 2 Day 1 only required for subjects enrolled in the food-effect expansion cohort**.

On Cycle 2 Day 1, study subjects in the expansion Cohort A only will be required to undergo PK testing after fed administration on Cycle 2 Day 1 only.

- PK testing conducted on Cycle 2 Day 1 will be similar to that on Cycle 1 Day 15 in respect to the timing of sample collection and evaluations. Subjects may be excused from the food-effect portion of the study if they are unable to consume the meal or feel they are unable to consume the meal.
- Subjects receiving INCB050465 in the fed state will have been fasted from food (not including water) overnight for at least 8 hours. A standardized high-fat, high-calorie breakfast will be given to these subjects approximately 30 minutes before administration of study drug. Subjects must consume the entire breakfast within 25 minutes, and study drug administration will begin 5 minutes after completing breakfast.
- The high-fat, high-calorie breakfast (50% kcal from fat) will consist of:
  - 2 eggs fried in butter
  - 2 strips of bacon
  - 1 English muffin with butter
  - 4 oz hash brown potatoes
  - and 8 oz whole milk
- Alternative menus with the same caloric and fat content may be substituted with the prior approval of the study sponsor.

For fasting subjects, a single dose of the study medication will be taken with 240 mL of water. Subjects will remain fasting and sitting or semirecumbent for 3 hours postdose, after which point a meal may be served. Subjects will abstain from water for 1 hour postdose.

Adjustments to the timing of blood sampling postdose may be made based on emerging PK data; however, no more than 8 postdose timepoints will be used, and the maximum scheduled timepoint will be no greater than 12 hours postdose. If possible, food should be withheld until 1 hour after study drug administration. [redacted] Subjects who meet criteria in Section 5.6.1 for intrasubject dose escalation must agree to perform full PK sampling during the first cycle treated at the higher dose level on Day 15.

7.7.2. Urine Sample Collection

Urine will be collected from each subject on Cycle 1 Day 15 after morning dose and a predose void. A complete urine output collection will be collected from hour 0 (after morning dose) through 8 hours after the first dose of study drug or through 12 hours after the morning dose if a 12-hour postdose PK sample is being performed. The time period and cumulative volume will be recorded and 2 aliquots will be provided to the sponsor according to the instructions provided in the Laboratory Manual. Urine output will be stored under refrigeration (5ºC) during the collection interval.

7.7.3. Bioanalytical Methodology and Analysis

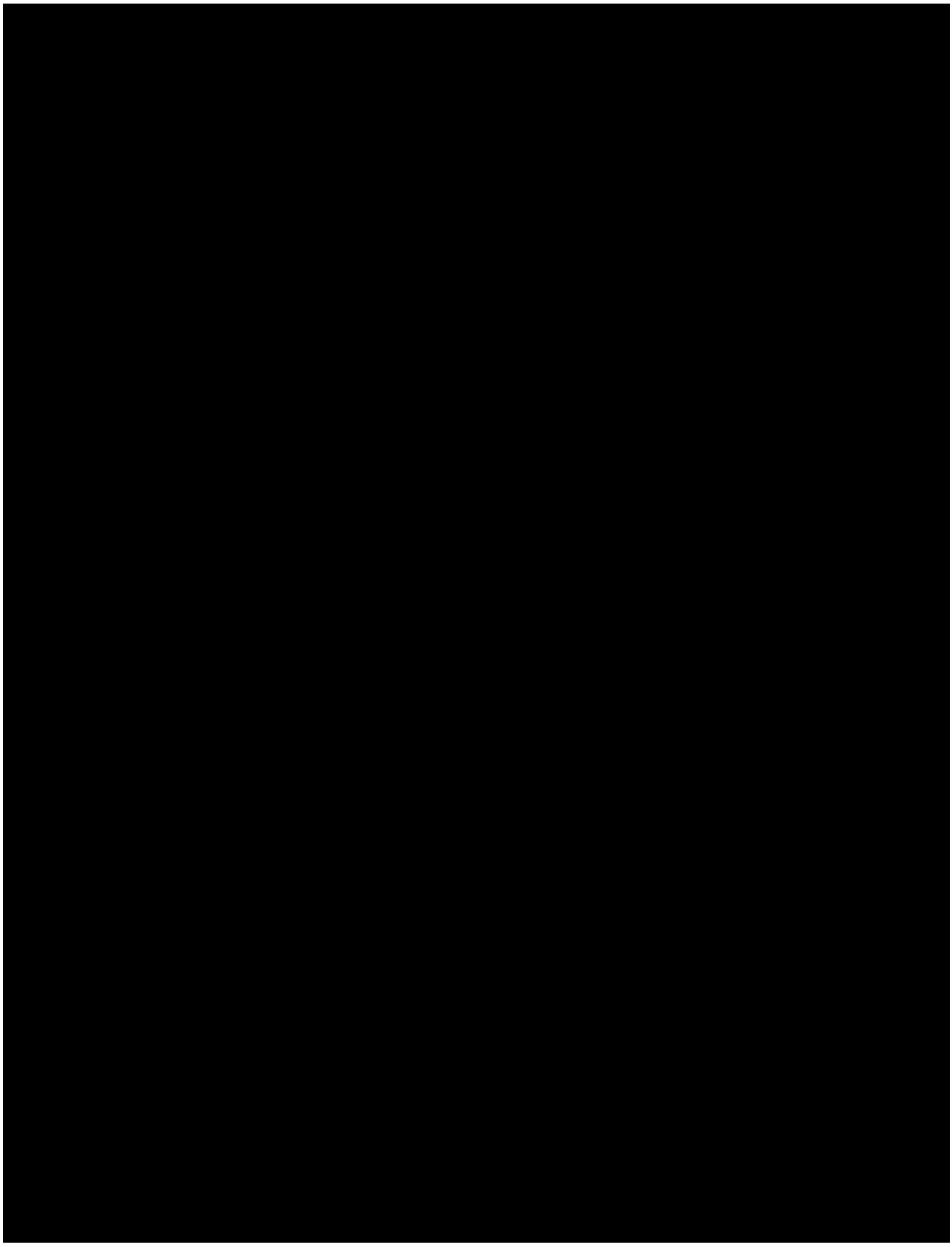
The plasma and urine samples will be analyzed for INCB050465 and INCB039110 by a validated assay and will be collected from all subjects enrolled in this study. [redacted] These samples will be analyzed by Incyte Corporation (Wilmington, DE) or its designee.

For each subject who completes study participation, PK parameters will be calculated from the plasma concentrations of INCB050465 and INCB039110 according to the model independent approach. Refer to Appendix B for a detailed list and description of the PK parameters.

7.7.4. Pharmacokinetic Analysis

The PK calculations will be performed, if appropriate, using commercial software such as WinNonlin® (Pharsight Corporation, Mountain View, CA). Nominal times will be used in all cases, except when the difference between the actual time and nominal time is > 5 minutes for samples collected up to 4 hours after administration and greater than 15 minutes for samples collected more than 4 hours after administration; in these cases, actual time will be used for PK analysis. Additional details of analyses will be described in the Statistical Analysis Plan.

[redacted]



[redacted]

7.10. Other Study Procedures

7.10.1. Drug Administration

After implementation of Amendment 10, subjects will be dispensed the appropriate amount of medication to self-administer study drug as per protocol until their next scheduled visit (scheduled no more than 12 weeks later). Subjects will continue to self-administer study medication, and compliance will continue to be assessed for INCB050465 and INCB039110.

7.10.1.1. Administration of INCB050465

Based on emerging PK and food-effect data (see Section 1.2.4 and the INCB050465 IB), subjects will self-administer INCB050465 tablets orally with water without regard to food, as directed by the investigator. For QD or once-weekly intervals, INCB050465 should be taken , at approximately the same time each day.* If BID doses are used, INCB050465 should be taken morning and evening at approximately 12-hour intervals.

* NOTE: Updated advice will be provided if emerging PK and food-effect data suggest that an improved PK profile may be achieved by administering INCB050465 with food or if food does not have a significant effect on the INCB050465 PK.

INCB050465 will be administered in the study clinic on days indicated in Table 5 and Table 7, and in Section 7.7.1. Subjects will attend the study visit having fasted overnight (for Cycle 1 Day 1 and Cycle 1 Day 15 for all subjects and also at Cycle 2 Day 1 for subjects participating in the food-effect study in Part 3 Expansion Cohort A), recorded the time of the prior administration of INCB050465 and time and content of prior meal, and having withheld the morning dose of INCB050465. At this visit, PK [redacted] sampling will be conducted.

7.10.1.2. Dispensing of INCB050465

An initial bulk supply of INCB050465 tablets will be provided to investigative sites before enrollment of the first subject. Thereafter, the site staff will contact the sponsor for resupply of INCB050465. When dispensing to subjects, the investigator or designee will remove the appropriate quantity of INCB050465 from their stock, dispense the medication, and enter the amount dispensed into the eCRF and drug accountability log. Full details will be provided in the Pharmacy Manual.

7.10.1.3. Assessment of Compliance With INCB050465

The study subject will return to the clinic with full, empty, and partially full bottles of INCB050465 tablets at the beginning of each treatment cycle or at routine visits or every 12 weeks or as defined by standard of care, and a compliance check (tablet count) will be performed by the clinic staff. Appropriate steps should be taken to optimize compliance.

7.10.1.4. Administration of INCB039110

Subjects will self-administer INCB039110 orally, with water, according to a QD regimen as directed by the investigator. INCB039110 should be taken on an empty stomach if possible

(refrain from food consumption during the period 2 hours before and 1 hour after INCB039110 administration) and can be administered at the same time as INCB050465. INCB039110 should be administered in the morning.

INCB039110 will be administered in the study clinic as indicated in Table 5; subjects will attend the study visit having fasted, recorded the time of the prior administration of INCB039110 and prior meal, and having withheld the morning dose of INCBC039110. At this visit, PK [redacted] sampling will be conducted. INCB039110 dose administration will be started on Cycle 1 Day 1 after INCB050465 PK sampling is complete.

7.10.1.5. Dispensation of INCB039110

For subjects enrolled in either Part 2 or Part 3 Expansion Cohort E, an initial bulk of INCB039110 will be provided to investigative sites prior to enrollment of the first subject. Thereafter, the site staff will contact the sponsor for resupply of INCB039110. When dispensing to subjects, the investigator or designee will remove the appropriate quantity of INCB039110 from their stock, dispense the medication, and enter the amount dispensed into the CRF and drug accountability log. Full details will be provided in the Study Manual.

7.10.1.6. Assessment of Compliance With INCB039110

For subjects enrolled in either Part 2 or Part 3 Expansion Cohort E the study subject will return to the clinic with full, empty, and opened/partially used bottles of INCB039110 at the beginning of each treatment cycle or at routine visits or every 12 weeks or as defined by standard of care, and a compliance check (tablet count) will be performed by the clinic staff. Appropriate steps should be taken to optimize compliance.

7.10.1.7. Sourcing and Administration of Standard of Care Agents

The standard of care agents described above will be supplied by the site. These agents are all administered by intravenous infusion in clinic.

7.10.1.8. Assessment of Compliance With Standard of Care Agents

The site will document the amount of infusion administered to the subject at each appropriate visit. This information will be captured in the eCRF.

7.10.1.9. Administration of Supportive Care

Supportive care, including GCSF for treatment of chemotherapy-induced neutropenia, will be supplied by the institution's pharmacy and administered according to the package insert and institutional guidelines.

7.10.2. Distribution of Subject Reminder Cards/Subject Diaries

Subjects will be provided with subject reminder cards at each visit. The subject reminder cards will indicate the date and time of the next visit. Reminder cards will include instructions specific for Day 8 and Day 15 study visits, at which time the subject will refrain from taking the study drug at home in the morning before the clinic visit. All necessary instructions, such as administration instructions for study drug, concomitant medications, and reminders of visits to conduct laboratory tests, should be provided to the subject in writing on this reminder card, or on

accompanying written materials. Subject diaries will be provided for the purpose of documenting study drug administration and AEs. The subject diary will have an area on which the date and time of the last dose taken before each visit will be recorded as well as the time (and content if applicable to the visit) of the last meal.

After implementation of Amendment 10, subjects will receive reminder cards that will include the date and time of the next visit and instructions for study treatment administration.

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions and Reporting

For the purposes of this Protocol, an AE is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur 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).

Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events page of the CRF. Conditions that were already present at the time of informed consent should be recorded on the Medical History page of the CRF. Adverse event monitoring 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.

Adverse events will be assessed according to the CTCAE version 4.03. The CTCAE severity Grade 5 (death) will not be used in this study; rather, information about deaths will be collected as an outcome of the event. 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.

As far as possible, each AE should be evaluated to determine:

- The severity grade (CTCAE Grade 1 to 4).
- Reasonable possibility that the AE is related to the study treatment: unrelated (no) or related (yes).
  - **NOTE: for subjects receiving combination therapy, causality assessment for each agent administered per study must be indicated.**
- Start and end dates, unless unresolved at final examination.
- Action taken with respect to study drug (eg, none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable).

- Outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- Whether it is serious, 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 a concomitant medication or nondrug therapy is given, this action should be recorded on the AE and Prior/Concomitant medications pages of the CRF.

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 it, and the outcome.

Disease progression should not be regarded or reported as an AE itself, unless it is associated with a separate AE.

Upon implementation of Amendment 10, AEs leading to treatment discontinuation and all SAEs regardless of causal relationship must be reported on the AE CRF.

8.2. Laboratory Test Abnormalities

8.2.1. Definitions and Reporting

Laboratory abnormalities that constitute an AE in their own right (are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug), should be recorded on the AE page of the CRF. 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, as per CTCAE, does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1, and/or per the investigator's discretion. A dose interruption or adjustment for the laboratory abnormality may be required (see Section 5.6) and should not contribute to the designation of a laboratory test abnormality as an SAE.

8.3. Serious Adverse Events

8.3.1. Definitions

A SAE is defined as an event that meets 1 of the following criteria:

- Is fatal or life-threatening (ie, immediate risk of dying).
- Results in persistent or significant disability or incapacity.
- Constitutes a congenital anomaly or birth defect.
- Is clinically meaningful (ie, defined as an event that jeopardizes the subject or requires potential medical or surgical intervention to prevent 1 of the outcomes listed above). Considered meaningful by the investigator as an important medical event that may not result in death, be life-threatening, or require hospitalization, but may be considered a SAE when, based upon appropriate medical judgment, it may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
  - Routine treatment or monitoring of the studied indication not associated with any deterioration in condition
  - Elective or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF.
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
  - Social reasons and respite care, in the absence of any deterioration in the subject's general condition.
  - Any SAEs that are expected due to the condition being treated, including if the SAE is a primary outcome measure, or where there has been a clear agreement with regulators not to consider these as SAEs, provided the information is collected elsewhere.

8.3.2. Reporting

To ensure subject safety, every SAE, regardless of suspected causality, occurring after the subject has signed the ICF and up to the last study visit, or up to 30 days after the subject has stopped study treatment, whichever is later, must be reported to the sponsor (or designee) within 24 hours of learning of its occurrence. Any SAEs experienced after this period should be reported to the sponsor (or designee) only if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as the follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Previously planned (before providing informed consent) surgeries should not be reported as SAEs unless the underlying medical condition worsens over the course of the study.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study drug (if there is more than 1), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the sponsor or its designee. The investigator must assess if there is a reasonable possibility that the SAE is related to the study treatment: unrelated (no) or related (yes).

Serious AEs related to unblinded comparator drugs or concomitant medications/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

The telephone and facsimile number of the sponsor's contact persons, specific to the study, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the CRF documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each recurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation, or if study drug was interrupted or discontinued.

If the SAE is not previously documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, a sponsor's associate 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.

Upon implementation of Amendment 10, all SAEs regardless of causal relationship will be reported as described above.

8.4. Emergency Unblinding of Treatment Assignment

Not applicable.

8.5. 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, the following procedures should occur:

- The investigator must notify the sponsor or its designee immediately.
- The study drug must be discontinued immediately.

- The subject must be withdrawn from the study.
- The EOT visit evaluations must be performed.
- The investigator must complete and submit the Pregnancy Initial and Follow-Up Report forms to the sponsor or its designee.
- A serum pregnancy test must be performed to confirm the urine pregnancy test result. (The serum test should be performed at the investigative site to ensure the test will be performed promptly and the result available immediately for review.)

If a negative serum test does not confirm the urine pregnancy test result, then:

- The investigator will use his or her expert judgment, based on an assessment of the potential benefit/risk to the subject, to determine if it is in the subject's best interest to resume study drug and continue participation in the study.

To ensure subject safety, each pregnancy in a subject during maternal or paternal exposures to study drug must be reported within 24 hours of learning of its occurrence. Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up to each pregnancy should be conducted 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 Study Pregnancy Form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the sponsor's study drug of any pregnancy outcome and follow-up to the first well-baby visit. **Any SAE experienced during pregnancy must be reported on the SAE Report Form and to the sponsor or its designee.**

8.6. Warnings and Precautions

No evidence available at the time of the approval of this study Protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided 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 needed. If new, significant risks are identified, they will be added to the ICF.

8.7. Data Monitoring Committee

A formal Data Monitoring Committee will not be used for this study. The sponsor will continuously monitor safety through frequent contact with the treating investigators, review of the clinical data, and formal study meetings. Routine 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.

8.8. Adverse Events of Special Interest

INCB050465 is a potent and selective PI3Kδ inhibitor, which is a key target in the BCR survival pathway in normal and malignant B-lymphocytes. In animal studies, lymphoid depletion was observed and may also occur in humans. This may result in infections, fever, or cytokine release resulting in fever, chills, hypotension, wheezing, and/or rash. Reversible minimal to mild hypospermatogenesis was observed in rats at doses that exceed the intended starting clinical dose and anticipated therapeutic dose in humans. For additional information on the risks of treatment with INCB050465 and INCB039110, see Sections 1.2.3, 1.3.5, and 1.4.4.

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.

The investigator or his/her designee is responsible for reporting a complete description of the product complaint and any associated AEs via email or other written communication to the Incyte contact.

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/safety population:** Subjects enrolled in the study who received at least 1 dose of INCB050465, INCB039110, rituximab, ifosfamide, carboplatin, and/or etoposide.
- **Per-Protocol (PP) population:** Subjects in the ITT/safety population who are sufficiently compliant with the Protocol. Details will be provided in the SAP.
- **PK [redacted] population:** Subjects in the ITT/safety population who had PK [redacted] data.

The ITT/safety population will be used for the summary of baseline, disposition, efficacy, and safety analyses. The PP population may be used in the sensitivity analysis of efficacy endpoints. The PK [redacted] population will be used in the summary of all PK [redacted] data.

9.2. Selection of Sample Size

The total sample size estimate is up to approximately 150 subjects in this study. Approximately 20 subjects will be enrolled in Part 1 monotherapy dose escalation, and approximately 12 subjects will be enrolled in Part 2 combination dose escalation. Expansion Cohort A will enroll between 15 and 30 subjects, and Cohorts B, C, D, and E will enroll up to 15 subjects each.

In Part 6, up to 12 subjects will be enrolled in the safety evaluation followed by an expansion cohort of up to15 subjects. The exact number of subjects treated will depend on the number of subjects required per dose level and the number of dose levels studied. During the 3 + 3 dose escalation in Part 1 and Part 2, the probabilities of dose escalation from that dose level for various DLT rates are given in Table 13.

Table 13: Probability of Dose Escalation for Specific Dose-Limiting Toxicity Rates During 3 + 3 Dose Escalation

True DLT Rate	Probability of Dose Escalation
10%	90.6%
20%	70.9%
30%	49.4%
40%	30.9%
50%	17.2%
60%	8.2%

Note that if escalation occurs at the highest dose level during the study, then the MTD is at or above the last dose level. If the study stops at the first dose, then the MTD is below the first dose level. In either of these cases, the prescribed doses may need to be altered in order to determine the MTD.

In the expansion cohorts the evaluation of 15 subjects, each will provide a ≥ 90% chance of identifying a toxicity with a true event rate of 15%.

9.3. Level of Significance

No hypothesis is being tested in the study. All CIs will be 95%.

9.4. Statistical Analyses

9.4.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; Version 9 or later) will be used for the generation of all tables, graphs, and statistical analyses. Descriptive summaries for continuous variables will include, but not be limited to, the number of observations, mean, standard deviation, median, minimum, and maximum. Descriptive summaries for categorical variables will include the number and percentage of subjects in each category.

Data will be summarized overall and by treatment cohorts based on the dose regimen initially assigned. In the event that several dose regimens tested are deemed substantially below the MTD, these doses may be combined for summary purposes.

9.4.2. Efficacy Analyses

The efficacy endpoints will be analyzed using the ITT and the PP populations.

Response status per investigator's assessment will be categorized at each response assessment visit as CR, very good partial response (VGPR; only among subjects with WM), partial response (PR), minor response (MR; only among subjects with WM), stable disease (SD), progressive

disease, or not evaluable (NE) per published criteria for lymphoma (Cheson et al 2014, Owen et al 2013 for WM) and CLL (Hallek et al 2008, Cheson et al 2012). In the unlikely situation that the subject does not have any disease at baseline, the best response will be denoted as no disease (ND).

Best overall response is the best response recorded during the study treatment before and including the first progressive disease, in the order of CR, PR, SD, progressive disease, NE, and ND.

A subject is considered an objective responder if they have a best overall response of CR or PR for lymphoma or CR, VGPR, PR, or MR for WM. The ORR is the proportion of objective responders. Subjects who do not have sufficient baseline or on-study response assessment information to be adequately assessed for response status will be included in the denominators in the calculation of ORR. ORR will be estimated with 95% CI, which will be calculated based on the exact method for binomial distributions. Best overall response will also be summarized.

For subjects with CLL, changes in peripheral blood leukemic cells from baseline to each post-treatment assessment will be summarized with mean, median, standard error, and 95% CIs.

For subjects with measurable lesions, target lesion sizes will be measured by sum of product of diameters (SPD). The best percent change from baseline, defined as the largest decrease in SPD during study will also be summarized, and a waterfall plot of best percent change will be generated. Note that for subjects who only have increases in SPD from baseline, the smallest increase will be considered as the best change from baseline.

9.4.3. Safety Analyses

The clinical safety data (vital signs, ECGs, routine laboratory tests, physical examinations, and AEs) will be summarized using descriptive statistics (eg, mean, frequency) using the safety population.

Summary tables may be replaced with listings when appropriate. For instance, an AE frequency table may be replaced with a listing if it only contains a few unique preferred terms reported on

relatively few subjects. Unless otherwise stated, table summaries will be limited to AEs occurring within 30 days of the last administration of study medication.

9.4.3.1. Adverse Events

A treatment-emergent AE (TEAE) is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study drug administration.

Unresolved missing onset date, causality, or severity will be handled according to the following rules:

- An unresolved missing causality will be considered treatment-related.
- An unresolved missing severity will be identified as an unknown severity.
- A unresolved missing onset date will be considered treatment-emergent, with the following examples illustrating exceptions:
  - If the stop/resolution date is before the first dose date on Day 1, then the AE will be considered as not being treatment-emergent.
  - If both the month and day are missing, and the last day of the year is before the first dose date on Day 1, then the AE will not be considered treatment-emergent.
  - If only the day is missing, and the last day of the month is before the first dose date on Day 1, then the AE will not be considered treatment-emergent.
  - If only the day is missing, and the first day of the month is after the first dose date on Day 1, then the AE will be considered treatment-emergent.

Adverse events will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA®) coding dictionary. Severity of AEs will be based on the NCI CTCAE version 4.03.

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, the AE will be considered to be treatment-related.

The number of subjects with DLTs during the first cycle of study medication and the type of DLT will be listed.

An overall summary of AEs will include number (%) of subjects reporting any TEAEs, any DLTs in Cycle 1, any SAEs, any Grade 3 or 4 TEAEs, any treatment-related TEAEs, any fatal TEAE, any TEAEs leading to dose interruption/reduction/discontinuation, and any TEAEs leading to study discontinuation.

Number (%) of subjects reporting any TEAEs, any SAEs, any Grade 3 or 4 TEAEs, any treatment-related TEAEs, any treatment-related SAEs, any treatment-related Grade 3 or 4 TEAEs, any fatal TEAE, any TEAEs leading to dose interruption/reduction/discontinuation, and any TEAEs leading to study discontinuation will be tabulated by system organ class and preferred term. Number (%) of subjects reporting any TEAEs and any treatment-related TEAEs will be tabulated by preferred term in decreasing order of frequency in the overall column, and by system organ class, preferred term, and maximum severity.

9.4.3.2. Clinical Laboratory Tests

The SI unit will be used for all 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 assessed for severity based on NCI CTCAE version 4.03. For specific laboratory parameters requiring clinical intervention to grade, the classification according to the quantitative component will be provided.

For numeric laboratory values, baseline value, postbaseline value, change from baseline, and percent change from baseline will be summarized by visit.

Shift summaries will be presented showing number and percentage of subjects with the laboratory values being low, normal, and high at baseline and at each of the scheduled postbaseline visits. The denominator for the percentage calculation will use the number of subjects in the baseline category (ie, low, high, normal, missing).

For the laboratory parameters that have CTCAE grading, shift tables will also be presented showing change in CTCAE severity grade from baseline to worst grade postbaseline. Separate tables will be provided for selected laboratory tests that have grading criteria in both high and low directions. All postbaseline values occurring within 30 days of last dose of study drug will be included when summarizing worst postbaseline grade. The denominator for the percentage calculation will be the number of subjects in the baseline category.

Categorical laboratory data will be tabulated by visit at baseline and postbaseline visits when necessary.

9.4.3.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, heart rate, and body temperature) at each assessment time. Criteria for clinically notable vital sign abnormalities are defined in Table 14. The abnormal values for subjects exhibiting clinically notable vital sign abnormalities will be listed.

Alert vital signs are defined as an absolute value outside the defined range and absolute percentage change greater than 25%. The abnormal values for subjects exhibiting alert vital sign abnormalities will be listed.

Table 14: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 mm Hg	< 85 mm Hg
Diastolic blood pressure	> 100 mm Hg	< 40 mm Hg
Heart rate	> 100 bpm	< 45 bpm
Temperature	> 38°C	< 35.5ºC

9.4.3.4. Electrocardiograms

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time. Average of all values before the first dose of study drug will be used as the baseline value. Criteria for clinically notable ECG abnormalities are defined in Table 15. The abnormal values for subjects exhibiting clinically notable ECG abnormalities will be listed.

Alert ECG values are defined as an absolute value outside the defined range and absolute percentage change > 25% (30% for QRS) interval. The abnormal values for subjects exhibiting alert vital sign abnormalities will be listed.

Outliers of QT, QTcB, and QTcF, defined as absolute values > 450 milliseconds or change from baseline > 30 milliseconds, will also be listed.

Table 15: Criteria for Clinically Notable ECG Abnormalities

Parameter	High Threshold	Low Threshold
QTcF	> 460 msec	< 295 msec
PR	> 220 msec	< 75 msec
QRS	> 120 msec	< 50 msec
QT	> 500 msec	< 300 msec
RR	> 1330 msec	< 600 msec

QTcF = Fridericia correction.

9.4.4. Other Analyses

[redacted]

- The PK parameters of INCB050465 and INCB039110 will be summarized by descriptive statistics by dose group and cohort. The log-transformed PK parameters of INCB050465 will be compared among the dose levels by using a 1-factor analysis of variance (ANOVA). Dose-dependent parameters (C_{max} and AUC) will be normalized to the lowest common dose before statistical comparisons. C_{max} and AUC will be evaluated using a power model, eg, $AUC = \alpha \cdot (dose^{\beta})$ or equivalently, $\log(AUC) = \log(\alpha) + \beta \cdot \log(dose)$, where linear dose proportionality is accepted if β is not significantly different from 1. Attainment of steady state will be assessed separately for each cohort by comparing trough plasma concentrations on Days 8 and 15 during Cycle 1.
- For the food-effect portion of the study, the log-transformed PK parameters of INCB050465 will be compared between the fed and fasted treatments using an ANOVA for a 1-way crossover design. The geometric mean relative bioavailability and 90% CIs will be calculated for comparing C_{max} and AUC between the fed (test) and fasted (reference) treatments.

9.5. Data Monitoring Committee

Not applicable.

9.6. Interim Analysis

Not applicable.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Investigational Product Description – INCB050465

10.1.1. Packaging, Labeling, and Preparation of Study Drug

INCB050465 tablets are provided in high-density polyethylene bottles; no preparation is required. All bottles of Incyte investigational product contain the following language: "Caution: New Drug—Limited by Federal Law to Investigational Use."

10.1.2. Formulation and Chemical Properties of INCB050465

Physical and chemical properties of INCB050465 are summarized in the INCB050465 IB. INCB050465 is formulated as 2.5 and 5 mg tablets (free-base equivalent). A tablet strength of 20 mg may also be used depending on the dose escalation of INCB050465.

10.1.3. Storage and Stability of INCB050465

INCB050465 drug product should be stored under ambient conditions at 15°C to 30°C (59°F to 86°F).

10.2. Investigational Product Description – INCB039110 (Comedication for Part 2 and Expansion Cohort E)

10.2.1. Packaging, Labeling, and Preparation of INCB039110

INCB039110 is provided in high-density polyethylene bottles of 35 tablets; no preparation is required. All bottles of Incyte investigational product contain the following language: "Caution: New Drug—Limited by Federal Law to Investigational Use."

10.2.2. Formulation and Chemical Properties of INCB039110

Physical and chemical properties of INCB039110 are summarized in the INCB039110 IB. INCB039110 is formulated as 100 mg (free-base equivalent) SR tablets. (The 100 mg formulation is referred to in the INCB039110 IB as SR3.)

10.2.3. Storage and Stability of INCB039110

The bottles of tablets should be stored under ambient conditions at 15°C to 30°C (59°F to 86°F).

10.3. Accountability, Handling, and Disposal of Study Drug

Responsibility for drug accountability at the study site rests with the investigator; however, the investigator may assign some of the drug accountability duties 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 will be expected to collect and retain all used, unused, and partially used containers of study drug until the end of the study. 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.

These records should include dates, quantities, batch or serial numbers (if available), and the unique code numbers (if available) assigned to the investigational product and study 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 correct study drug specified.

Completed accountability records will be archived by the site. At the completion 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 site destruction of investigational supply, prior written approval must be obtained from Incyte.

11. STUDY ADMINISTRATION

11.1. Data Management

11.1.1. Data Collection

The investigator will be provided with a CRF for each subject. Entries made in the CRF must be verifiable against source documents; any discrepancies should be explained and documented. The investigator will be responsible for reviewing all data and CRF entries and will sign and date the designated pages in each subject's CRF, verifying that the information is true and correct. The investigator is responsible for the review and approval of all responses.

11.1.2. Data Management

Data management will be performed from CRFs. All CRF data will be entered into a validated database. 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 will be authorized for lock once all defined procedures are completed.

11.2. Study Monitoring

Qualified representatives of the sponsor or its designee, "study monitors," will monitor the study according to a predetermined monitoring plan. Monitoring visits provide the sponsor with the opportunity to:

- Evaluate the progress of the study.
- Verify the accuracy and completeness of CRFs.
- Assure that all Protocol requirements, applicable laws and/or regulations, and investigator's obligations are being fulfilled.
- Resolve any inconsistencies in the study records.

The investigator must allow the study monitors to periodically review, at mutually convenient times during the study and after the study has been completed, all CRFs and office, hospital, and laboratory records supporting the participation of each subject in the study. The CRFs and other documentation supporting the study must be kept up-to-date by the investigator and the research staff at the investigative site. These study materials must be available for review by the study monitor, and/or other qualified representatives of the sponsor or its designee, at each monitoring visit.

The study monitor will review the various records of the study (CRFs, subject medical and laboratory records, and other pertinent data). The study monitor will verify the CRF data against original source documentation for accuracy and completeness. The study monitor will identify data discrepancies and collaborate with the investigator and research staff to resolve the discrepancies in a timely manner. Protocol deviations will also be identified and recorded on a "Protocol Deviation Log." The study monitor will follow an "Issue Escalation" plan in order to ensure that each issue identified during a monitoring visit is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements.

11.3. Protocol Adherence

The principal investigator must obtain IRB or IEC approval for the investigation. Initial IRB or IEC approval and all materials approved by the IRB or IEC for this study including the subject ICF and recruitment materials must be maintained by the investigator and made available for inspection.

Each investigator must adhere to the Protocol as described in this document and agree that changes to the Protocol, with the exception of medical emergencies, must be discussed and approved, firstly, by the sponsor or its designee and, secondly, by the IRB or IEC. Each investigator is responsible for enrolling subjects who have met the Protocol inclusion and exclusion criteria. The IRB or IEC that granted original approval, or the IRB or IEC currently responsible for overseeing the conduct of the study, must be notified of all changes in and deviations from the Protocol that may increase risk to the subject, and/or that may adversely affect the rights of the subject or validity of the investigation. The investigator must send a copy of the approval letter from the IRB or IEC to the sponsor or its designee and retain the original in the site study regulatory file.

Major eligibility deviations must be reported to the IRB or IEC in accordance with the IRB or IEC requirements. During the course of the study, the monitor must notify the sponsor or its designee of subjects found not to have met eligibility criteria. The medical monitor, in collaboration with the investigator, will determine if the subject should be withdrawn from the study.

11.4. Financial Disclosure

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, are required before study initiation to submit a completed clinical investigator Financial Disclosure Request 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. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new investigators or subinvestigators added to the covered clinical study during its conduct must also submit a completed clinical investigator Financial Disclosure Request 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 obligation to report to the sponsor or its designee any changes to the financial information previously reported. The clinical investigators will also be reminded that they must report any changes in their financial information for a period of 1 year after completion of the covered clinical study.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Sponsor Audits

At some point during the study, individuals from the sponsor's Quality Assurance department and/or their authorized representative may visit the investigator's site to conduct an audit of the study. The purpose of this visit will be to determine the investigator's adherence to the Protocol, applicable regulations, and the sponsor's procedures, in addition to assessing the accuracy of the study data. Before initiating this audit, the investigator will be contacted by the sponsor to arrange a convenient time for this visit. The investigator and staff are expected to cooperate with the auditors and allow access to all subject records supporting the CRFs and other study-related documents.

12.2. Inspection by Regulatory Authorities

At some point during the investigational product's development program, a regulatory authority may visit the investigator to conduct an inspection of the study and the site. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the CRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for purposes of conducting an inspection.

13. ETHICS

13.1. Ethical Conduct of the Study

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, GCPs as defined in Title 21 of the US CFR Parts 50, 54 56, 312, and Part 11, as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

13.2. Written Informed Consent

Informed consent documentation that includes both information about the study and the ICF will be prepared and given to the subject. This document will contain all elements required by the ICH E6 Guideline for GCP and any additional elements required by local regulations. The document must be in a language understandable to the subject and must specify who informed the subject. Where required by local law, the person who informs the subject must be a physician.

The principal investigator at each center will ensure that the subject is given full and adequate verbal and written information about the nature, purpose, and the possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue study drug and withdraw from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated ICF must be obtained before conducting any study procedures. The principal investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject. The investigator should inform the subject's primary physician about the subject's participation in the study if the subject has a primary physician and if the subject agrees to the primary physician being informed.

Preparation of the ICF is the responsibility of the investigator and must include all elements required by the ICH GCP, and applicable regulatory requirements, and must adhere to the ethical principles that have their origin in the Declaration of Helsinki. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and approve all changes to site-specific ICFs. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to subject records. Before the beginning of the study, the IRB or IEC must provide the investigator with written approval/favorable opinion of the written ICF and any other information to be provided to the subjects.

13.3. Ethics Review

It is the responsibility of the investigator to assure that all aspects of the ethics review are conducted in accordance with the Declaration of Helsinki as described in the ICH E6: Guideline for GCP, and/or local laws, whichever provides the greatest level of protection for the study participants. The Protocol and any information supplied to the subject to obtain informed consent, including written ICFs, subject recruitment procedures (eg, advertisements), and written information to be provided to subjects (information leaflets), must be reviewed and approved by a qualified IRB/IEC before enrollment of participants in the study. Before initiation of the study,

the sponsor or its designee must receive documentation of the IRB or IEC approval, which specifically identifies the study/protocol, and a list of the committee members.

The principal investigator is responsible for informing the IRB or IEC of any amendment to the Protocol in accordance with local requirements. Protocol amendments and revisions to the ICF must be submitted to and approved by the IRB or IEC.

Investigators must submit progress reports to the IRB or IEC in accordance with the IRB or IEC requirements and local regulations. Annual re-approval of the study must be obtained. Copies of progress reports and annual re-approvals must be sent to the sponsor or its designee.

The principal investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The sponsor or its designee will provide this information to the principal investigator.

When the sponsor or its designee provides the investigator with a safety report, the investigator must promptly forward a copy to the IRB or IEC.

After completion or termination of the study, the investigator must submit a final report to the IRB or IEC and to the sponsor or its designee.

The investigator, as part of the records retention requirements for the study, must maintain documentation of all submissions, correspondence, and approvals to and from the IRB or IEC.

Each clinical investigator is responsible to conduct the study in accordance with the Protocol, all applicable laws, regulations, and GCP according to ICH guidelines.

13.4. Data Privacy

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.

14. DATA HANDLING AND RECORDKEEPING

14.1. Inspection of Records

The sponsor or its designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

The investigator must ensure that all records pertaining to the conduct of the clinical study (as listed above) are adequately maintained for a period of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal termination of clinical development of the investigational product.

14.2. Retention of Records

The principal investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved, 2 years following the termination of the test article for investigation. If it becomes necessary for the sponsor or the regulatory authority to review any documentation relating to the study, the investigator must permit access to such records.

The investigator must not destroy any records associated with the study without receiving approval from Incyte. 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.

Whenever possible, an original recording of an observation must be retained as the source document. However, a photocopy of a record is acceptable, provided it is legible and is a verified copy of the original document.

All CRF 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 CRF data and audit trail.

14.3. Confidentiality

Subject names will not be supplied to the sponsor or its designee if applicable. Only the subject number and subject's initials will be recorded in the CRF, 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.

15. 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. 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. The signed agreement is 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. PHARMACOKINETIC ANALYTICAL PARAMETERS

C_{ave}	Average steady-state plasma concentration ($AUC_{0\text{-}12h}$/12h or $AUC_{0\text{-}24h}$/24h)
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration during the dosing interval
T_{max}	Time to maximum plasma concentration
$AUC_{0\text{-}t}$	Area under the single-dose plasma concentration-time curve from Hour 0 to the last quantifiable measurable plasma concentration, calculated by the linear trapezoidal rule for increasing concentrations and the log trapezoidal rule for decreasing concentrations
$AUC_{0\text{-}\tau}$ (ie, $AUC_{0\text{-}12h}$ or $AUC_{0\text{-}24h}$)	Area under the steady-state plasma concentration-time curve over 1 dosing interval (ie, from Hour 0 to 12 for BID administration or from Hour 0 to 24 for QD administration), calculated by the linear trapezoidal rule for increasing concentrations and the log trapezoidal rule for decreasing concentrations
λ_z	Apparent terminal phase disposition rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase
$t_{½}$	Apparent plasma terminal phase disposition half-life (whenever possible), where $t_{½} = (\ln 2) / \lambda_z$
Cl/F	Oral dose clearance
V_z/F	Apparent oral dose volume of distribution
Fluctuation	Steady-state fluctuation ($[C_{max} – C_{min}]/C_{ave}$)

In addition, the following PK parameters may be calculated, whenever possible, for each subject based on the urine INCB050465 concentrations:

A_e	Amount of drug excreted in the urine over sampling interval
Cl_r	Renal clearance, where $Cl_r = A_e/AUC$
% Excreted or f_e	percent excreted in the urine, where % Excreted = 100 (A_e/dose)

Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as WinNonlin® (Pharsight Corporation, Mountain View, CA). Additional details of analyses will be described in the Statistical Analysis Plan.

APPENDIX C. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Source: Oken et al 1982.

APPENDIX D. RESPONSE CRITERIA FOR LYMPHOMA

LYMPHOMA RESPONSE CRITERIA – The Lugano Classification (Cheson et al 2014)

Site	PET–Based Response	CT/MRI-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.	• ≥ 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 value. • When no longer visible, 0 × 0 mm. For a node > 5 mm × 5 mm but smaller than normal, use actual measurement for calculation.
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, consideration should be given for further evaluation with MRI or biopsy at interval scan.	Not applicable.

Site	PET–Based Response	CT/MRI-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 one of the following):**
Individual target nodes/nodal lesions	Individual target nodes/nodal lesions: • Score 4 or 5[a] 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 end-of-treatment 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 ○ An increase in LDi or SDi from nadir ▪ 0.5 cm for lesions ≤ 2 cm ▪ 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.

5PS = 5-point scale; LDi = longest transverse diameter of lesion; MRI = magnetic resonance imaging; 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.

APPENDIX E. RESPONSE CRITERIA FOR CLL

CLL- DEFINITION OF RESPONSE, RELAPSE AND REFRACTORY DISEASE MODIFIED FROM IWGCLL (Hallek et al 2008, Cheson et al 2012)

Complete Response (CR)

CR requires all of the following criteria as assessed:

1. Absence of clonal lymphocytes in the peripheral blood.
2. Absence of significant lymphadenopathy (eg, Lymph nodes > 1.5 cm in diameter) by physical examination and in CT scan of the chest abdomen and pelvis.
3. No hepatomegaly or splenomegaly by physical examination and confirmed by CT scan.
4. Absence of constitutional symptoms.
5. Blood counts above the following values:
    a. Neutrophils > 1.5×10^9/L without the need exogenous growth factors.
    b. Platelets > 100×10^9/L without the need for exogenous growth factors.
    c. Hemoglobin > 110 g/L without the red blood cell transfusion or need for exogenous erythropoietin.
6. A marrow aspirate and biopsy should be performed if clinical and laboratory results listed in criteria 1 through 5 demonstrate that a CR has been achieved. The marrow should be assessed by flow cytometry and immunohistochemistry to demonstrate that the marrow is free of clonal B-lymphocytes. If marrow is hypocellular a repeat marrow should be conducted in about 4 to 6 weeks provided criteria 1 through 5 are still satisfied.

Partial Response (PR)

To define a PR, the following parameters need to be documented for a minimum of 2 months duration. Constitutional symptoms persisting for more than 1 month should be recorded.

1. A decrease in the number of blood lymphocytes by 50% or more from the values before therapy. Note: Persistent lymphocytosis should not interfere with the time of designation of a PR, which should be based more on the other measurable aspects of the disease than on lymphocytosis.
2. Reduction in lymphadenopathy by CT scan as defined by the following:
    a. A decrease in lymph node size by 50% or more in the sum products of up to 6 lymph nodes or in 1 lymph node diameter if only a single lymph node was present before therapy.
    b. No increase in any lymph node and no new enlarged lymph node. In small lymph nodes (< 2 cm) an increase of < 25% is not considered to be significant.
3. A reduction in the noted pretreatment enlargement of the spleen or liver by 50% or more, as detected by CT scan (clinical studies) or palpation (general practice).

4. The blood count should show one of the following:
    a. Neutrophils > 1.5×10^9 /L without the need for exogenous growth factors.
    b. Platelets > 100×10^9 /L without the need for exogenous growth factors
    c. Hemoglobin > 11.0 g/dL without the red blood cell transfusion or need for exogenous erythropoietin.

Progressive Disease*

Progressive disease during or after therapy is characterized by at least one of the following that is confirmed with repeated observations and incorporates indicators of progressive disease that are not typically associated with tumor flare OR rely on indicators of progressive disease that do not resolve after use of measures to mitigate the signs or symptoms of tumor flare:

1. Lymphadenopathy:
    a. Appearance of any new lesion such as enlarged lymph nodes (> 1.5 cm), splenomegaly, hepatomegaly or other organ infiltrates.
    b. An increase by 50% or more in greatest determined diameter of any previous site. A lymph node of 1 to 1.5 cm must increase by 50% or more to a size greater than 1.5 cm in the longest axis. A lymph node of more than 1.5 cm must increase to more than 2.0 cm in the longest axis.
    c. An increase of 50% or more in the sum of the product of diameters of multiple nodes.
    d. Appearance of new lesions such as new lymphadenopathy (> 1.5 cm), splenomegaly, hepatomegaly or other organ infiltrates.
2. An increase in the liver or spleen size by 50% or more or the *de novo* appearance of hepatomegaly or splenomegaly.
3. An increase in the number of blood lymphocytes by 50% or more with at least 5,000 B-lymphocytes/µL AND at least 1 sign or symptom of disease progression. Lymphocytosis alone should not be considered progressive disease.
4. Transformation to a more aggressive histology (eg, Richter syndrome). This diagnosis should be established by lymph node biopsy.
5. Occurrence of cytopenia (neutropenia, anemia or thrombocytopenia) attributable to CLL.

* Including modified criteria as referenced in Cheson et al 2012.

Stable Disease

Patients who have not achieved a CR or a PR and who have not exhibited PD will be considered to have stable disease (which is equivalent to a nonresponse).

APPENDIX F. RESPONSE ASSESSMENT IN WALDENSTRÖM MACROGLOBULINEMIA

Categorical Response Definitions in Waldenström Macroglobulinemia

Response Category	Response Definition
Complete Response	• Absence of serum monoclonal IgM protein by immunofixation • Normal serum IgM level • Complete resolution of extramedullary disease, ie, lymphadenopathy and splenomegaly if present at baseline • Morphologically normal bone marrow aspirate and trephine biopsy
Very Good Partial Response	• Monoclonal IgM protein is detectable ≥ 90% reduction in serum IgM level from baseline[a] • Complete resolution of extramedullary disease, ie, lymphadenopathy/splenomegaly if present at baseline • No new signs or symptoms of active disease
Partial Response	• Monoclonal IgM protein is detectable ≥ 50% but < 90% reduction in serum IgM level from baseline[a] • Reduction in extramedullary disease, ie, lymphadenopathy/splenomegaly if present at baseline • No new signs or symptoms of active disease
Minor Response	• Monoclonal IgM protein is detectable ≥ 25% but < 50% reduction in serum IgM level from baseline[a] • No new signs or symptoms of active disease
Stable Disease	• Monoclonal IgM protein is detectable < 25% reduction and < 25% increase in serum IgM level from baseline[a] • No progression in extramedullary disease, ie, lymphadenopathy/splenomegaly • No new signs or symptoms of active disease
Progressive Disease	• ≥ 25% increase in serum IgM level[a] from lowest nadir (requires confirmation) and/or • Progression in clinical features attributable the disease

[a] Sequential changes in IgM levels may be determined either by M protein quantification by densitometry or total serum IgM quantitation by nephelometry.
Source: Owen et al 2013.

APPENDIX G. PROHIBITED AND RESTRICTED MEDICATIONS

In Vivo CYP3A4 Inhibitors

Precipitant	Therapeutic Class	Object[1] (oral, unless otherwise specified)	AUC_{ratio}	PMID or NDA #	Published
Potent CYP3A Inhibitors (yielding substrate AUCr > 5)					
indinavir /RIT	Protease Inhibitors	alfentanil	36.5	19225389	2009 Mar
tipranavir/RIT	Protease Inhibitors	midazolam	26.91	20147896	2010 June
ritonavir	Protease Inhibitors	midazolam	26.41	20002087	2009 Dec
cobicistat (GS-9350)	None	midazolam	19.03	20043009	2010 Mar
indinavir	Protease Inhibitors	vardenafil	16.25	NDA # 021400	2003 Aug
ketoconazole	Antifungals	midazolam	15.9	8181191	1994 May
troleandomycin	Antibiotics	midazolam	14.8	15536460	2004 Dec
saquinavir / RIT	Protease Inhibitors	midazolam	12.48	19792991	2009 Oct
itraconazole	Antifungals	midazolam	10.8	8181191	1994 May
voriconazole	Antifungals	midazolam	9.63	21937987	2011 Nov
telaprevir	Antivirals	midazolam	9.17	NDA # 201917	2011
mibefradil	Calcium Channel Blockers	midazolam	8.86	14517191	2003 Oct
clarithromycin	Antibiotics	midazolam	8.39	16432272	2006 Feb
lopinavir / RIT	Protease Inhibitors	aplaviroc	7.71	16934050	2006 Sep
elvitegravir / RIT	Treatments of AIDS	midazolam IV	6.8	18815591	2009 Jan
posaconazole	Antifungals	midazolam	6.23	19302901	2009 Feb
nelfinavir	Protease Inhibitors	simvastatin	6.07	11709322	2001 Dec
telithromycin	Antibiotics	midazolam	6.0	NDA# 021144	2004
grapefruit juice DS[2]	Food Products	midazolam	5.95	12953340	2003 Aug
conivaptan	Diuretics	midazolam	5.76	NDA # 021697	2005
nefazodone	Antidepressants	midazolam	5.44	14551182	2003 Nov
saquinavir	Protease Inhibitors	midazolam	5.18	10430107	1999 Jul
boceprevir	Antivirals	midazolam	5.05	NDA # 202258	2011
Moderate CYP3A Inhibitors (AUCr ≥ 2 and < 5)					
fluconazole	Antifungals	midazolam	4.93	16172184	2005 Oct
atazanavir / RIT	Protease Inhibitors	maraviroc	4.9	18333863	2008 Apr
darunavir	Protease Inhibitors	saquinavir	4.9	NDA # 021976	2006
erythromycin	Antibiotics	midazolam	4.42	8453848	1993 Mar
diltiazem	Calcium Channel Blockers	midazolam	4.06	21209240	2011 Nov
darunavir / RIT	Protease Inhibitors	sildenafil	4.0	NDA # 021976	2006
dronedarone	Antiarrhythmics	simvastatin	3.66	NDA # 022425	2009
atazanavir	Protease Inhibitors	maraviroc	3.57	18333863	2008 Apr
aprepitant	Antiemetics	midazolam	3.29	12891225	2003 Aug
casopitant	Antiemetics	midazolam	3.13	20840445	2010 Oct
amprenavir	Protease Inhibitors	rifabutin	2.93	11158747	2001 Feb
imatinib	Antineoplastic Agents	simvastatin	2.92	14612892	2003 Nov
verapamil	Calcium Channel Blockers	midazolam	2.92	8198928	1994 Mar
grapefruit juice	Food Products	midazolam	2.39	10546919	1999 Oct
tofisopam	Benzodiazepines	midazolam	2.36	17989974	2008 Jan
cyclosporine	Immunosuppressants	midazolam	2.21	21753749	2011 Sep
ciprofloxacin	Antibiotics	sildenafil	2.12	16372380	2005 Dec
schisandra sphenanthera	Herbal Medications	midazolam	2.05	19552749	2009 May
cimetidine	H-2 Receptor Antagonists	midazolam	2.02	6152615	1984 Sep
FK1706	Central Nervous System Agents	midazolam	2.01	19889885	2010 Feb
Weak CYP3A Inhibitors (AUCr ≥ 1.25 and < 2)					
tabimorelin	Hormone Replacement	midazolam	1.93	12610745	2003 Feb
ranolazine	Cardiovascular Drugs	simvastatin	1.89	NDA # 021526	2006
fosaprepitant (IV)	Antiemetics	midazolam	1.76	21209230	2011 Dec
Seville orange juice	Food Products	felodipine	1.76	11180034	2001 Jan
chlorzoxazone	Muscle Relaxants	midazolam	1.68	11736864	2001 Nov
M100240	Antihypertensive Agents	midazolam	1.66	15051745	2004 Apr
fluvoxamine	Antidepressants	midazolam	1.66	14551182	2003 Nov
ranitidine	H-2 Receptor Antagonists	midazolam	1.66	6135440	1983 Jun

Precipitant	Therapeutic Class	Object[1] (oral, unless otherwise specified)	AUC_{ratio}	PMID or NDA #	Published
Weak CYP3A Inhibitors (AUCr ≥ 1.25 and < 2) (continued)					
goldenseal	Herbal Medications	midazolam	1.63	17495878	2008 Jan
clotrimazole	Antifungals	midazolam	1.61	20233179	2010 Feb
tacrolimus	Immunosuppressants	midazolam	1.61	21753749	2011 Sep
cilostazol	Antiplatelets	lovastatin	1.56	10702889	1999
peppermint oil	Food Products	felodipine	1.55	12235445	2002 Sep
roxithromycin	Antibiotics	midazolam	1.47	7995324	1994
propiverine	Anticholinergics	midazolam	1.46	16183781	2005 Dec
isoniazid	Antibiotics	triazolam	1.46	6140941	1983 Dec
oral contraceptives	Oral contraceptives	triazolam	1.44	6149030	1984 Nov
delavirdine	NNRTIs	indinavir	1.44	9665503	1998 Jul 1
atorvastatin	HMG CoA Reductase Inhibitors (Statins)	midazolam IV	1.41	12911366	2003 Sep
tolvaptan	Vasopressin Antagonists	lovastatin	1.41	NDA # 022275	2009
linagliptin	Dipeptidyl Peptidase 4 Inhibitors	simvastatin	1.34	20497745	2010 June
resveratrol	Food Products	buspirone	1.33	20716633	2010 Sept
lacidipine	Calcium Channel Blockers	simvastatin	1.33	11259986	2001 Feb
cranberry juice	Food Products	midazolam	1.33	19114462	2009 Mar
pazopanib	Kinase Inhibitors	midazolam	1.32	20881954	2010 nov
nilotinib	Kinase Inhibitors	midazolam	1.3	NDA # 020068	2007
AMD070	Fusion Inhibitors	midazolam	1.29	18362694	2008 Apr
alprazolam	Benzodiazepines	buspirone	1.29	8300893	1993 Nov
amlodipine	Calcium Channel Blockers	simvastatin	1.28	16097365	2005 Mar
bicalutamide	Antiandrogens	midazolam	1.27	15509184	2004
sitaxentan	Endothelin Receptor Antagonists	sildenafil	1.27	20078609	2010 Jan
azithromycin	Antibiotics	midazolam	1.27	8720318	1996 Feb
ginkgo	Herbal Medications	midazolam	1.25	17050793	2006 Nov

In Vivo CYP3A Inducers

Inducers	Object (oral, unless otherwise specified)	% ↓ AUC	% ↑ oral CL	Precipitant Regimen (oral)	Published	PMID or NDA#
Potent Inducers (AUC decreased by ≥ 80% or CL increased by more than 5 fold (400%))						
rifampin	budesonide	99.7	36904.5	600 mg QD (7 days)	2005	15726657
mitotane	midazolam	94.5	Not Provided	maximum of 3.5 g TID (chronic therapy)	2011	21220434
avasimibe	midazolam	93.5	Not Provided	750 mg/day (7 days)	2003	12766253
phenytoin	nisoldipine	89.5	Not Provided	200-450 mg/day (chronic treatment)	1996	8917062
carbamazepine	quetiapine	86.6	643.1	200 mg TID (26 days)	2006	16390352
St John's Wort	midazolam	80.0	Not Provided	300 mg TID (14 days)	2006	16341856
rifabutin	delavirdine	Not Provided	458.0	300 mg QD (14 days)	1997	9224961
phenobarbital	verapamil	76.6	400.9	100 mg QD (21 days)	1988	3392664
Moderate Inducers (AUC decreased by 50-80% or CL increased by 2-5 fold (100-400%))						
ritonavir and St. Johns wort	midazolam	77.2	Not Provided	ritonavir: 300 mg BID and SJW: 300 mg TID (14 days)	2010	19924124
tipranavir and ritonavir	saquinavir	75.6	Not Provided	tipranavir: 500 mg and ritonavir: 200 mg BID (14 days)	2008	18176328
bosentan	sildenafil	69.0	239.8	62.5-125 mg BID (8 weeks)	2005	15963102
nafcillin	nifedipine	62.6	145.1	500 mg 4 times daily (5 days)	2003	12814453
[talviraline]	indinavir	61.7	181.2	500 mg TID (14 days)	1999	10516944
efavirenz	simvastatin acid	60.4	Not Provided	600 mg QD (15 days)	2005	15980690
modafinil	triazolam	57.6	35.7	200-400 mg QD (28 days)	2002	11823757
etravirine	sildenafil	56.7	Not Provided	800 mg BID (13.5 days)	2008	NDA# 022187
Weak Inducers (AUC decreased by 20-50% or CL increased by less than 2 fold (100%))						
garlic	saquinavir	44.7	Not Provided	caplet of GarliPure BID (20 days)	2002	11740713
amprenavir	lopinavir	43.0	Not Provided	700 mg BID (2-4 weeks)	2005	15668539
[troglitazone]	simvastatin	37.7	Not Provided	400 mg QD (24 days)	2001	11361054
sorafenib	sirolimus	36.9	Not Provided	200 mg BID (11 days)	2010	21045832
rufinamide	triazolam	36.7	53.4	400 mg BID (11.5 days)	2008	NDA # 021911
[pleconaril]	midazolam	34.6	52.8	400 mg TID (6 days)	2006	16467135
gingko	midazolam	33.7	52.6	120 mg BID (28 days)	2008	18205997
vinblastine	midazolam IV	33.2	48.8	not provided (4 cycles)	2010	20959500
nevirapine	indinavir	32.5	Not Provided	200 mg QD (14 days), then BID (19 days)	1999	10191212
armodafinil (R-modafinil)	midazolam	32.2	54.7	100-250 mg/day (31 days)	2008	18076219
prednisone	tacrolimus	29.0	Not Provided	1.5 mg/kg/day	2005	15787787