Official Title:	**A Phase 2, Multicenter, Open-Label Study of INCB050465, a PI3Kδ Inhibitor in Relapsed or Refractory Follicular Lymphoma (CITADEL-203)**
NCT Number:	NCT03126019
Document Date:	Clinical Study Protocol Amendment Version 9: 23 December 2019

Clinical Study Protocol

INCB 50465-203

A Phase 2, Multicenter, Open-Label Study of INCB050465, a PI3Kδ Inhibitor, in Relapsed or Refractory Follicular Lymphoma (CITADEL-203)

Product:	**INCB050465**
IND Number:	**121,474**
EudraCT Number:	**2017-001624-22**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation 1801 Augustine Cut-Off Wilmington, DE 19803**
Original Protocol (Version 0):	**01 MAR 2017**
Amendment (Version) 1:	**15 MAR 2017**
Amendment (Version) 2:	**15 AUG 2017**
Amendment (Version) 3:	**11 SEP 2017**
Amendment (Version) 4:	**25 OCT 2017**
Amendment (Version) 4-CAN:	**12 DEC 2017**
Amendment (Version) 5:	**17 JAN 2018**
Amendment (Version) 6:	**11 JUL 2018**
Amendment (Version) 7:	**04 SEP 2018**
Amendment (Version) 8:	**06 DEC 2018**
Amendment (Version) 9:	**23 DEC 2019**

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

INVESTIGATOR'S AGREEMENT

I have read the INCB 50465-203 Protocol Amendment 9 (Version 9 dated 23 DEC 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

Title of Study: A Phase 2, Multicenter, Open-Label Study of INCB050465, a PI3Kδ Inhibitor, in Relapsed or Refractory Follicular Lymphoma (CITADEL-203)

Protocol Number: INCB 50465-203 | **Study Phase:** 2

Indication: Relapsed or refractory follicular lymphoma

Objectives	Endpoints
Primary	
To assess the efficacy of INCB050465 in terms of objective response rate (ORR) in subjects with relapsed or refractory follicular lymphoma (FL).	ORR defined as the percentage of subjects with a complete response (CR) or partial response (PR) as defined by revised response criteria for lymphomas, as determined by an Independent Review Committee (IRC).
Secondary	
To assess complete response rate (CRR).	CRR defined as the percentage of subjects with a CR as defined by revised response criteria for lymphomas, as determined by an IRC.
To assess the duration of response (DOR).	DOR defined as the time from first documented evidence of CR or PR until disease progression or death from any cause among subjects who achieve an objective response, as determined by radiographic disease assessment provided by an IRC.
To assess progression-free survival (PFS).	PFS defined as the time from the date of the first dose of study treatment until the earliest date of disease progression, as determined by radiographic disease assessment provided by an IRC, or death from any cause.
To assess overall survival (OS).	OS defined as the time from the date of the first dose of study treatment until death from any cause.
To assess best percentage change in target lesion size.	Best percentage change in target lesion size from baseline, where target lesion size is measured by the sum of the product of the diameters of all target lesion sizes.
To characterize the safety and tolerability of INCB050465.	Safety measured by clinical assessments, including vital signs and physical examinations, 12-lead electrocardiograms (ECGs), chemistry and hematology laboratory values, and adverse events (AEs).
[redacted]	

[redacted]

This is a Phase 2, multicenter, open-label study of 120 subjects in which the first 50 subjects will be assigned at 1:1 ratio to 2 treatment groups: Group A and Group B. Subjects in treatment Group A will receive INCB050465 20 mg once daily for 8 weeks followed by 20 mg once weekly; subjects in treatment Group B will receive INCB050465 20 mg once daily for 8 weeks followed by 2.5 mg once daily. The remaining 70 subjects will be allocated to one of the 2 treatment groups to better understand the safety and efficacy of that treatment regimen. The treatment group will be selected after evaluation of emerging safety and efficacy data from this and other monotherapy studies of INCB050465 in NHL that are evaluating the same or similar dosing regimens and will be implemented after the first 50 subjects are enrolled. Subjects allocated to the non-selected treatment regimen may switch to the selected treatment regimen or remain on their current treatment regimen, provided they have not met study-treatment withdrawal criteria, and there are no safety concerns for their current treatment regimen. There will be no re-baselining for subjects who switch treatment regimens, and all subjects will continue to follow the same assessment schedule. Furthermore, no changes will be made to the primary analysis.

Subjects will be evaluated for ORR by an IRC and followed for CRR, DOR, PFS, OS, and safety. Subjects may receive treatment until disease progression, death, unacceptable toxicity, or consent withdrawal.

An interim futility analysis is planned when the first 50 subjects (Group A and Group B combined) have been evaluated for response or have permanently discontinued study treatment because of disease progression, withdrawal of consent, or death. The study will be terminated for futility if ≤ 18 of the 50 subjects have responded (ie, CR or PR) based on assessments provided by the IRC; otherwise the study will continue. A timely assessment of response will be performed to avoid the risk of overenrollment.

Study Population: Subjects with histologically confirmed diagnosis of FL (Grade 1, 2, or 3a) who have received at least 2 prior systemic therapies.

Key Inclusion Criteria:

- Aged 18 years or older.
- Histologically confirmed, relapsed or refractory, follicular B-cell non-Hodgkin lymphoma (NHL) (FL) Grade 1, 2, and 3a.
- Ineligible for hematopoietic stem cell transplant.
- Must have been treated with at least 2 prior systemic therapies.

- Radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥ 1 lesion that measures > 1.5 cm in the longest dimension and ≥ 1.0 cm in the longest perpendicular dimension as assessed by computed tomography (CT) or magnetic resonance imaging (MRI).
- Subjects must be willing to undergo an incisional, excisional, or core needle lymph node or tissue biopsy or provide a lymph node or tissue biopsy from the most recent available archival tissue.
- ECOG performance status 0 to 2.

Key Exclusion Criteria:

- Known histological transformation from indolent NHL to diffuse large B-cell lymphoma.
- History of central nervous system lymphoma (either primary or metastatic).
- Prior treatment with idelalisib, other selective phosphatidylinositol 3-kinase (PI3K) δ inhibitors, or a pan-PI3K inhibitor.
- Prior treatment with a Bruton's tyrosine kinase inhibitor (eg, ibrutinib).
- Allogeneic stem cell transplant within the last 6 months, or autologous stem cell transplant within the last 3 months before the date of the first dose of study treatment.
- Active graft-versus-host disease.
- Hepatitis B (HBV) or hepatitis C (HCV) infection: Subjects positive for hepatitis B surface antigen or hepatitis B core antibody will be eligible if they are negative for HBV-DNA; these subjects should be considered for prophylactic antiviral therapy. Subjects positive for anti-HCV antibody will be eligible if they are negative for HCV-RNA.

INCB050465 Dosage and Mode of Administration: INCB050465 will be administered orally at a dose of 20 mg once daily for 8 weeks followed by 20 mg once weekly (Group A) or 20 mg once daily for 8 weeks followed by 2.5 mg once daily (Group B).

Required concomitant medications: All subjects must receive prophylaxis against *Pneumocystis jirovecii* pneumonia from the start of study treatment and should continue for 2 to 6 months after the last dose of study treatment.

Study Schedule/Procedures: Screening and study visits that include a physical examination, clinical laboratory tests, and an assessment of AE and treatment compliance will be conducted. The study visits will occur every 2 weeks for the first 8 weeks, then every 4 weeks thereafter. [redacted] then every 24 weeks thereafter until progressive disease (PD); and for cytomegalovirus analysis every 4 weeks. [redacted] Subjects will undergo a tumor biopsy at screening unless suitable, archived material is available.

During screening, subjects will have an objective assessment of disease status performed by CT scan or MRI. Subjects will also have a bone marrow biopsy performed at screening unless the subject has undergone a recent bone marrow biopsy. Disease status will be assessed (using the same modality from screening) every 8 weeks through Week 24, then every 12 weeks through Week 96, and then every 24 weeks thereafter until PD. On-study bone marrow biopsies will be required only if needed to confirm a CR.

Subjects withdrawn from study treatment for reasons other than disease progression will be followed for disease assessment until either radiologic disease progression, the start of a new anticancer therapy, consent withdrawal, or death (whichever occurs first). After permanently discontinuing study treatment, subjects will be followed every 12 weeks for subsequent anticancer therapies and survival.

Estimated Duration of Participation: Subject participation from screening through follow-up is expected to average approximately 25 months, which includes the following:

- A screening period lasting up to 28 days.
- A treatment period lasting as long as the subject is receiving benefit, tolerating the regimen, and has not met withdrawal criteria (approximately 52 weeks).
- A safety follow-up period lasting 30 to 35 days.
- A disease and survival follow-up period until the end of the study.

At the end of the study, subjects who have completed at least 24 months of study participation (starting from first dose of INCB050465), who remain on active study treatment, and who have no evidence of progressive disease will have the option to continue on monotherapy with INCB050465 provided within a rollover Protocol, as local law permits.

Estimated Number of Subjects: Approximately 120 subjects will be enrolled. The first 50 subjects will be assigned at 1:1 to Group A (INCB050465 20 mg once daily for 8 weeks followed by 20 mg once weekly) and Group B (INCB050465 20 mg once daily for 8 weeks followed by INCB050465 2.5 mg once daily). The remaining 70 subjects will be assigned to the selected treatment group (ie, either treatment Group A or treatment Group B).

Principal Coordinating Investigator:

- United States: [redacted], MD, [redacted], USA
- EU: [redacted], MD, PhD, [redacted], Czech Republic

Statistical Methods:

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.

Sample Size:

Approximately 120 subjects will be enrolled and assigned to either treatment Group A or Group B. If the true ORR is 51% for subjects in Group A and Group B, then with 120 total subjects, there is approximately 93% probability of observing the lower bound of the 95% confidence interval (CI) of ORR $\geq$ 35%.

Primary Analysis:

The ORR as determined by the IRC and its 95% exact binomial CIs will be calculated. The primary efficacy analyses will be conducted when all subjects in the full analysis set who have achieved a response (ie, PR or CR) according to the IRC have had approximately 12 months of follow-up from the onset of response.

Secondary Analyses:

The CRR as determined by the IRC and its 95% exact binomial CIs will be calculated. Kaplan-Meier estimation of median DOR (per IRC), PFS (per IRC), and OS will be provided with respective 95% CIs. Best percentage change from baseline in target lesions size will be summarized descriptively. All safety data, including AEs, laboratory data, vital signs, and ECGs, will be summarized descriptively.

Level of Significance:

There will not be any statistical comparison between the two groups. Two-sided 95% CIs will be reported for all analyses when appropriate.

Interim Analysis:

An interim futility analysis is planned when the first 50 subjects (Group A and Group B combined) have been evaluated for response or have permanently discontinued study treatment because of disease progression, withdrawal of consent, or death. The study will be terminated for futility if ≤ 18 of the 50 subjects have responded (ie, CR or PR) based on assessments provided by the IRC; otherwise the study will continue.

Independent Data Monitoring Committee: An independent Data Monitoring Committee (IDMC) will be established and will review data at predetermined intervals as specified in the IDMC charter.

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LIST OF ABBREVIATIONS

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

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BID	twice daily
CI	confidence interval
[redacted]	[redacted]
CFR	Code of Federal Regulations
CMV	cytomegalovirus
CR	complete response
CRR	complete response rate
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
EMA	European Medicines Agency
[redacted]	[redacted]
[redacted]	[redacted]
FDA	Food and Drug Administration
FL	follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GCP	Good Clinical Practice
HBs	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus

Abbreviation	Definition
HL	Hodgkin lymphoma
[redacted]	[redacted]
HSCT	hematopoietic stem cell transplant
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent Data Monitoring Committee
IEC	independent ethics committee
IN	Investigator Notification
irAE	immune-related adverse event
IRB	institutional review board
IRC	Independent Review Committee
ITT	intent-to-treat
IWRS	interactive web response system
LD	longest dimension
LDi	longest dimension transverse diameter of lesion
LPD	longest perpendicular dimension
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MRI	magnetic resonance imaging
NHL	non-Hodgkin lymphoma
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PI3K	phosphatidylinositol 3-kinase
PJP	*Pneumocystis jiroveci* pneumonia
[redacted]	[redacted]
PP	per protocol
PPD	cross-product of the longest transverse diameter and perpendicular diameter
PR	partial response
QD	once daily
R-chemo	rituximab + chemotherapy
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone
RNA	ribonucleic acid
SAE	serious adverse event
SCT	stem cell transplant

Abbreviation	Definition
SD	stable disease
SDi	shortest axis perpendicular to the longest transverse diameter
SmPC	Summary of Product Characteristics
SPD	sum of the product of the perpendicular diameters for multiple lesions
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
[redacted]	[redacted]

1. INTRODUCTION

1.1. Follicular Lymphoma

Non-Hodgkin lymphoma is the most common hematologic malignancy, with over 385,000 new cases diagnosed in 2012 (Torre et al 2015). Follicular lymphoma, a subtype of NHL, is the second most prevalent form of NHLs overall, accounting for approximately 1 in 5 cases of NHL, and is the most common form of indolent (slow-growing) NHLs. More than 75,000 people are estimated to be diagnosed with FL annually worldwide (Shankland et al 2012).

Follicular lymphoma is defined as a lymphoma of germinal center B cells, including centrocytes and centroblasts, that has at least a partially follicular pattern. These bone marrow–derived cells undergo somatic hypermutation and class switching of the B-cell receptors, which leads to immunoglobulin diversity and selects B cells that produce high-affinity antibodies (Kahl and Yang 2016). Central to the early transformation and pathophysiology of FL is the t(14;18)(q32;18) translocation found in approximately 90% of FL and that leads to overexpression of BCL2 (Pastore et al 2015). Follicular lymphoma is also positive for the B-cell markers CD10, CD19, CD22, and usually CD20 but is always negative for CD5 (Barekman et al 2001).

The 2008 WHO classification system (Swerdlow et al 2016) divides FL into grades based on the proportion of centrocytes to centroblasts. Cases with more centroblasts tend to be more aggressive and are more likely to transform in to diffuse large-cell lymphoma (Kahl and Yang 2016). Grade 1 is defined as 0 to 5 centroblasts per high powered field (HPF), Grade 2 is 6 to 15 centroblasts per HPF, and Grade 3 is > 15 centroblasts per HPF. Grade 3 can be subclassified into 3a and 3b, with the latter distinguished by an absence of centrocytes. FL3b appears to be biologically distinct compared with the other grades, with frequent absence of both t(14;18) and CD10 expression and increased p53 and MUM1/IRF4 expression. The clinical distinction between FL3a and FL3b has not been shown to date (NCCN 2014).

Although FL is a biologically heterogeneous disease with widely varying outcomes, the prognosis for individual patients can be made based on clinical and laboratory findings. The most widely used risk model for FL is the FLIPI, which includes 5 adverse prognostic factors: age older than 60 years, Ann Harbor Stage III to IV, hemoglobin less than 120 g/L, 4 or more involved nodal areas, and elevated serum lactate dehydrogenase (Solal-Céligny et al 2004; Appendix E). [redacted]

While effective treatments exist for FL, relapse is frequent and is followed by aggressive disease often leading to death within 1 to 2 years. Based on an analysis of 588 patients receiving R-CHOP as initial FL therapy, approximately 20% of patients experienced early PD, defined as PD within 2 years of diagnosis. The 5-year OS was 50% in the early PD group compared with 90% in patients without early PD (Casulo et al 2015). Thus, despite significant progress in the management of patients with FL, an unmet need exists.

1.2. Treatment for Follicular Lymphoma

Some patients with early stage FL (Ann Harbor Stage I or II) who develop symptoms may be treated with radiation therapy alone. Advanced stage (Ann Harbor Stage III-IV), Grade 1 to 3a FL is often treated according to the degree of tumor burden (low versus high) and the presence or absence of FL symptoms (eg, fever, night sweats, unexplained weight loss, etc). Asymptomatic patients with a low tumor burden may be candidates for watchful waiting, whereas those with a high tumor burden may receive R-chemo. Symptomatic patients with a low tumor burden may receive either single-agent rituximab or R-chemo, whereas patients with a high tumor burden may receive R-chemo with or without maintenance rituximab. Although the majority of patients will respond to these first-line therapies, the natural history of FL is characterized by continuous relapse.

There are several options for patients with FL that relapse after initial treatment (Kahl and Yang 2016). The use of single-agent bendamustine was approved by the US FDA in 2008 for use in patients with indolent B-cell NHL that progressed within 6 months of treatment with rituximab (Treanda® 2013). In 2016, the US FDA and the European Commission approved the use of obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance in FL patients whose disease progressed within 6 months of prior rituximab-based therapy (Sehn et al 2016, Gazyva® 2016). Stem cell transplant is another option available to some patients after relapse.

The first-in-class PI3Kδ inhibitor idelalisib (Zydelig 2016) was granted accelerated approval in 2014 by the US FDA based on a single-arm study enrolling FL subjects (N = 72) who were refractory to at least 2 prior therapies (Gopal et al 2014). The approved indication was for the treatment of patients with relapsed follicular B-cell NHL who had received at least 2 prior systemic therapies. Idelalisib was also approved in Europe, based on the same study, for adult patients with FL that is refractory to 2 prior lines of treatment. In September of 2017, a pan PI3K inhibitor, copanlisib (Aliqopa 2017), was also granted accelerated approval by the US FDA based on a single-arm study enrolling FL subjects (N = 104) who had received at least 2 prior systemic therapies (Patnaik et al 2016). The ORR for idelalisib in a double-refractory FL population was 54% (Zydelig 2016); the ORR for copanlisib in patients with relapsed or refractory FL who had received at least 2 prior therapies was 59% (Aliqopa 2017). Other agents (eg, lenalidomide, venetoclax, ibrutinib) are being evaluated in clinical studies.

1.3. INCB050465

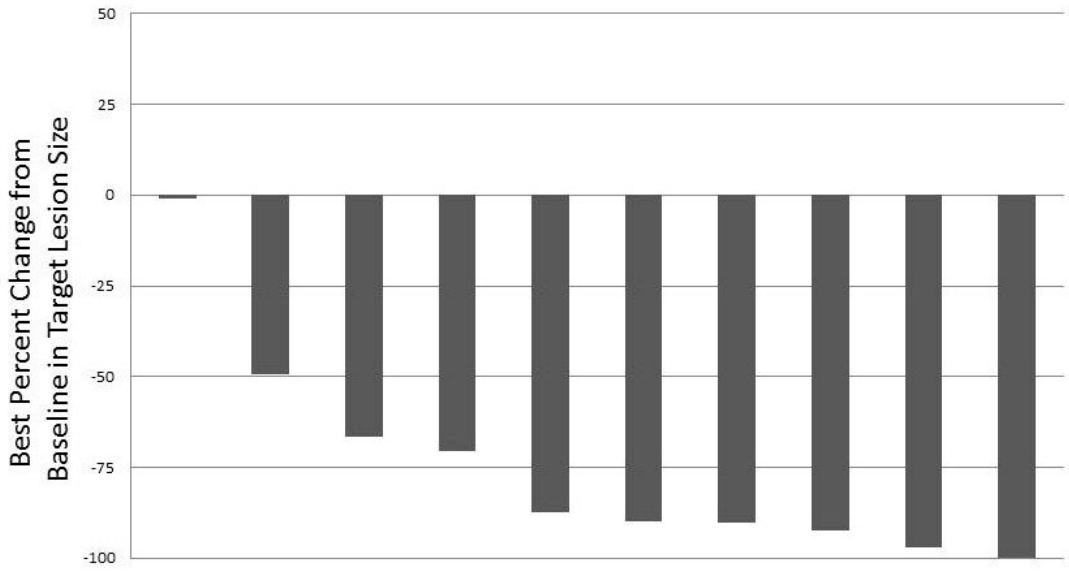
Phosphatidylinositol 3-kinases belong to a family of lipid signaling kinases that phosphorylate phosphoinositides of the inositol ring (Cantley 2002). Phosphatidylinositol 3 kinases are divided into 3 classes (Class I, II, and III) according to their structure, regulation, and substrate specificity. 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. Phosphatidylinositol-3,4,5-trisphosphate 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.

INCB050465 is a potent inhibitor of PI3Kδ (IC_{50} value = 1.1 ± 0.5 nM), with approximately 20,000-fold selectivity for the other PI3K family members. INCB050465 does not significantly inhibit (< 30% inhibition) a broad panel of kinases when tested at a concentration of 100 nM (refer to the INCB050465 IB). 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. Compared with 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 (INCB050465 IB). The IC_{90} for pAKT inhibition of Pfeiffer cells in human whole blood is 77nM (INCB050465 IB). Preclinical toxicology studies supported evaluation of INCB050465 in human clinical studies (INCB050465 IB).

INCB050465 is being evaluated as a monotherapy in a Phase 1/2, dose-escalation and expansion study (INCB 50465-101, NCT02018861, Phillips et al 2016). As of 01 MAR 2017, data were available for 63 subjects who received INCB050465 administered orally QD or QD for 9 weeks followed by QW. Starting in NOV 2016, subjects were switched to QW dosing if they had been on study treatment for > 9 weeks (Ramchandren et al 2017). The median duration of treatment for all subjects was 114 days (range 7-520). Nonhematological adverse events observed in ≥ 20% of subjects were nausea (38%), diarrhea/colitis (35%), fatigue (29%), vomiting (27%), cough (24%), rash (22%), and dizziness (21%). New or worsening Grade ≥ 3 anemia, thrombocytopenia, and neutropenia occurred in 5%, 10%, and 22% of subjects, respectively. No ≥ Grade 3 nonhematological treatment-related AEs were reported in ≥ 10% of subjects. Serious AEs that occurred in ≥ 2 subjects included diarrhea/colitis (n = 6) and hypotension (n = 3) and ventricular tachycardia, pyrexia, pneumonia, exfoliative dermatitis, syncope, and bacteremia (n = 2 each). Twelve (19%) of the 63 subjects discontinued study treatment due to the following AEs: diarrhea (n = 2), exfoliative dermatitis (n = 2), colitis, cytomegalovirus colitis, pneumonitis, rash, psoriasis, neutropenia, pneumonia, and hypercalcemia (n = 1 each). 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 01 MAR 2017, 28 objective responses as reported by investigators were observed in 57 evaluable subjects with DLBCL, FL, HL, marginal zone lymphoma, chronic lymphocytic leukemia, and mantle cell lymphoma. These results include 8 objective responses among the 11 evaluable subjects with FL; all but 1 of the objective responses occurred by the time of the 9-week disease assessment. Among the 8 objective responses, 6 demonstrated > 75% reduction in their target lesions (see Figure 1). The longest duration of study treatment among subjects with FL was approximately 14 months, with 3 of the evaluable subjects ongoing.

Figure 1: Best Percentage Change From Baseline in Target Lesion Size in Follicular Lymphoma Subjects From Study INCB 50465-101



Note: Of the 11 evaluable subjects, 1 subject did not have a complete, postbaseline disease assessment and is therefore not represented. The best response for this subject was PD.

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 (Phillips et al 2016). Refer to the INCB050465 IB for further details.

1.4. Study Rationale

The PI3Kδ inhibitor idelalisib was approved for the treatment of patients in the United States with relapsed follicular B-cell NHL who have received at least 2 prior systemic therapies. In September of 2017 the PI3K inhibitor copanlisib was also approved in the Unites States for the same patient population (Aliqopa 2017). Idelalisib was approved in the European Union for the treatment of adult patients with FL that is refractory to 2 prior lines of treatment. The population of patients that are refractory to 2 lines of systemic therapy is substantially smaller than the population that has relapsed or refractory disease after 2 prior systemic therapies. The relapsed patient population is currently underserved by the available approved therapies and, like the double-refractory population, represents an unmet medical need. This is especially true in patients that are ineligible for HSCT. To address the unmet medical need of both populations, and to enroll the study in a timely fashion, the study will allow subjects who have either relapsed or refractory disease after at least 2 prior systemic therapies and who are ineligible for HSCT. INCB050465 is a potent and selective PI3Kδ inhibitor and has demonstrated rapid and deep objective responses in subjects with relapsed FL (see Section 1.3).

This study is designed to evaluate the ORR of INCB050465 in subjects with relapsed or refractory FL who have received at least 2 prior systemic therapies and who are ineligible for HSCT. Given that copanlisib was recently granted accelerated approval in this patient population on the basis of ORR by the US FDA, idelalisib can no longer be considered the standard of care in the United States and consequently is not a relevant comparator for new PI3K inhibitors. It is also not feasible to replace idelalisib with copanlisib, which is currently approved only in the United States. Study INCB 50465-203 will therefore evaluate only INCB050465.

Subjects will receive INCB050465 administered orally at a dose of 20 mg QD for 8 weeks. Based on an *ex vivo* whole blood assay, the 20 mg QD dose provides exposure ranging from approximately 2-fold above the IC_{90} at trough to 19-fold above the IC_{90} at peak. Data as of 02 SEP 2016 show that of the 11 NHL subjects who were administered 20 mg QD, 10 achieved an objective response at the time of first disease assessment (9 weeks). However, among all evaluable subjects with an objective response (n = 20), 7 subjects (35%) discontinued study treatment due to an AE. Consequently, after receiving 20 mg QD of INCB050465 for 8 weeks, subjects will receive either 20 mg once weekly or 2.5 mg QD of INCB050465.

The once-weekly regimen is proposed to maintain response while providing time off from pathway inhibition, which may reduce the frequency of AEs leading to study treatment withdrawal. Pharmacodynamic data from Study 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 × 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 (Aliqopa 2017).

The continuous QD regimen of INCB050465 has demonstrated prolonged responses in both aggressive and indolent NHL. One subject with FL who received a 10 mg QD dose achieved a complete metabolic response and remained on study treatment for approximately 13 months before withdrawing due to an AE (Grade 2 psoriasis). The 2.5 mg QD regimen is proposed to provide approximately 86% inhibition of the PI3K pathway on average but could reduce the frequency of AEs that lead to study treatment withdrawal.

1.5. Potential Risks and Benefits of the Treatment Regimen

A summary of AEs, SAEs, and efficacy observed in the ongoing Study INCB 50465-101 is provided (Section 1.3). Similar to other PI3K inhibitors, diarrhea/colitis, pneumonitis, infections, severe cutaneous reactions, and neutropenia were observed in Study INCB 50465-101. In Study INCB 50465-101, 8 of the 11 evaluable subjects with FL had an objective response. The longest duration on study treatment for these subjects was approximately 14 months. Refer to the INCB050465 IB for additional information.

There are no preclinical data available to date on the potential phototoxicity of INCB050465. Therefore, subjects enrolled in this study taking INCB050465 will be instructed by the site staff to take precaution to protect themselves from the sun/ultraviolet light. This includes wearing long sleeves, long trousers, hats, and sunglasses.

2. STUDY OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are presented in Table 1.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of INCB050465 in terms of ORR in subjects with relapsed or refractory FL.	ORR defined as the percentage of subjects with a CR or PR as defined by revised response criteria for lymphomas, as determined by an IRC.
Secondary	
To assess CRR.	CRR defined as the percentage of subjects with a CR as defined by revised response criteria for lymphomas (Cheson et al 2014), as determined by an IRC.
To assess DOR.	DOR defined as the time from first documented evidence of CR or PR until disease progression or death from any cause among subjects who achieve an objective response, as determined by radiographic disease assessment provided by an IRC.
To assess PFS.	PFS defined as the time from the date of the first dose of study treatment until the earliest date of disease progression, as determined by radiographic disease assessment provided by an IRC, or death from any cause.
To assess OS.	OS defined as the time from the date of the first dose of study treatment until death from any cause.
To assess best percentage change in target lesion size.	Best percentage change in target lesion size from baseline, where target lesion size is measured by the sum of the product of the diameters of all target lesion sizes.
To characterize the safety and tolerability of INCB050465.	Safety measured by clinical assessments, including vital signs and physical examinations, 12-lead ECGs, chemistry and hematology laboratory values, and AEs.
[redacted]	

3. SUBJECT ELIGIBILITY

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

3.1. Subject Inclusion Criteria

A subject who meets all of the following criteria may be included in the study:

1. Aged 18 years or older.
2. Histologically confirmed, relapsed or refractory, follicular B-cell NHL (FL) Grade 1, 2, and 3a.
3. Ineligible for HSCT.
4. Must have been treated with at least 2 prior systemic therapies.
5. Radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥ 1 lesion that measures > 1.5 cm in the LD and ≥ 1.0 cm in the LPD) as assessed by CT or MRI.
6. Subjects must be willing to undergo an incisional, excisional, or core needle lymph node or tissue biopsy or provide a lymph node or tissue biopsy from the most recent available archival tissue.
7. ECOG performance status 0 to 2 (see Appendix C).
8. Life expectancy ≥ 12 weeks.
9. Adequate hematologic, hepatic, and renal function (values must not be achieved with growth factors):
    a. ANC ≥ 1.0×10^9/L.
    b. Hemoglobin ≥ 8.0 g/dL.
    c. Platelet count ≥ 50×10^9/L.
    d. Total bilirubin ≤ 1.5 × ULN. Subjects with documented history of Gilbert's syndrome and in whom total bilirubin elevations are accompanied by elevated indirect bilirubin are eligible.
    e. ALT/AST ≤ 2.5× ULN or ≤ 5 × ULN in the presence of liver metastases.
    f. Calculated creatinine clearance ≥ 50 mL/min by the Cockcroft-Gault Equation or the estimated glomerular filtration rate ≥ 50 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease formula.

10. Willingness to avoid pregnancy or fathering children based on the criteria below:
    a. Woman of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea and > 45 years of age.)
    b. Woman of childbearing potential who has a negative serum pregnancy test (see Table 7) and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.
    c. Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through at least 93 days after the last dose of study treatment. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.

3.2. Subject Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study:

1. Known histological transformation from indolent NHL to DLBCL.
2. History of central nervous system lymphoma (either primary or metastatic).
3. Prior treatment with idelalisib, other selective PI3Kδ inhibitors, or a pan-PI3K inhibitor.
4. Prior treatment with a Bruton's tyrosine kinase inhibitor (eg, ibrutinib).
5. Allogeneic SCT within the last 6 months, or autologous SCT within the last 3 months before the date of study treatment administration.
6. Active graft-versus-host disease.
7. Use of immunosuppressive therapy within 28 days of the date of study treatment administration. Immunosuppressive therapy includes, but is not limited to, cyclosporine A, tacrolimus, or high-dose corticosteroids. Subjects receiving corticosteroids must be at a dose level ≤ 10 mg/day within 7 days of the date of study treatment administration.
8. Receipt of anticancer medications or investigational drugs within the following intervals before the date of study treatment administration:
    a. < 10 weeks from completion of any radio- or toxin-immunoconjugates.
    b. < 6 weeks for mitomycin-C or nitrosoureas.
    c. < 4 weeks for immunotherapy.
    d. < 3 weeks for radiotherapy.
    e. < 2 weeks for any investigational agent or other anticancer medications.
9. Prior treatment-related toxicities have not resolved to ≤ Grade 1 prior to study treatment administration except for stable chronic toxicities (≤ Grade 2) not expected to resolve (eg, stable Grade 2 peripheral neurotoxicity).
10. Concurrent anticancer therapy (eg, chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, hormonal therapy, investigational therapy, or tumor embolization).

11. Use or expected use during the study of any prohibited medications, including potent CYP3A4 inhibitors or inducers (see Appendix B and consult your local pharmacist) within 14 days or 5 half-lives (whichever is longer) before the date of study treatment administration.
12. Significant concurrent, uncontrolled medical condition including, but not limited to, renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, neurological, cerebral, or psychiatric disease.
13. Current or previous other malignancy within 3 years of study entry, except cured basal or squamous cell skin cancer, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma *in situ* of the cervix, or other noninvasive or indolent malignancy without sponsor approval.
14. History of stroke or intracranial hemorrhage within 6 months of the date of study treatment administration.
15. Chronic or current active infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment, and exposure to a live vaccine within 30 days of study treatment administration.
16. Known human immunodeficiency virus (HIV) infection or positivity on immunoassay. Note: HIV screening test is optional for subjects enrolled in the United States, but subjects with known HIV infection in the United States will be excluded.
17. Hepatitis B (HBV) or hepatitis C (HCV) infection: Subjects positive for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody will be eligible if they are negative for HBV-DNA; these subjects should be considered for prophylactic antiviral therapy. Subjects positive for anti-HCV antibody will be eligible if they are negative for HCV-RNA.
18. Clinically significant cardiac disease, including unstable angina, acute myocardial infarction, and or cardiac conduction issues within 6 months of the date of study treatment administration.
19. Current New York Heart Association Class II to IV congestive heart failure or uncontrolled arrhythmia.
20. Presence of an abnormal ECG that 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 3 ECGs is < 450 milliseconds.
21. Unable to swallow and retain oral medication, malabsorption syndrome, disease significantly affecting gastrointestinal function, total resection of the stomach or small bowel, ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
22. Known hypersensitivity or severe reaction to INCB050465 (IB) or any of the excipients.
23. History of serious allergic reactions including anaphylaxis and toxic epidermal necrolysis.

24. Inadequate recovery from toxicity and/or complications from a major surgery before study treatment administration.
25. Currently pregnant or breastfeeding.
26. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study treatment and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.
27. Inability to comprehend or unwilling to sign the ICF.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is a Phase 2, multicenter, open-label study evaluating 2 INCB050465 treatment regimens based on the primary endpoint of ORR. Subjects with relapsed or refractory FL (Grades 1, 2, or 3a) who have received at least 2 prior systemic therapies and who are ineligible for HSCT will be screened for eligibility. A total of approximately 120 subjects will be enrolled. The first 50 subjects enrolled will be assigned at a 1:1 ratio to treatment Group A (INCB050465 20 mg QD for 8 weeks followed by 20 mg once weekly) and treatment Group B (INCB050465 20 mg QD for 8 weeks followed by INCB050465 2.5 mg QD; see Figure 2). The remaining 70 subjects will be allocated to one of the 2 treatment groups to better understand the safety and efficacy of that treatment regimen. The treatment group will be selected after evaluation of emerging safety and efficacy data from this and other monotherapy studies of INCB050465 in NHL that are evaluating the same or similar dosing regimens and will be implemented after the first 50 subjects are enrolled. Subjects allocated to the non-selected treatment regimen may switch to the selected treatment regimen or remain on their current treatment regimen, provided they have not met study-treatment withdrawal criteria, and there are no safety concerns for their current treatment regimen. There will be no re-baselining for subjects who switch treatment regimens, and all subjects will continue to follow the same assessment schedule. Furthermore, no changes will be made to the primary analysis. The study treatments will be administered orally.

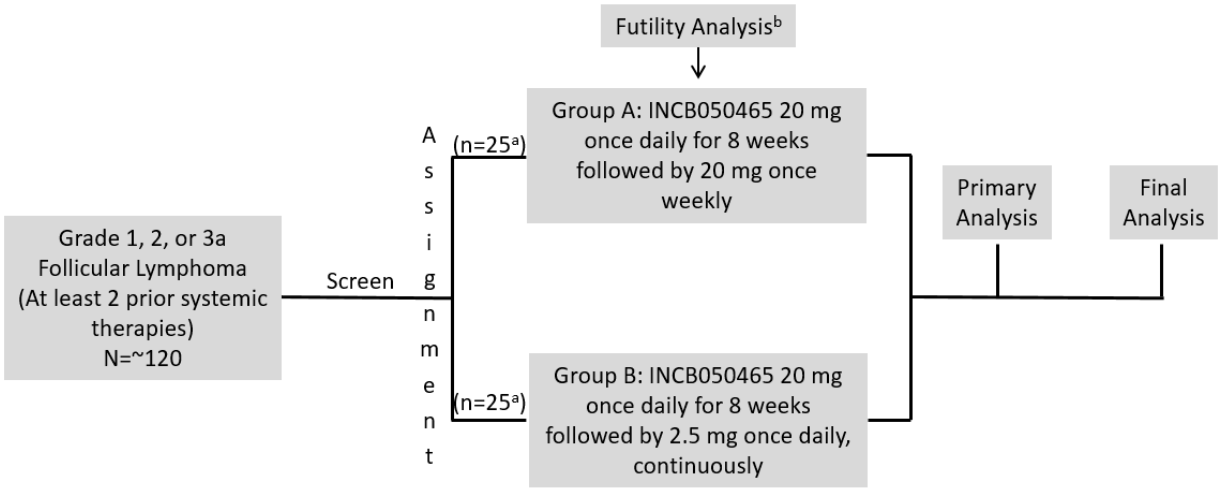
Subjects will be evaluated for ORR by an IRC and followed for CRR, DOR, PFS, OS, and safety. Subjects may receive treatment until disease progression, death, unacceptable toxicity, or consent withdrawal.

An interim futility analysis is planned when the first 50 subjects have been evaluated for response or have permanently discontinued study treatment because of disease progression, withdrawal of consent, or death. The study will be terminated for futility if ≤ 18 of the 50 subjects have responded (ie, CR or PR) based on assessments provided by the IRC; otherwise the study will continue. A timely assessment of response will be performed to avoid the risk of overenrollment.

Subjects will be monitored for safety and efficacy periodically until disease progression, death, unacceptable toxicity, or withdrawal of informed consent. An IDMC will review safety data periodically as stated in the IDMC charter.

After treatment discontinuation, subjects will be followed for safety and survival. Subjects who have discontinued study treatment due to reasons other than disease progression will be followed for either radiologic disease progression, the start of a new anticancer therapy, or death, whichever comes first. It is expected that the final analysis will occur no later than 2 years after the first dose of INCB050465 is administered to the last subject treated.

Figure 2: Study Design



[a] The first 50 subjects will be assigned at a 1:1 ratio to treatment Group A and treatment Group B. The remaining 70 subjects will be enrolled to the selected treatment Group (ie, either Group A or Group B).

[b] A futility analysis will be performed when the first 50 subjects have been evaluated for response.

4.2. 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. Safety will be objectively assessed using NCI CTCAE v4.03 (NCI 2009) guidelines; response will be assessed by an IRC using the Lugano classification (Cheson et al 2014).

4.3. Number of Subjects

4.3.1. Planned Number of Subjects

The study will enroll approximately 120 subjects across approximately 90 sites.

4.3.2. Replacement of Subjects

No subjects will be replaced at any time during this study.

4.4. Duration of Treatment and Subject Participation

After signing the ICF, screening assessments may be completed over a period of up to 28 days. Each subject enrolled in the study may continue to receive study treatment in continuous 28-day intervals. If the subject discontinues study treatment, the treatment period will end, and the subject will enter the 30 to 35-day safety follow-up period, after which the subject will enter the survival follow-up period (see Section 6.4). Subject participation is expected to average approximately 25 months.

4.5. Overall Study Duration

The study begins when the first subject signs the ICF. The end of the study will occur when **all** subjects have discontinued from the study (see Section 5.7) **or** have completed at least 24 months of study participation (starting from the first dose of study treatment). It is estimated that the study will take approximately 1.0 year to accrue 120 subjects and that the final analysis will be performed no later than 2 years after the first dose of study treatment is administered to the last subject treated. Subjects who are still on study treatment and who have no evidence of progressive disease at the end of the study will have the option to continue on monotherapy with INCB050465 provided within a rollover Protocol, as local law permits (see Section 5.8).

4.6. Study Termination

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

The sponsor may terminate the study electively or do so if required by a regulatory agency or upon advice from the IDMC. If the study is terminated prematurely, then the sponsor will notify the investigators, the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study. The IDMC will recommend termination of the study if warranted, as described in the IDMC charter (see also Section 9.5).

5. TREATMENT

5.1. Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

Study sites will enter subject demographic and baseline data into the IWRS to receive a subject number and treatment allocation.

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

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

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

For subjects who signed an ICF but are not allocated study treatment and for subjects who are allocated study treatment but were not treated, refer to the eCRF Completion Guidelines for instruction on which eCRFs to complete.

5.1.2. Randomization and Blinding

Not applicable.

5.2. Study Treatment

5.2.1. Description and Administration of INCB050465

The description and administration of INCB050465 is presented in Table 2.

Table 2: Description and Administration of INCB050465

Compound name	INCB050465
Dosage strengths	1 mg, 2.5 mg, 5 mg, and 20 mg
Form	Tablet
Active compound	INCB050465
Route of administration	Oral
Dose and regimen for Group A	20 mg QD for 8 weeks followed by 20 mg once weekly
Dose and regimen for Group B	20 mg QD for 8 weeks followed by 2.5 mg QD
Instructions	INCB050465 will be taken orally with water without regard to food [redacted] INCB050465 should be taken at approximately the same time each day.

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 once weekly dose regimen, if the dose is missed by more than 2 days, the subject should skip the dose and take the next scheduled dose.

5.2.2. Supply, Packaging, and Labeling

INCB050465 will be provided as 1 mg, 2.5 mg, 5 mg, and 20 mg tablets packaged in high-density polyethylene bottles. No preparation is required.

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

5.2.3. Storage

Bottles of INCB050465 tablets should be stored at ambient conditions (15°C-30°C or 59°F-86°F).

5.2.4. Instruction to Subjects for Handling INCB050465

The subject must be instructed in the handling of INCB050465 as follows:

- To store study treatment at room temperature.
- To remove from the study treatment bottle only the number of tablets needed at the time of administration.
- Not to remove doses in advance of the next scheduled administration.
- To make every effort to take doses on schedule.
- To report any missed doses.
- To keep INCB050465 in a safe place and out of reach of children.
- To bring all used and unused study treatment kits to the site at each visit.

5.3. Treatment Compliance

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

5.4. Treatment Interruptions and Adjustments

5.4.1. Criteria and Procedures for Dose Interruptions and Reductions of INCB050465

Treatment with INCB050465 may be interrupted for up to 14 days to allow for resolution of toxicity. Subjects may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the subject unsuitable for further participation in the study. The treating investigator should contact the sponsor to discuss the case of any subject whose treatment has been interrupted for more than 14 days before restarting treatment with INCB050465.

5.4.1.1. Dose Modifications

Dose modification guidance for AEs that have been previously observed in subjects receiving INCB050465 or are potential class-effect AEs are provided (see Table 3 and Table 5). The starting dose and dose reduction levels of INCB050465 are provided (see Table 4). Individual decisions regarding dose interruption and 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 treatment and the subject's underlying condition. Adverse events that have a clear alternative explanation or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose-reduction guidelines.

Table 3: Guidelines for Interruption and Restarting INCB050465

ADVERSE EVENT	ACTION TAKEN
Chemistry	
• AST and/or ALT is Grade 3 (> 5.0 × ULN). Note: In subjects with liver metastasis–related elevations at baseline, contact sponsor to discuss clinical management and possible dose reductions.	**Step 1:** Interrupt INCB050465 and monitor weekly until the toxicity has resolved to ≤ Grade 1. **Step 2:** Restart INCB050465 at next lower dose with medical monitor approval. Monitor as clinically indicated.
Hematology	
• Grade 3 ANC (< 1.0×10^9/L). • Platelet count is Grade 2 (50 to < 75×10^9/L) for subjects who enrolled with platelets > 100×10^9/L. • Platelet count is Grade 3 (< 50×10^9/L) for subjects who enrolled with platelets ≤ 100×10^9/L.	**Step 1:** Interrupt INCB050465 up to 14 days until the toxicity has resolved to ≤ Grade 1 or pretherapy baseline. For Grade 3 ANC, monitor at least weekly. **Step 2:** Restart INCB050465 at same dose; monitor as clinically indicated.
• Grade 4 ANC (< 0.5×10^9/L). • Grade 3 or Grade 4 febrile neutropenia. • Platelet count is Grade 4 (< 25×10^9/L).	**Step 1:** Interrupt INCB050465 up to 14 days until the toxicity has resolved ≤ Grade 2. (Monitor ANC at least weekly.) **Step 2:** Restart INCB050465 at same dose. Monitor as clinically indicated. If recurs, start at next lower dose.

Table 3: Guidelines for Interruption and Restarting INCB050465 (Continued)

ADVERSE EVENT	ACTION TAKEN
Other toxicities	
• Diarrhea/colitis.	See Table 5.
• 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.
• 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 Grade 2 toxicity unless otherwise specified.	Continue INCB050465 and treat the toxicity; monitor as clinically indicated.
• Any Grade 3 toxicity, if clinically significant and not manageable by supportive care unless otherwise specified.	**Step 1:** Interrupt INCB050465 up to 14 days 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. If interrupted for > 14 days, contact the medical monitor for approval to restart INCB050465. Monitor as clinically indicated.
• Any recurrent Grade 3 toxicity after 2 dose reductions.	Discontinue INCB050465 administration and follow-up per Protocol. Exceptions require approval of sponsor.
• Any other Grade 4 toxicity.	Discontinue INCB050465 administration and follow-up per Protocol. Exceptions require approval of sponsor.

CMV = cytomegalovirus; IV = intravenous; PCR = polymerase chain reaction.

Table 4: Dose Levels and Reductions for INCB050465

Timepoint	Dose (Group A)	Dose (Group B)
Starting dose	20 mg QD for 8 weeks (Day 1 through Day 56)	20 mg QD for 8 weeks (Day 1 through Day 56)
First dose reduction	10 mg QD	10 mg QD
Second dose reduction	5 mg QD	5 mg QD
Week 9 (Day 57) onward	20 mg once weekly[a]	2.5 mg QD[b]
First dose reduction	10 mg once weekly	1 mg QD[c]
Second dose reduction	5 mg once weekly	NA

[a] All subjects will receive 20 mg once weekly at Week 9 (Day 57) regardless of prior dose level, unless a dose modification of a switch to a QW schedule before Week 9 is required for diarrhea/colitis management (see Table 5).
[b] All subjects will receive 2.5 mg QD at Week 9 (Day 57) regardless of prior dose level, unless a dose modification of a switch to a QW schedule is required for diarrhea/colitis management (see Table 5).
[c] Further dose modification due to diarrhea or colitis for subjects on 1 mg QD is permitted (see Table 5).

5.4.1.2. Supportive Care Guidelines for Diarrhea/Colitis

Subjects should be informed to immediately report to the investigator any event of diarrhea. Treatment with INCB050465 may be interrupted or modified according to the guidelines in Table 5 to allow for resolution of diarrhea/colitis.

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).

Table 5: Guidelines for Dose Modification of INCB050465 for Diarrhea/Colitis

<table>
<tr><th>ADVERSE EVENT</th><th>ACTION TAKEN</th></tr>
<tr><td>• Diarrhea (Grade 1).</td><td>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 5.4.1.2). Monitor approximately every 48 hours until resolved. If not improved after 48 hours, treat per guidance for Grade 2.</td></tr>
<tr><td>• Diarrhea (Grade 2).</td><td>Step 1: Interrupt INCB050465. Perform work-up for infection (including CMV, C. difficile, etc) immediately. Initiate or continue supportive care (see Section 5.4.1.2). Monitor approximately every 48 hours until resolution.
Step 2: If improved within 48 hours and/or infection* is confirmed, restart INCB050465 at the same schedule and dose after resolved to ≤ Grade 1 and continue to monitor.
*For infectious diarrhea/colitis, follow institutional standard-of-care guidelines and restart INCB050465 according to clinical judgement after resolved to ≤ Grade 1. Consult with medical monitor if needed.
Step 3: If not improved within 48 hours and infection is ruled out, start oral steroids, or consider IV steroids if participant is being given IV fluids. If no improvement with oral steroids, switch to IV steroids.
Step 4: When diarrhea resolves to ≤ Grade 1, continue supportive care and taper steroids according to institutional standard of care. When taper is complete (eg, no steroid or ≤ 10 mg/day prednisone or equivalent) and diarrhea is ≤ Grade 1, restart INCB050465 at the next lower dose with approval of the medical monitor (see Table 4 for dose levels).
Step 5: If Grade 2 diarrhea reoccurs, treat per guidance for diarrhea (≥ Grade 3)/noninfectious colitis.
Step 6: If ≥ Grade 2 diarrhea reoccurs a third time, permanently discontinue INCB050465.</td></tr>
<tr><td>• Diarrhea (≥ Grade 3).
• Noninfectious colitis (any grade; confirmed or suspected).</td><td>Step 1: Interrupt INCB050465. Perform work-up for infection (including CMV, C. difficile, etc) immediately. Initiate or continue supportive care (see Section 5.4.1.2). Consider colonoscopy with biopsy for diarrhea ≥ Grade 3 and/or if symptoms[a] suggestive of colitis. Monitor every 48 hours until resolution.
Step 2: If infection* is ruled out, start oral steroids, or consider IV steroids if participant is being given IV fluids. If no improvement with oral steroids within 48 hours, switch to IV steroids.
*For infectious diarrhea/colitis, follow institutional standard of care guidelines and restart parsaclisib according to clinical judgement after resolved to ≤ Grade 1. Consult with medical monitor if needed.
Step 3: When diarrhea/colitis resolves to ≤ Grade 1, continue supportive care and taper steroids according to institutional standard of care. When taper is complete (eg, no steroid or ≤ 10 mg/day prednisone or equivalent) and diarrhea/colitis is ≤ Grade 1, restart INCB050465 as described herein and with approval of the medical monitor. Continue to monitor.
<table>
<tr><th>INCB050465 Current Dose</th><th>Dose Modification</th></tr>
<tr><td>Any dose with QD dosing</td><td>20 mg QW regardless of Treatment A or B assignment</td></tr>
<tr><td>20 or 10 mg QW</td><td>Restart next lower dose</td></tr>
<tr><td>5 mg QW</td><td>Permanently discontinue</td></tr>
</table>
Step 4: If ≥ Grade 3 diarrhea/colitis (any grade) reoccurs, permanently discontinue INCB050465.</td></tr>
</table>

[a] Diarrhea accompanied by abdominal pain and/or mucus or blood in stool.

5.4.1.3. Supportive Care Guidelines for Neutropenia and Thrombocytopenia

Neutropenia and thrombocytopenia appear to be PI3Kδ class-effect toxicities. Investigators should ensure that subjects understand the need to seek medical care when they have conditions that could become life-threatening in the presence of cytopenias (eg, neutropenic fever or bleeding with low platelets). Subjects should be instructed to report immediately any signs of infection, unexpected bleeding, or sudden, extremely painful headaches.

5.4.1.4. Definition for Immune-Related Adverse Events

Adverse events of a potential immunologic etiology, or irAEs, may be defined as an AE consistent with an immune phenomenon associated with study treatment exposure after all other etiologies have been eliminated. Immune-related AEs may be expected based on previous experience with INCB050465 and other PI3K inhibitors. Special attention should be paid to AEs that may be suggestive of potential irAEs. Based on emerging data from the ongoing Study INCB 50465-101, most irAEs occur after the first 9 weeks of study treatment administration. However, an irAE could occur at any time. Suspected irAEs should be discussed with the medical monitor when possible.

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of drug-related AEs with potential immunologic etiology are outlined in Table 3 and Section 5.4.1.2. For each AE, attempts should be made to rule out other causes, including but not limited to metastatic disease or bacterial or viral infection, which might require specific supportive care.

5.5. Study Treatment Discontinuation

The decision to discontinue study treatment will not constitute study completion. In the event that study treatment is discontinued, the treatment period will be considered complete, and the follow-up periods will begin.

5.5.1. Criteria for Study Treatment Discontinuation

Subjects **must** permanently discontinue study treatment for any 1 of the following:

- The subject has experienced an unacceptable toxicity defined as follows:
  - Occurrence of an AE that is related to study treatment 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.
  - Persistent AE requiring a delay of therapy for more than 2 weeks (14 days) unless a greater delay has been approved by the sponsor.
- The subject is unable to tolerate study treatment.
- The subject has an objective radiographic tumor response of PD/PMD.
- Further participation would be injurious to the subject's health or well-being, in the investigator's medical judgment.
- The subject becomes pregnant.

- Informed consent is withdrawn. Note: Consent withdrawn means that the subject can no longer be followed. Subjects may choose to discontinue study treatment and remain in the study to be followed for disease progression and survival per the schedule of assessments.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

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

- If a subject is noncompliant with study procedures or study treatment administration in the investigator's opinion, then the sponsor should be consulted for instruction on handling the subject.

5.5.2. Procedures for Study Treatment Discontinuation

If a subject discontinues study treatment, then the following should occur:

- The reason(s) for discontinuation must be documented in the subject's medical record and in the eCRF.
- The EOT visit should be performed.
- If the EOT visit coincides with a regular study visit, then the EOT evaluations will supersede those of that scheduled visit, and the data will be entered in the EOT visit in the eCRF.
- The date of the EOT visit should be recorded in the IWRS.
- Subjects must be followed for safety for no less than 30 days after the EOT visit or until study treatment–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

If a subject discontinues study treatment and actively withdraws consent for collection of all follow-up data, then no additional data will be collected. However, subjects may withdraw consent for study treatment, but continue to be assessed for disease progression and survival per the schedule of assessments.

5.6. Concomitant Medications

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

5.6.1. *Pneumocystis Jirovecii* Prophylaxis

All subjects 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 2016). 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 for PJP prophylaxis. Prophylaxis should be given while subjects are receiving study treatment and should continue for 2 to 6 months after the last dose of study treatment.

The prophylactic agents will be obtained from commercial supplies and will be reimbursed by Incyte. Investigators are responsible for ensuring that subjects receive commercially available supplies of the selected prophylactic agents as required per Protocol. Incyte may provide prophylactic agents where required by applicable law or regulation or under other limited circumstances when a subject may not otherwise have access to these therapies. The contents of the label will be in accordance with all applicable regulatory requirements. Further details are available in the Pharmacy Manual.

5.6.2. Restricted Medications

- Use of systemic corticosteroid doses ≤ 10 mg/day prednisone (or equivalent) is permitted but discouraged from the screening visit through EOT.
- Short courses of systemic corticosteroid doses > 10 mg/day prednisolone or equivalent are permitted only in the case of severe or life-threatening complications that cannot be controlled with other drugs, but are otherwise discouraged from the screening visit through EOT.
- Use of weak or moderate inducers or inhibitors of CYP3A4 (see Appendix B and consult your local pharmacist) is discouraged, and investigators should seek other options where possible.
- For subjects receiving INC050465, P-glycoprotein substrates of clinical relevance should be used with caution (ie, aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan).
- Localized radiotherapy will be permitted if administered as treatment for pain or impending compression fractures and with prior approval of the medical monitor.

5.6.3. Prohibited Medications and Therapies

- Use of potent inducers and inhibitors of CYP3A4 are prohibited (see Appendix B and consult your local pharmacist). Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole.
- Apart from the study treatments, the use of any anticancer medications as described (see Section 3.2) through the 30-day follow-up is prohibited.
- Exposure to a live vaccine within 30 days of study treatment through 3 months after the last dose of INCB050465.

5.7. Criteria for Study Discontinuation

A subject will be discontinued from the study for any 1 of the following reasons:

- The subject has died.
- The subject is considered lost-to-follow-up when he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site (eg, after 3 telephone calls and/or a certified letter or local equivalent).
- Informed consent is withdrawn.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB or IEC.

5.8. Treatment After the End of the Study

At the end of the study as defined in Section 6.5, subjects who have completed at least 24 months of study participation (starting from the first dose of study treatment), who remain on active study treatment, and who have no evidence of progressive disease will have the option to continue on monotherapy with INCB050465 provided within a rollover Protocol, as local law permits.

6. STUDY ASSESSMENTS

See the schedule of assessments (Table 6) and schedule of laboratory assessments (Table 7) for the timing of all assessments. All assessments mandated throughout the study must be performed on a calendar schedule; delays in treatment administration will not delay performance of assessments. By convention, Week 4, Week 8, Week 12, etc, means the completion of 4, 8, or 12 weeks, respectively. A table of clinical laboratory analytes to be assessed (Table 8) is provided. The order of assessments is suggested by the order listed within the schedule of assessments. See Sections 6 and 7 for instructions on each assessment. Further details of study procedures and assessments can be found in the study reference manual.

Table 6: Schedule of Assessments

Procedure	Section	Screening	Treatment			EOT	Follow-Up		
							Safety	Disease	Survival
		Day -28 to -1	Day 1[a]	Every 4 Weeks Through Week 48 (± 3 Days)	Every 12 Weeks From Week 48 (± 1 Week)		EOT + 30-35 Days		Every 12 Weeks (± 1 Week)
Informed consent	7.1	X							
Contact IWRS	7.2	X	X	X	X	X			
Inclusion & exclusion criteria	3	X	X						
Demography and medical history	7.3.1	X							
[redacted]									
Prior/concomitant medications	7.4	X	X	X	X	X	X		
AE assessment	7.5.1	X	X	X	X	X	X		
Comprehensive physical exam	7.5.2	X[c]				X			
Disease-specific physical exam	7.5.2.1		X	X	X		X		
Vital signs	7.5.3	X	X	X	X	X	X		
12-lead ECG	7.5.4	X	X	X[d]	X	X	X		
ECOG status	7.5.5	X	X	X	X	X	X		
CT/MRI scan	7.6.1	X[e]		Every 8 weeks through Week 24 (± 1 week), then every 12 weeks through Week 96, and then every 24 weeks thereafter until PD				X[b]	
Bone marrow exam	7.6.2	X[f]							
PJP prophylaxis	5.6.1		X[g]						
Study drug dispensing	5.1.1		X	X	X				
Study drug compliance	5.3		X	X	X	X			
Study drug administration at site	7.7.1		X	X[h]					
Disease follow-up	6.4.2							X[b]	
Survival follow-up	6.4.3								X[i]

[a] All procedures are to be performed before administration of study treatment.

[redacted]

[c] Height required at screening only.
[d] Week 4, Week 12, and every 12 weeks thereafter. See Section 7.5.4 for additional instructions.
[e] If CT is not available, is not practicable, or is contraindicated, then an MRI may be substituted. Every effort must be made to use the same modality for disease assessment throughout the study for each individual subject. Lesion assessment must be done for the neck, chest, abdomen, and pelvis.
[f] Required at baseline except for reasons provided in Section 7.6.2. If disease is present in bone marrow at baseline, a bone marrow biopsy is required to confirm CR.
[g] PJP prophylaxis will continue for 2 to 6 months after the last dose of study treatment.
[redacted]
[i] May be conducted by phone or email.

Table 7: Schedule of Laboratory Assessments

Laboratory Tests	Section	Screening	Treatment				EOT	Safety Follow-Up
		Day -28 to -1	Day 1	Every 4 Weeks Through Week 48 (± 3 Days)	Every 12 Weeks From Week 48 (± 1 Week)	Other		EOT + 30-35 Days
Serum chemistries	7.5.6.1	X	X[a]	X	X		X	X
Hematology[b]	7.5.6.1	X	X[a]	X	X	X[c]	X	X
Serology	7.5.6.3	X				X[d]	X	
Serum pregnancy	7.5.6.2	X[e]					X	X
Urine pregnancy	7.5.6.2					X[f]		
HIV testing	7.5.6.4	X[g]						
[redacted]								
Tumor biopsy	7.8.5	X[l]				X[l]		

[a] Day 1 assessments may be omitted if the screening tests occurred in the preceding 7 days. If needed, Day 1 blood draws should be performed before administration of study treatment.
[b] Hematology samples will be collected every 2 weeks for the first 8 weeks.
[c] Week 2 and Week 6 (± 3 days).
[d] Samples for CMV DNA analysis only will be collected every 4 weeks from Day 1.
[e] Only for females of childbearing potential; negative pregnancy test must be obtained within 14 days before administration of study treatment. May be performed by the central laboratory or the investigative site laboratory.
[f] Only for females of childbearing potential. Must be conducted every 4 weeks from Day 1.
[g] Optional for subjects enrolled in the United States.
[redacted]
[l] Subjects must be willing to undergo an incisional or excisional lymph node or tissue biopsy or provide a lymph node or tissue biopsy from the most recent available archival tissue. An optional biopsy should be collected at the time of progression if possible but may be collected at other times for safety or efficacy.

Table 8: Laboratory Tests: Required Analytes

Serum Chemistries	Hematology	Serology	Pregnancy Testing (Performed Locally)
Albumin Alkaline phosphatase ALT AST Bicarbonate Blood urea nitrogen C-reactive protein Calcium Chloride Creatinine Glucose Lactate dehydrogenase Phosphate Potassium Sodium Total bilirubin Direct bilirubin (if total bilirubin is > ULN) Indirect bilirubin (if total bilirubin is > ULN) Total protein Uric acid	Complete blood count, including: Hemoglobin Hematocrit Platelet count (absolute) Red blood cell count White blood cell count Differential count, including: Basophils Eosinophils Lymphocytes Monocytes Neutrophils Absolute values must be provided for: WBC differential laboratory results: Lymphocytes Neutrophils	HBsAg HBsAg antibody Hepatitis B core antibody HBV-DNA HCV antibody HCV-RNA CMV DNA HIV antibody (immunoassay)[a]	Only for female subjects of childbearing potential (see Table 7). Pregnancy tests (serum or urine) should be repeated if required by local regulations.

Note: Additional tests may be required, as agreed by investigator and sponsor, based on emerging safety data.
[a] Optional for subjects enrolled in the United States.

6.1. Screening

Screening is the interval between signing the ICF and the date of study treatment administration (Day 1). Screening may not exceed 28 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process. Central laboratory results for serum chemistry, hematology, and serology will be used to determine eligibility. Serum pregnancy tests may be performed either centrally or locally.

Procedures conducted as part of the subject's routine clinical management (eg, imaging study) and obtained before signing of informed consent may be used for screening or baseline purposes, provided that the procedure meets the Protocol-defined criteria and has been performed in the screening interval. All information associated with eligibility requirements must be entered into the appropriate eCRF pages.

Results from the screening visit evaluations will be reviewed by the investigator to confirm subject eligibility before enrollment or the administration of study drug. Tests with results that fail eligibility requirements may be repeated during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before administration of study drug will be used to determine subject eligibility. 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). Such subjects will be assigned a new subject ID number.

6.2. Treatment

The treatment period begins on the date of study treatment administration (Day 1). This day must be no more than 28 days after the subject has signed the ICF. Dates for subsequent study visits will be determined based on this day and should occur within the visit windows outlined in the schedule of assessments (see Table 6 and Table 7) unless delayed for safety reasons. Subjects may receive treatment until disease progression, death, unacceptable toxicity, or consent withdrawal.

6.3. End of Treatment

There is no predefined EOT. If a subject permanently discontinues study treatment, then the EOT visit should be conducted. The subject should be encouraged to return for the safety follow-up visit.

6.4. Follow-Up

6.4.1. Safety Follow-Up

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

If a subject is scheduled to begin a new anticancer therapy before the end of the safety follow-up period, then the safety follow-up visit should be performed before new anticancer therapy is started. Once new anticancer therapy has been initiated, the subject will move into the survival follow-up period.

6.4.2. Disease Status Follow-Up

Subjects who discontinue study treatment for a reason other than disease progression will continue to be followed for disease assessments by radiologic imaging and [redacted] per the schedule of assessments (see timepoints for CT/MRI [redacted] in Table 6). Every effort should be made to collect information regarding disease status until any 1 of the following occurs:

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

6.4.3. Survival Follow-Up

Once a subject has received the last dose of study drug, confirmed disease progression, or started a new anticancer therapy, the subject moves into the survival follow-up period. The site will use continuing subject records to supply data on subsequent treatment regimens, tumor assessments (if discontinued treatment for a reason other than progression), and OS in the eCRF.

For subjects who do not intend to return to the study investigator for their ongoing care, follow-up should be maintained to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.5. End of Study

The end of the study will be when **all** subjects have met any of the study discontinuation criteria in Section 5.7 **or** have completed at least 24 months of study participation (starting from first dose of INCB050465).

At the end of the study, subjects who have completed at least 24 months of study participation, who remain on active study treatment, and who have no evidence of progressive disease will have the option to continue on monotherapy with INCB050465 provided within a rollover Protocol, as local law permits.

6.6. Unscheduled Visits

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

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7.1. Administration of Informed Consent Form

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

7.2. Interactive Response Technology Procedure

The IWRS will be contacted to obtain a subject ID number when a subject enters screening. Upon determining that the subject is eligible for enrollment, the IWRS will be contacted to obtain the treatment assignment. Additionally, the IWRS will be contacted at each regular study visit to update the study treatment supply (see Section 5.1.1 and Table 6).

7.3. Demography and Medical History

7.3.1. Demographics and Medical History

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

7.4. Prior and Concomitant Medications and Procedures

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

For consideration of prior lines of therapy, a treatment is considered a new line of therapy if any of the following 3 conditions are met:

- Start of a new line of treatment after discontinuation of a previous line: If a treatment regimen is discontinued for any reason and a different regimen is started, it should be considered a new line of therapy. A regimen is considered to have been discontinued if all the drugs in that given regimen have been stopped. A regimen is not considered to have been discontinued if some of the drugs of the regimen, but not all, have been discontinued.
- The unplanned addition or substitution of 1 or more drugs in an existing regimen: Unplanned addition of a new drug or switching to a different drug (or combination of drugs) due to any reason is considered a new line of therapy.
- Stem cell transplant: In subjects undergoing > 1 SCT, each SCT (autologous or allogeneic) should be considered a new line of therapy regardless of whether the conditioning regimen used is the same or different.

  Note: A therapy administered before an SCT, the subsequent SCT, and planned maintenance therapy after the SCT is considered 1 line of therapy.

7.5. Safety Assessments

7.5.1. Adverse Events

Adverse events will be monitored from the time the subject signs the ICF. Subjects will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study (see Section 8.1.2 and Section 8.3.2). In order to avoid bias in eliciting AEs, subjects will be asked general, nonleading questions such as "How are you feeling?" All AEs (serious and nonserious) must be recorded on the source documents and eCRFs regardless of the assumption of a causal relationship with the study drug. The definition, reporting, and recording requirements for AEs are described in Section 8.

7.5.2. Comprehensive Physical Examinations

Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

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

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

7.5.2.1. Disease-Specific Physical Examination

A disease-specific physical examination will be a symptom-directed evaluation and will include assessment(s) of the body systems or organs, as indicated by subject disease and symptoms, AEs, or other findings as determined by the investigator or designee. A disease-specific physical examination must include a measurement of the subject's body weight (within 1 lb or 0.5 kg) and an evaluation of any AEs or symptoms that the subject has previously reported.

7.5.3. Vital Signs

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

7.5.4. Electrocardiograms

All 12-lead ECGs will be performed with the subject in a recumbent or semirecumbent position after 5 minutes of rest. Baseline ECGs will be obtained during screening using a single measurement but can be performed in triplicate if the single QTc measurement is > 450 milliseconds (corrected by Fridericia; see Section 3.2). Electrocardiograms will also be obtained during the Day 1 visit (triplicate measurements) before the subject receives the first dose of study drug. Triplicate ECGs will be performed predose and 1.5 hours (± 15 minutes) after receiving study treatment at the Week 4 visit. When triplicate ECGs are being obtained, individual measurements should be performed 5 minutes (± 3 minutes) apart. All 12-lead ECGs obtained at subsequent timepoints (single measurements) will be compared with the baseline 12-lead ECGs as follows:

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

If a single measurement demonstrates a QTc interval > 500 milliseconds, 2 more ECGs should be obtained over a brief period, and the averaged QTc intervals should be used to determine whether the study treatment should be interrupted.

Twelve-lead ECGs will be acquired using an ECG analysis system with analysis and printing capabilities, as well as digital transmission capabilities to a central capture module at the ECG laboratory. The investigator and research staff will receive adequate training by a qualified person on the use and operation of the analysis system. The successful digital submission of a 12-lead ECG, meeting quality standards, to the central ECG laboratory by the site must be ensured before enrollment of the first subject. The study reference manual for procedures that must be followed for the recording and transmission of ECGs and the operator's manual with instructions for operating the digital capture module will be shipped to the site along with the device. 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 discontinue a subject's participation in the study based on an ECG flagged as "Abnormal, Clinically

Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate. Twelve-lead ECGs that are identified by the investigator as "Abnormal, Clinically Significant" will be sent to the sponsor's medical monitor for review.

The overall ECG interpretation will be indicated by a flagging system that will help distinguish between a normal ECG, ECG abnormalities where no further investigation is required, and ECG abnormalities where study exclusion, further cardiovascular investigation, and/or prompt action may be necessary depending on the clinical context. A suitable flag will be included in the "Overall ECG Interpretation" section of the report when an ECG is considered to be technically unacceptable or uninterpretable. If several different abnormalities exist corresponding to different levels of flagging, then the label will reflect the most severe level. Flagging by the central expert cardiologist of these significant abnormalities should only be regarded as a suggestion. This service is intended to assist the investigator in his/her interpretation of the ECG and decision-making. It is not intended to replace the investigator's expert judgment and knowledge of the subject's medical condition.

7.5.5. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group performance status (Oken et al 1982; see Appendix C) will be assessed. Performance status must be assessed by a medically qualified individual and recorded in the eCRF.

7.5.6. Laboratory Assessments

Blood draws for laboratory assessments will occur at study visits indicated (see Table 7). Specific laboratory assessments are provided (see Table 8).

All laboratory assessments, including those conducted during unscheduled visits, will be performed at a central laboratory unless otherwise specified.

Note: A local laboratory assessment (including reference ranges) will be entered into the eCRF only if there is no accompanying central laboratory assessment and the local laboratory assessment caused a change in patient management (eg, a dose interruption or reduction) or was an AE or SAE.

7.5.6.1. Chemistry and Hematology

All chemistry and hematology assessments (see Table 7 and Table 8) will be performed from blood samples collected using institutional best practices.

7.5.6.2. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential (see Section 3.1) as shown (see Table 7). At screening, the serum pregnancy test may be performed centrally or locally. Urine pregnancy tests will be conducted as shown (see Table 7). If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test.

If the serum pregnancy test is negative after a positive urine test, the investigator will assess the potential benefit/risk to the subject and determine whether it is in the subject's best interest to resume study treatment and continue participation in the study.

7.5.6.3. Serology

Serology assessments (see Table 8) will be performed at a central laboratory.

7.5.6.4. HIV Screening Test

Subjects enrolled outside of the United States must have an HIV immunoassay test during screening to ensure negative HIV status before Day 1. This test is optional for subjects enrolled in the United States.

7.6. Efficacy Assessments

7.6.1. Computed Tomography Scan or Magnetic Resonance Imaging

Subjects will undergo a diagnostic-quality CT or MRI to evaluate measurable disease. If CT/MRI assessment was performed as standard of care before signing of the ICF but within 28 days of Day 1, then the results from that assessment must be recorded in the eCRF if used in lieu of a study-specific assessment. Assessments will be performed on the neck, chest, abdomen, and pelvis.

The disease assessment schedule also applies to those subjects who discontinue study treatment for reasons other than disease progression until disease progression, start of new anticancer therapy, withdrawal of consent, end of the study, or death, whichever occurs first. Imaging should not be delayed for interruption of study treatment.

7.6.2. Bone Marrow Examination

Bone marrow examination is required as a baseline assessment except in the following circumstances:

- Subject had a bone marrow examination performed as per standard of care within approximately 60 days from the first dose of study treatment.
- Subject had a bone marrow examination performed after the last treatment for NHL and the results showed lymphoma involvement of the bone marrow.

Subsequently, bone marrow examination will be performed and the sample(s) sent to a local histopathology laboratory to confirm CR, or as clinically indicated. [redacted] If the bone marrow does not have lymphoma involvement at baseline, a repeat marrow examination is not required to confirm indication of CR on imaging. [redacted]

All bone marrow examinations should include a unilateral aspiration and biopsy, when feasible.

The pathology report result from the bone marrow examination will be captured in the eCRF.

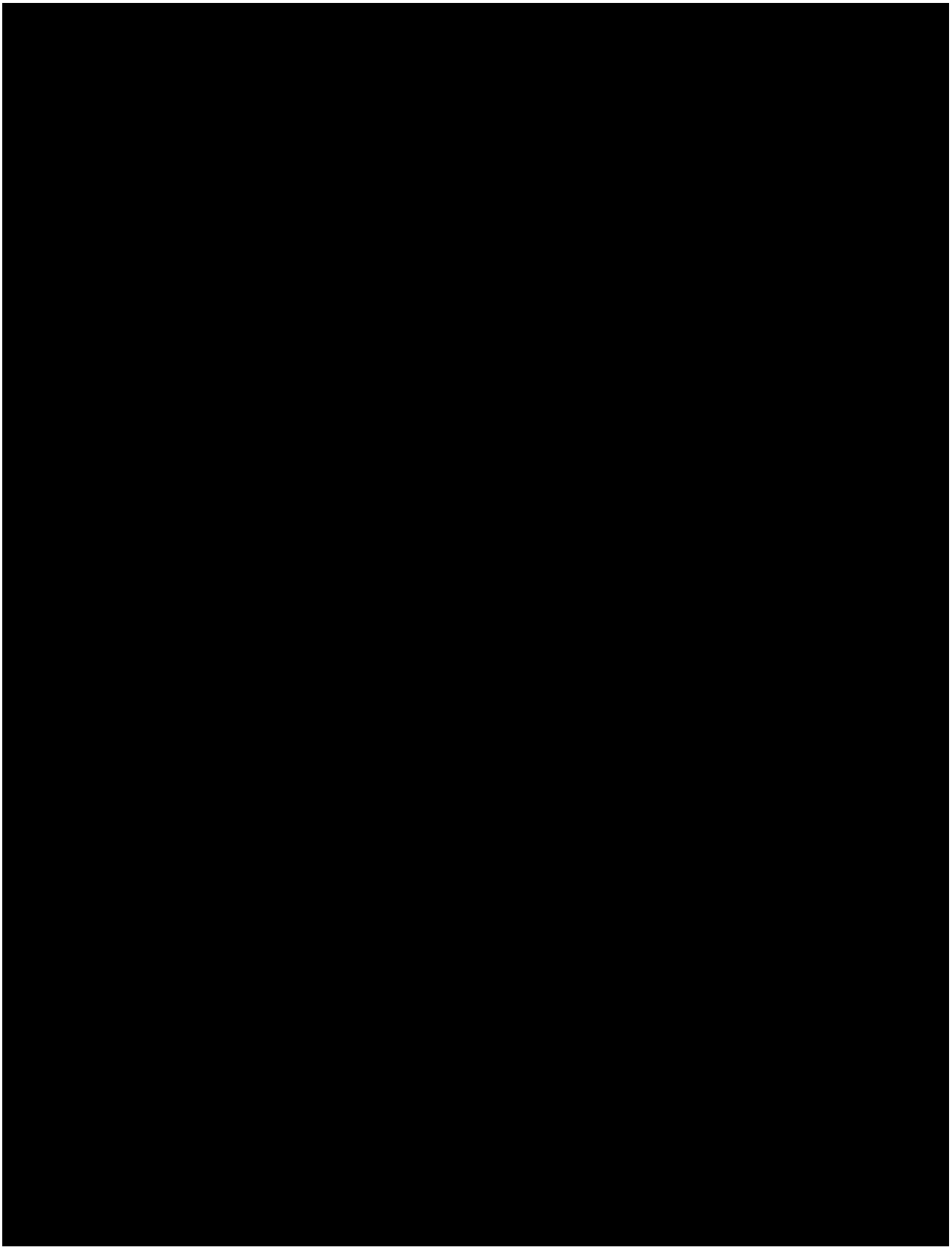
Note: Bone marrow biopsies and aspirates collected at screening should be evaluated locally. These materials are not to be sent to the central laboratory or the sponsor.

[redacted]

7.6.4. Independent Review Committee

All imaging (CT or MRI) will be submitted to the central radiology vendor for review. Imaging data and applicable clinical data will be reviewed and response assessed using the CT-based response criteria of the Lugano Classification (Cheson et al 2014; see Appendix D) by independent reviewers as described in the Imaging Charter.

[redacted]



[redacted]

7.8.5. Tumor

Subjects must have an available archival tumor biopsy sample or be willing to undergo a pretreatment tumor biopsy at baseline. Tumor tissue may be obtained on study for purposes of analyzing safety, efficacy, [redacted]

[redacted]

7.9. Other Study Procedures

7.9.1. Distribution of Subject Reminder Cards

Subjects will be provided with a reminder card at each visit.

The subject reminder card will indicate the date/time of the next visit and will also remind the subjects of which days they should not take their morning dose before coming to the clinic (see Section 7.7). The reminder cards for the Week 4 and Week 12 visits will have an area on which to record the date and time of the last dose taken (from the previous day for the Week 4 visit and most recent dose for the Week 12 visit) and the time of the most recent meal before the visit.

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions

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

8.1.2. Reporting

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

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

The severity of AEs will be assessed using CTCAE v4.03 (NCI 2009) Grades 1 through 5. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death due to AE

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

- The severity grade (CTCAE Grade 1 to 5).
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no).
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug.
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per serious adverse event (SAE) definition provided in Section 8.3.1.

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

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

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

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

8.2. Laboratory Test Abnormalities

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

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 AE does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1. A dose modification for the laboratory abnormality may be required (see Section 5.4.1) and should not contribute to the designation of a laboratory test abnormality as an SAE.

8.3. Serious Adverse Events

8.3.1. Definitions

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

- Is fatal or life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
  - A routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
  - An elective surgery or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF.
  - A treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE and not resulting in hospital admission.
  - Any social reasons and respite care, in the absence of any deterioration in the subject's general condition.
- Results in persistent or significant disability, incapacity, or a substantial disruption of a person's ability to conduct normal life functions.
- Constitutes a congenital anomaly or birth defect.
- Is considered to be an important medical event or a medically significant event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above.

8.3.2. Reporting

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

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

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

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

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

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

8.4. Emergency Unblinding of Treatment Assignment

Not applicable.

8.5. Adverse Events of Special Interest

Specific AEs, or groups of AEs, will be followed as part of standard safety monitoring activities.

- ALT ≥ 5 × ULN
- AST ≥ 5 × ULN
- Colitis
- Diarrhea ≥ Grade 2
- Rash ≥ Grade 2
- Intestinal perforation
- Pneumonitis
- *Pneumocystis jirovecii* infection
- CMV infection
- Herpes simplex virus infection
- Varicella zoster virus infection
- Exfoliative dermatitis

8.6. Pregnancy

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

- The study drug must be discontinued immediately (female subjects only; see Section 5.4.1 for the maximum permitted duration of study drug interruption).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

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

8.7. Warnings and Precautions

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

8.8. Independent Data Monitoring Committee

An independent Data Monitoring Committee (IDMC) will be formed. The IDMC will consist of qualified individuals who are not involved with the conduct of the study. The establishment, composition, roles, duties, and responsibilities of the IDMC are addressed in the approved IDMC charter.

8.9. Product Complaints

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

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

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

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

9. STATISTICS

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.

9.1. Study Populations

The full analysis set includes all subjects enrolled in the study who received at least 1 dose of INCB050465. The full analysis set will be used for the summary of demographics, baseline characteristics, subject disposition, and analyses of all efficacy data.

The safety population includes the same set of subjects as the full analysis set. This population will be used for all safety analyses.

[redacted]

9.2. Selection of Sample Size

Approximately 120 subjects will be enrolled and assigned to either treatment Group A or Group B. The first 50 subjects will be assigned at a 1:1 ratio to 2 treatment groups, and the remaining 70 subjects will be allocated to the selected treatment group based on the emerging safety and efficacy data from this and other monotherapy studies of INCB050465 in NHL that are evaluating the same or similar dosing regimens. If the true ORR is 51% for subjects in Group A and Group B, then with 120 total subjects, there is approximately 93% probability of observing the lower bound of the 95% confidence interval (CI) of ORR $\geq$ 35%.

9.3. Level of Significance

There will not be any statistical comparison between the 2 groups. Two-sided 95% CIs will be reported for all analyses when appropriate.

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

9.4.1.1. Primary Efficacy Analyses

The primary endpoint ORR is the percentage of subjects with a CR or PR as defined by revised response criteria for lymphomas (Cheson et al 2014) per IRC. The ORR as determined by the IRC and its 95% exact binomial CIs will be calculated. Subjects whose baseline disease assessment or on-study response assessments cannot be adequately assessed for response will be considered as nonresponders. These subjects will be included in the denominators in the calculations of ORR.

The primary efficacy analyses will be conducted when all subjects in the full analysis set who have achieved a response (ie, PR or CR) according to the IRC have had approximately 12 months of follow-up from the onset of response.

Subgroups will be formed based on the following subject characteristics and baseline variables:

- Age: ≤ 65 years, > 65 years
- Gender: male, female
- Geographic region: Europe, North America, Rest of World

Subgroups may be further divided or combined based on emerging data. The ORR and its 95% CIs will be provided for each subgroup. A forest plot will be created to summarize the variability in ORRs across subgroups.

9.4.1.2. Secondary Efficacy Analyses

Complete response rate is the percentage of subjects with a CR as defined by revised response criteria for lymphomas, as determined by an IRC. The CRR determined by the IRC and its 95% exact binomial CIs will be calculated.

Duration of response is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause among subjects who achieve an overall response, as determined by IRC. For subjects who have not progressed and are still alive at the time of the analysis, DOR will be censored on the day of last evaluable disease assessment. For subjects who have discontinued study or have started other anticancer treatment, DOR will be censored on the day of last evaluable disease assessment documenting absence of PD before the discontinuation or the start of the new anticancer treatment. Kaplan-Meier estimation of median DOR per IRC and its 95% CIs will be provided.

Progression-free survival is defined as the time from the date of the first dose of study drug to the first documented disease progression as determined by IRC, or death due to any cause, whichever occurs first. For subjects who have not progressed and are still alive at the time of the analysis, PFS will be censored on the day of last evaluable disease assessment. For subjects who have discontinued study or have started other anticancer treatment, PFS will be censored on the day of last evaluable disease assessment documenting absence of PD before the discontinuation or the start of the new anticancer treatment. For subjects who have no baseline or no postbaseline disease assessment, PFS will be censored with censored duration of 1 day. Kaplan-Meier estimation of median PFS per IRC and its 95% CIs will be provided.

Overall survival is defined as the time from the date of the first dose of study drug to death due to any cause. For subjects who are still alive at the time of the analysis, OS will be censored on the date the subject is last known to be alive. The Kaplan-Meier estimation of median OS and its 95% CIs will be provided.

For subjects with measurable lesions at baseline, target lesion sizes will be measured by sum of the product of the diameters of all target lesions. The best percentage change from baseline, defined as the largest decrease in target lesion sizes during the study, will be summarized descriptively. Note that for subjects who only have increases in target lesion sizes from baseline, the smallest increase will be considered as the best change from baseline. Target lesions considered "too small to measure" will be assigned a default value of 5 mm × 5 mm for purposes

of this analysis. Likewise, target lesions identified as "not present" at postbaseline assessments will be assigned 0 mm for this analysis. In the event that a target lesion is unaccounted for in a particular postbaseline timepoint (ie, the assessment is missing or NE), then the overall sum of target lesions will not be evaluable for that postbaseline timepoint.

[redacted]

9.4.2. Safety Analyses

9.4.2.1. Adverse Events

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study treatment and within 30 days of the last administration of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study treatment administration. Adverse events will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the NCI CTCAE v4.03 (NCI 2009) using Grades 1 through 5.

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

9.4.2.2. Clinical Laboratory Tests

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

Laboratory data will be classified into Grades 1 through 4 using CTCAE v4.03 (NCI 2009). The following summaries will be produced for the laboratory data:

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

9.4.2.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities (see Table 10), and subjects exhibiting clinically notable vital sign abnormalities will be listed. A value will be considered an "alert" value if it is outside the established range and shows a > 25% change from baseline.

Table 10: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 mmHg	< 85 mmHg
Diastolic blood pressure	> 100 mmHg	< 40 mmHg
Pulse	> 100 bpm	< 45 bpm
Temperature	> 38ºC	< 35ºC
Respiratory rate	> 24 breaths/min	< 12 breaths/min

9.4.2.4. Electrocardiograms

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time. Electrocardiogram results will be reviewed for clinically notable abnormalities according to predefined criteria (see Table 11). Subjects exhibiting clinically notable ECG abnormalities will be listed.

Table 11: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF	> 450 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.

9.4.2.5. Adverse Events of Special Interest

Adverse events of special interest (see Section 8.5) will be summarized as detailed in the Statistical Analysis Plan.

[redacted]

9.5. Analyses for the Data Monitoring Committee

Preplanned analyses of safety will be provided to the IDMC as specified in the IDMC charter. In addition, the IDMC will make recommendations to the sponsor at the planned interim futility analysis (see Section 9.6). The process by which the IDMC will make recommendations and decisions will be documented in the IDMC charter.

9.6. Interim Analysis

An interim futility analysis is planned when the first 50 subjects (Group A and Group B combined) have been evaluated for response or have permanently discontinued study treatment because of disease progression, withdrawal of consent, or death. The study will be terminated for futility if ≤ 18 of the 50 subjects have responded (ie, CR or PR) based on assessments provided by the IRC; otherwise the study will continue. A timely assessment of response will be performed to avoid the risk of overenrollment.

10. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

10.1. Investigator Responsibilities

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

The investigator will be responsible for:

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

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

10.2. Accountability, Handling, and Disposal of Study Drug

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

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

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the subjects were provided the specified study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study subjects.

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

10.3. Data Management

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

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

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

10.4. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that sensitive personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable. Appropriate consent for collection, use and disclosure and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws.

Subject names will not be supplied to the sponsor or its designee. Only the subject number will be recorded in the eCRF; 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 appropriate technical and organizational measures as required by local data protection laws.

10.5. Financial Disclosure

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

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

10.6. Publication Policy

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

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

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

Such methods include:

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

For Male Subjects Participating in the Study

In addition to the aforementioned contraceptive methods, male subjects must also use a condom during intercourse from the time of first dose of study treatment and through at least 93 days after last dose of study treatment. Males who have had a vasectomy qualify as having met the requirement for a highly effective birth control method.

[1] Contraception methods that in the context of this guidance are considered to have low user dependency.
[2] Vasectomised partner is a highly effective method of avoiding pregnancy provided 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.
[3] 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. CYP3A INHIBITORS AND INDUCERS

CYP3A inhibitors or inducers may alter INCB050465 concentration. These include but are not limited to the drugs listed below.

CYP3A Inhibitors

Inhibitor	Therapeutic Class
Potent CYP3A Inhibitors	
VIEKIRA PAK	Antivirals
indinavir /RIT	Protease Inhibitors
tipranavir/RIT	Protease Inhibitors
ritonavir	Protease Inhibitors
cobicistat (GS-9350)	None
ketoconazole	Antifungals
indinavir	Protease Inhibitors
troleandomycin	Antibiotics
telaprevir	Antivirals
danoprevir / RIT	Antivirals
elvitegravir / RIT	Treatments of AIDS
saquinavir / RIT	Protease Inhibitors
lopinavir / RIT	Protease Inhibitors
itraconazole	Antifungals
voriconazole	Antifungals
mibefradil	Calcium Channel Blockers
LCL161	Cancer Treatments
clarithromycin	Antibiotics
posaconazole	Antifungals
telithromycin	Antibiotics
grapefruit juice DS	Food Products
conivaptan	Diuretics
nefazodone	Antidepressants
nelfinavir	Protease Inhibitors
saquinavir	Protease Inhibitors
ribociclib	Kinase Inhibitors
idelalisib	Kinase Inhibitors
boceprevir	Antivirals

Moderate CYP3A Inhibitors	
erythromycin	Antibiotics
fluconazole	Antifungals
atazanavir / RIT	Protease Inhibitors
darunavir	Protease Inhibitors
diltiazem	Calcium Channel Blockers
darunavir / RIT	Protease Inhibitors
dronedarone	Antiarrhythmics
crizotinib	Kinase Inhibitors
atazanavir	Protease Inhibitors
letermovir	Antivirals
GSK2647544	Alzheimer's Disease & Dementia Treatments
aprepitant	Antiemetics
casopitant	Antiemetics
amprenavir	Protease Inhibitors
faldaprevir	Antivirals
imatinib	Antineoplastic Agents
verapamil	Calcium Channel Blockers
netupitant	Antiemetics
nilotinib	Kinase Inhibitors
grapefruit juice	Food Products
tofisopam	Benzodiazepines
cyclosporine	Immunosuppressants
ACT-178882	Renin Inhibitors
ciprofloxacin	Antibiotics
Magnolia vine (Schisandra sphenanthera)	Herbal Medications
isavuconazole	Antifungals
cimetidine	H-2 Receptor Antagonists
FK1706	Central Nervous System Agents

Weak CYP3A Inhibitors	
tabimorelin	Hormone Replacement
amlodipine	Calcium Channel Blockers
ranolazine	Cardiovascular Drugs
breviscapine	Herbal Medications
lomitapide	Other Antilipemics
fosaprepitant (IV)	Antiemetics
Seville orange (Citrus aurantium) juice	Food Products
amiodarone	Antiarrhythmics
diosmin	Herbal Medications
chlorzoxazone	Muscle Relaxants
M100240	Antihypertensive Agents
fluvoxamine	Antidepressants
ranitidine	H-2 Receptor Antagonists
goldenseal	Herbal Medications
clotrimazole	Antifungals
tacrolimus	Immunosuppressants
palbociclib	Kinase Inhibitors
cilostazol	Antiplatelets
ticagrelor	Antiplatelets
peppermint oil	Food Products
ivacaftor	Cystic fibrosis treatments
GSK2248761	Transcriptase Inhibitors
Guan Mai Ning	Herbal Medications
osilodrostat	Adrenal Steroidogenesis Inhibitors
AZD2327	Depression Treatments
piperine	Food Products
resveratrol	Food Products
roxithromycin	Antibiotics
suvorexant	Hypnotics - Sedatives
propiverine	Anticholinergics
isoniazid	Antibiotics
berberine	Herbal Medications
oral contraceptives	Oral contraceptives
delavirdine	NNRTIs
daclatasvir	Antivirals
simeprevir	Protease Inhibitors
atorvastatin	HMG CoA Reductase Inhibitors (Statins)
tolvaptan	Vasopressin Antagonists

almorexant	Hypnotics - Sedatives
GSK1292263	Other Antilipemics
evacetrapid	CETP inhibitors
linagliptin	Dipeptidyl Peptidase 4 Inhibitors
grazoprevir *(ingredient of Zepatier)*	Antivirals
lacidipine	Calcium Channel Blockers
cranberry juice	Food Products
pazopanib	Kinase Inhibitors
fostamatinib	Other
everolimus	Immunosuppressants
blueberry juice	Food Products
flibanserin	Central Nervous System Agents
lapatinib	Kinase Inhibitors
brodalumab	Immunomodulators Biologics
AMD070	Fusion Inhibitors
alprazolam	Benzodiazepines
Tong Xin Luo	Herbal Medications
glecaprevir and pibrentasvir	Antivirals
bicalutamide	Antiandrogens
sitaxentan	Endothelin Receptor Antagonists
azithromycin	Antibiotics
obeticholic acid	Miscellaneous Agents
ginkgo	Herbal Medications
teriflunomide	Other Immunomodulators

CYP3A Inducers

Inducers	Therapeutic class
Potent Inducers	
rifampin	Antibiotics
mitotane	Other Antineoplastics
avasimibe	Other Antilipemics
rifapentine	Antibiotics
apalutamide	Antiandrogens
phenytoin	Anticonvulsants
carbamazepine	Anticonvulsants
enzalutamide	Antiandrogens
St John's Wort extract	Herbal Medications
lumacaftor	Cystic Fibrosis Treatments
rifabutin	Antibiotics
phenobarbital	Anticonvulsants
Moderate Inducers	
ritonavir and St. Johns wort	None
semagacestat	Alzheimer's Treatments
efavirenz	NNRTIs
tipranavir and ritonavir	Protease Inhibitors
dabrafenib	Kinase Inhibitors
lesinurad	Antigout and Uricosuric Agents
bosentan	Endothelin Receptor Antagonists
genistein	Food Products
thioridazine	Antipsychotics
nafcillin	Antibiotics
talviraline	NNRTIs
lopinavir	Protease Inhibitors
modafinil	Psychostimulants
PF-06282999	Myeloperoxidase Inactivators
etravirine	NNRTIs
lersivirine	NNRTIs
telotristat ethyl	Antidiarrheals

Weak Inducers	
eslicarbazepine	Anticonvulsants
telaprevir	Antivirals
daclatasvir and asunaprevir and beclabuvir	Antivirals
amenamevir	Antivirals
garlic	Food Products
bexarotene	Other Antineoplastics
sarilumab	Immunomodulators Biologics
artesunate and mefloquine	Antimalarials
amprenavir (fosamprenavir)	Protease Inhibitors
raltegravir	HIV-Integrase Strand Transfer Inhibitors
vemurafenib	Kinase Inhibitors
troglitazone	Thiazolidinediones
dicloxacillin	Antibiotics
sorafenib	Kinase Inhibitors
rufinamide	Anticonvulsants
sirukumab	Immunomodulators Biologics
pleconaril	Antivirals
ginseng	Herbal Medications
boceprevir	Antivirals
sulfinpyrazone	Antigout and Uricosuric Agents
ginkgo	Herbal Medications
vinblastine	Vinca Alkaloids
nevirapine	NNRTIs
armodafinil (R-modafinil)	Psychostimulants
ticagrelor	Anticoagulants and Antiplatelets
LCL161	Cancer Treatments
vicriviroc and ritonavir	Treatments of AIDS
ritonavir	Protease Inhibitors
prednisone	Corticosteroids
oxcarbazepine	Anticonvulsants
danshen	Herbal Medications
clobazam	Benzodiazepines
echinacea	Herbal Medications
ticlopidine	Anticoagulants and Antiplatelets
isavuconazole	Antifungals
brivaracetam	Anticonvulsants
Stribild	Treatments of AIDS
pioglitazone	Thiazolidinediones

VIEKIRA PAK	Antivirals
dexamethasone	Corticosteroids
terbinafine	Antifungals
quercetin	Food Products
glycyrrhizin	Herbal Medications
aprepitant	Neurokinin-1 Receptor Antagonists
pretomanib (PA-824)	Antibiotics
safinamide	MAO-B Inhibitors
oritavancin	Antibiotics
AZD 7325	Anxiolytics
methylprednisolone	Corticosteroids
topiramate	Anticonvulsants

APPENDIX C. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Eastern Cooperative Oncology Group Performance Scores

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

Source: Oken et al 1982.

APPENDIX D. LUGANO CLASSIFICATION FOR RESPONSE ASSESSMENT (CT-BASED ONLY)

Site	CT-Based Response
	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi.
Nonmeasured lesion	Absent.
Organ enlargement	Regress to normal.
New lesions	None.
Bone marrow	Normal by morphology; if indeterminate, immunohistochemistry negative.
	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	• ≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites. • When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default. • When no longer visible, 0 × 0 mm. For a node > 5 mm × 5 mm but smaller than normal, use actual measurement.
Nonmeasured lesions	Absent/regressed, but no increase.
Organ enlargement	Spleen must have regressed by > 50% in length beyond normal.
New lesions	None.
Bone marrow	Not applicable.
	Stable disease
Target nodes/nodal masses, extranodal lesions	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for PD are met.
Nonmeasured lesions	No increase consistent with progression.
Organ enlargement	No increase consistent with progression.
New lesions	None.
Bone marrow	Not applicable.

Site	CT-Based Response
	Progressive disease (requires at least 1 of the following)
Individual target nodes/nodal lesions	PPD progression: • An individual node/lesion must be abnormal with all of the following: – LDi > 1.5 cm. – Increase by ≥ 50% from PPD nadir. – Increase in LDi or SDi from nadir: ○ 0.5 cm for lesions ≤ 2 cm. ○ 1.0 cm for lesions > 2 cm. • In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15 cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. • New or recurrent splenomegaly. • New or clear progression of pre-existing 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.

CT = computed tomography; EOT = end of treatment; LDi = longest transverse diameter of lesion; MRI = magnetic resonance imaging; PPD = cross-product of the longest transverse diameter and perpendicular diameter; SDi = shortest axis perpendicular to the longest transverse diameter; SPD = sum of the product of the perpendicular diameters for multiple lesions.

APPENDIX E. FOLLICULAR LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX

Follicular Lymphoma International Prognostic Index (FLIPI)

Scoring System		
Parameter	**Value**	**Point Score**
Age	>60 years of age	1
Ann Arbor stage	Stage III or IV	1
Hemoglobin level	<120 g/L (12.0 g/dL or 6.37 mmol/L)	1
Serum LDH	>ULN	1
Number of Nodal Sites	>5	1

Risk Group by FLIPI Total Point Score	
Risk Group	**Total Point Score**
Low	≤1
Intermediate	2
High	≥3

Abbreviations: LDH , lactate dehydrogenase; ULN, upper limit of normal

APPENDIX F. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	15 MAR 2017
Amendment (Version) 2:	15 AUG 2017
Amendment (Version) 3:	11 SEP 2017
Amendment (Version) 4:	25 OCT 2017
Amendment (Version) 4-CAN:	12 DEC 2017
Amendment (Version) 5:	17 JAN 2018
Amendment (Version) 6:	11 JUL 2018
Amendment (Version) 7:	04 SEP 2018
Amendment (Version) 8:	06 DEC 2018
Amendment (Version) 9:	23 DEC 2019

Amendment 9 (23 DEC 2019)

Overall Rationale for the Amendment: The primary purpose of this amendment is to provide additional guidance on dose modification in the event of diarrhea and colitis and to define the end of the study, including the option to receive continued treatment with INCB050465 in a rollover protocol.

1. **Section 5.4.1.1, Dose Modifications (Table 3: Guidelines for Interruption and Restarting INCB050465; Table 4: Dose Levels and Reductions for INCB050465); Section 5.4.1.2, Supportive Care Guidelines for Diarrhea/Colitis (Table 5: Guidelines for Dose Modification of INCB0050465 for Diarrhea/Colitis)**

   Description of change: Revision to text pertaining to interruptions and restarting INCB050465 for adverse events of diarrhea and colitis.

   Rationale for change: To provide additional dose modifications of INCB050465 for diarrhea and colitis.

2. **Synopsis; Section 4.5, Overall Study Duration; Section 5.8, Treatment After the End of the Study; Section 6.5, End of Study**

   Description of change: Text and new section added to describe that subjects who are receiving active study treatment and have no evidence of progressive disease at the end of the study will have the option to continue on INCB050465 provided within a rollover Protocol.

   Rational for change: To clarify what treatment options are available at the end of the study.

3. **Synopsis (Estimated Number of Subjects, Statistical Methods); Section 4.1, Overall Study Design; Section 4.3.1, Planned Number of Subjects; Section 4.5, Overall Duration; Section 9.2, Selection of Sample Size; Section 9.4.1.1, Primary Efficacy Analyses**

   Description of change: Increased the target enrollment from approximately 100 to approximately 120 subjects and changed the timing of the primary analysis.

   Rational for change: To align with recommendations from the US FDA.

4. **Synopsis (Estimated Duration of Participation); Section 4.4, Duration of Treatment and Subject Participation; Section 4.5, Overall Study Duration; Section 5.7, Criteria for Study Discontinuation; Section 6.5, End of Study**

   Description of change: Text and new section added to define the following: a) criteria for a subject to be discontinued from the study and b) the end of study.

   Rational for change: To clarify when a subject will be discontinued from the study and when the study will end.

5. **Synopsis (Study Schedule/Procedures); Section 6, Study Assessments (Table 6: Schedule of Assessments)**

   Description of change: Changed frequency of study treatment dispensation and assessment of compliance from every 4 weeks to every 12 weeks starting at Week 48.

   Rationale for change: To reduce the burden of extra pharmacy visits for the subjects.

6. **Section 9.1, Study Populations**

   Description of change: Removed the PP population.

   Rationale for change: For a single-arm, open-label study, the determination of subjects to be excluded from the PP population is post hoc and may not be done objectively; thus, analysis based on this population may not be meaningful.

7. **Section 9.4.2.4, Electrocardiograms (Table 11: Criteria for Clinically Notable Electrocardiogram Abnormalities)**

   Description of change: Changed high threshold of QTcF interval from > 460 msec to > 450 msec for analysis purposes.

   Rationale for change: To comply with the categories outlined in FDA Guidance for Industry (E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs) used to characterize outliers in QTc values.

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

This amendment also incorporates the following from Protocol Administrative Change 3 dated 23 MAY 2019:

[redacted]

Amendment 8 (06 DEC 2018)

Overall Rationale for the Amendment: The primary purpose of the amendment is to stop the 1:1 allocation of subjects after the 50th subject has enrolled and to enroll the remaining 50 subjects to only one of the 2 treatment regimens being evaluated.

1. **Synopsis; Section 4.1, Overall Study Design (Figure 2: Study Design); Section 9.2, Selection of Sample Size**

   Description of change: Revised to state that after 50 subjects are enrolled, the remaining 50 subjects will be enrolled to only one of the 2 treatment regimens being evaluated in this study. Patients allocated to the unselected treatment will be allowed to cross over.

   Rationale for change: To increase the number of subjects administered one of the 2 treatment regimens, leading to a better understanding of the long-term safety and efficacy of that treatment regimen.

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

   Description of change: Revised language pertaining to the protection of personal data.

   Rationale for change: To comply with the General Data Protection Regulation 2016/679.

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

Amendment 7 (04 SEP 2018)

Overall Rationale for the Amendment: The primary purpose of this amendment is to provide a list of CYP3A inhibitors and inducers.

1. **Section 3.2, Subject Exclusion Criteria; Section 5.6.2, Restricted Medications; Section 5.6.3, Prohibited Medications and Therapies; Appendix B, CYP3A Inhibitors and Inducers**

   Description of change: Added tables of CYP3A inhibitors and inducers in Appendix B. These tables were updated and modified compared to the previous versions, which had been removed from Protocol Version 6 and placed in the Pharmacy Manual.

   Rationale for change: These tables were returned to the Protocol by the request of the European Health Authority.

Amendment 6 (11 JUL 2018)

Overall Rationale for the Amendment: The primary purpose of this amendment is to modify the dose reduction schedules.

1. **Section 5.4.1.1, Dose Modifications (Table 4, Dose Levels for INCB050465)**

   Description of change: Modified the dose reduction schedules.

   Rationale for change: The new schedules are being implemented to ensure that all subjects will remain on a QD dosing schedule for the first 8 weeks (56 days) and to provide consistency between Treatments A and B.

2. **Section 5.4.1.1, Dose Modifications (Table 3, Guidelines for Interruption and Restarting INCB050465)**

   Description of change: Redefined "Grade 3 or Grade 4 ANC with an oral temperature of at least 38.5°C OR with Grade ≥ 3 infection" as Grade 3 or Grade 4 febrile neutropenia. Allowance is made to restart INCB050465 at the same dose after Grade 4 ANC, Grade 4 platelet count, or Grade 3 or Grade 4 febrile neutropenia resolve to ≤ Grade 2, rather than Grade 1, regardless of attribution.

   Rationale for change: A restart at the same dose level regardless of attribution is allowed to provide study doctors flexibility in subject management. Dosing is allowed to begin at ≤ Grade 2 to be consistent with eligibility criteria, which start at Grade 2 for neutrophil and platelet counts.

3. **Section 7.5.6, Laboratory Assessments**

   Description of change: Clarified the scenarios in which a local laboratory assessment may be performed and in which cases local laboratory values would be entered into the eCRF.

   Rationale for change: Clarification.

4. **Section 7.6.2, Bone Marrow Examination**

   Description of change: Clarified that bone marrow collected at screening and postbaseline should be sent to a local histopathology laboratory. [redacted]

   Rationale for change: Clarification.

5. **Section 3.1, Subject Inclusion Criteria (Inclusion Criterion 9d)**

   Description of change: Inclusion Criterion 9d was revised to allow subjects with whose total bilirubin values are > 1.5 × ULN to enroll if the elevation is due to Gilbert's syndrome.

   Rationale for change: Gilbert's syndrome is a hereditary condition characterized by intermittent, unconjugated hyperbilirubinemia in the absence of hepatocellular damage and hemolysis. Consistent with other PI3Kδ inhibitors, elevated bilirubin due to Gilbert's syndrome is not expected to alter the risk/benefit profile for subjects taking INCB050465.

6. **Section 7.4, Prior and Concomitant Medications and Procedures**

   Description of change: Added a definition for lines of therapy.

   Rationale for change: Definitions were added to improve consistency for calculation of prior lines of therapy.

7. **Section 3.2, Subject Exclusion Criteria; Section 5.6.2, Restricted Medications; Section 5.6.3, Prohibited Medications and Therapies; Appendix B, Cytochrome P450 Inhibitors and Cytochrome P450 Inducers**

   Description of change: Deleted Appendix B and references to Appendix B.

   Rationale for change: Information was moved to the Pharmacy Manual.

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

Amendment 5 (17 JAN 2018)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The primary purpose of this amendment is to institute hematology testing every 2 weeks for the first 8 weeks of dosing.

1. **Synopsis; Section 6, Study Assessments (Table 6, Schedule of Laboratory Assessments)**

   Description of change: Study visits were added at Week 2 and Week 6 for hematology testing.

   Rationale for change: Requested by the US FDA.

2. **Section 5.5.1, Criteria for Study Treatment Discontinuation**

   Description of change: The following bullet has been deleted from Section 5.5.1:

   If a subject is found not to have met eligibility criteria, then the medical monitor and investigator will collaborate to determine whether the subject should be withdrawn from the study.

   Rationale for change: Requested by Health Canada.

3. **Section 5.4.1.2, Supportive Care Guidelines for Neutropenia and Thrombocytopenia**

   Description of change: Provided instructions to investigators to remind subjects to report signs or symptoms of infection, bleeding, or sudden, extremely painful headaches.

   Rationale for change: Requested by the US FDA.

4. **Section 5.6.2, Restricted Medications; Section 5.6.3, Prohibited Medications and Therapies**

   Description of change: Radiation therapy was removed from Section 5.6.3 as it was redundant with Section 3.2 (exclusion criterion 10), which lists excluded, concurrent anticancer therapies. A description of permitted radiotherapy was added to Section 5.6.2. The length of time a live vaccine is prohibited was added to Section 5.6.3.

   Rationale for change: Administration of localized radiotherapy in cases of pain or impending compression fractures may be permitted to allow subjects who are otherwise benefitting to continue study treatment. The length of time a live vaccine is prohibited was added to align with other clinical studies within the INCB050465 development program..

[redacted]

7. **Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

   Description of change: Provided information for male contraception methods.

   Rationale for change: Informational.

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

Amendment 4-CAN (12 DEC 2017)

Overall Rationale for the Amendment:

To remove a criterion for study treatment discontinuation per Health Canada's request.

1. **Section 5.5.1, Criteria for Study Treatment Discontinuation**

   Description of change: The following bullet has been deleted from Section 5.5.1:

   - If a subject is found not to have met eligibility criteria, then the medical monitor and investigator will collaborate to determine whether the subject should be withdrawn from the study.

   Rationale for change: To meet Health Canada requirements.

Amendment 4 (25 OCT 2017)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to remove the comparator arm (idelalisib) from the study.

This amendment includes the changes to Protocol INCB 50465-203 Amendment 3 (11 SEP 2017) summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. **Title; Synopsis; Section 1, Introduction; Section 2, Study Objectives and Endpoints; Section 3.2, Subject Exclusion Criteria; Section 4.1, Overall Study Design; Section 4.2, Measures Taken to Avoid Bias; Section 4.3.1, Planned Number of Subjects; Section 4.5, Overall Study Duration; Section 5.1.2, Randomization and Blinding; Section 5.2, Study Treatments; Section 5.4, Treatment Interruptions and Adjustments; Section 5.6, Concomitant Medications; Section 6, Study Assessments (Table 6, Schedule of Assessments; Table 7, Schedule of Laboratory Assessments); Section 6.1, Screening; Section 6.2, Treatment; Section 7.2, Interactive Response Technology Procedure; 7.4, Prior and Concomitant Medications and Procedures; 7.5.6.1, Chemistry and Hematology; Section 7.6, Efficacy Assessments; Section 7.7.1, Blood Sample Collection; Section 9, Statistics; Appendix A, Information Regarding Effectiveness of Contraceptive Methods.**

   Description of change: The comparator arm, idelalisib, was removed from the study, allowing for removal of the biweekly assessments for ANC and liver enzymes required for idelalisib and reduction in the number of subjects from 180 to 100.

   Rationale for change: A PI3K inhibitor, copanlisib, was recently granted accelerated approval by the US Food and Drug Administration in the patient population being evaluated in this study. Therefore, the PI3Kδ inhibitor, idelalisib, can no longer be considered the standard of care in the US and consequently is not a relevant comparator for new PI3K inhibitors. It is also not feasible to replace idelalisib with copanlisib, which is currently approved only in the US. This change allows the number of subjects to be reduced from 180 to 100.

2. **Section 3.1, Inclusion Criteria**

   Description of change: Removed South Korea–specific age requirement.

   Rationale for change: Study will not be conducted in South Korea

3. **Section 3.2, Subject Exclusion Criteria**

   Description of change: Exclusion criterion 17 (liver disease) was updated.

   Rationale for change: As there have been no reported HBV or HCV reactivations in INCB 50465-101, the exclusion criterion was amended to align with those of approved PI3K inhibitors.

4. **Section 5.2.1.2, Supply, Packaging, and Labeling; Section 5.6.1, *Pneumocystis Jirovecii* Prophylaxis**

   Description of change: Moved text describing procurement of drugs required for PJP prophylaxis.

   Rationale for change: Administrative.

6. **Appendix E, Lugano Classification for Response Assessment**

   Description of change: Removed the column describing PET-based criteria of response.

   Rationale for change: The study is based on CT/MRI only.

7. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment, including the addition of all summary of changes to Appendix G.

Amendment 3 (11 SEP 2017)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to address changes requested by the European Regulatory Agency.

This amendment includes the changes to Protocol INCB 50465-203 Amendment 2 (15 AUG 2017) summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

[redacted]

2. **Section 9.4.1.1, Primary Efficacy Analyses**

   Description of change: Added a description of the subgroup analysis, which will include subgroups based on age, gender, and geographic region that can be further divided or combined based on emerging data.

   Rationale for change: Requested by the European Regulatory Agency.

[redacted]

Amendment 2 (15 AUG 2017)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to address changes requested by the European Regulatory Agency.

This amendment includes the changes to Protocol INCB 50465-203 Amendment 1 (15 MAR 2017) summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. **Title page**

   Description of change: The EudraCT number has been added (2017-001624-22).

   Rationale for change: Informational.

2. **Synopsis; Section 6, Study Assessments (Table 7)**

   Description of change: The frequency of cytomegalovirus analysis was increased to every 4 weeks.

   Rationale for change: Requested by European Regulatory Agency.

3. **Section 3.2, Subject Exclusion Criteria (criterion 16); Section 6, Study Assessments (Tables 7 and 8); Section 7.5.6.4, HIV Screening Test**

   Description of change: Revised to require that subjects enrolled outside the United States have an HIV test at screening.

   Rationale for change: Requested by European Regulatory Agency.

4. **Section 5.4.2, Criteria and Procedures for Dose Interruptions or Adjustments of Idelalisib**

   Description of change: Clarified that investigators should follow the individual product package insert for safety assessments for idelalisib.

   Rationale for change: Requested by European Regulatory Agency.

5. **Section 6, Study Assessments (Table 7)**

   Description of change: Stated that blood counts should be monitored at least weekly in subjects receiving either idelalisib or INCB050465 while ANC is $< 1.0 \times 10^9$/L, and referenced the product package insert and Section 5.4, respectively.

   Rationale for change: Requested by European Regulatory Agency.

6. **Section 6, Study Assessments (Table 7)**

   Description of change: Added a serum pregnancy test at the safety follow-up visit for women of child-bearing potential.

   Rationale for change: Requested by European Regulatory Agency.

7. **Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

   Description of change: Revised to require that women receiving idelalisib who are using hormonal contraceptives add a barrier method as a second form of contraception, and removed the statement that the investigational medicinal products (IMP), which included INCB050465, may reduce the efficacy of hormonal contraceptives.

   Rationale for change: The addition of a barrier method was requested by European Regulatory Agency per the SmPC. The statement that the IMP may reduce the efficacy of hormonal contraceptives was removed as the IMP includes INCB050465, which unlike idelalisib, is not a CYP3A4 inhibitor and therefore has no effect on hormonal contraception.

8. **Synopsis; Section 2, Study Objectives and Endpoints (Table 1)**

   Description of change: The primary objective was revised to state the threshold for conducting a superiority analysis.

   Rationale for change: Requested by European Regulatory Agency.

9. **Synopsis; Section 9, Statistics**

   Description of change: Clarified that descriptive summaries for categorical variables will include the number and percentage of subjects in each category, and that the descriptive summaries for continuous variables will include the number of observations, mean, standard deviation, median, minimum, and maximum.

   Rationale for change: Requested by European Regulatory Agency.

10. **Synopsis; Section 9.4.1.1, Primary Efficacy Analyses**

    Description of change: Clarified that the point estimates and confidence intervals (CIs) will be calculated for the primary endpoint of objective response rate for INCB050465 and idelalisib and their difference, and clarified the timing for the primary endpoint.

    Rationale for change: Requested by European Regulatory Agency.

11. **Section 9.4.1.1, Primary Efficacy Analyses**

    Description of change: Clarified that subjects without sufficient baseline or on-study response assessment information to be adequately assessed for response status will be considered as nonresponders and included in the denominators in the calculations of ORR.

    Rationale for change: Requested by European Regulatory Agency.

12. **Section 9.4.1.3, Other Efficacy Analyses**

    Description of change: Clarified that ORR, complete response rate (CRR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS) will be summarized by treatment groups. Point estimates and 95% CIs will be provided for ORR and CRR. Kaplan-Meier estimations of median DOR, PFS, and OS and their 95% CIs will also be calculated for each group.

    Rationale for change: Requested by European Regulatory Agency.

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

Amendment 1 (15 MAR 2017)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to align the visit schedule nomenclature with other CITADEL protocols.

This amendment includes the changes to the Protocol INCB 50465-203 (01 MAR 2017) summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. **Synopsis; Section 6, Study Assessments (Tables 6 and 7); Section 7.5.4, Electrocardiograms; Section 7.7.1, Blood Sample Collection (Table 9); Section 7.9.1, Distribution of Subject Reminder Cards**

   Description of change: The study visits were changed to Weeks 4, 8, 12, etc (instead of Day 1 of Week 5, 9, 13, etc). A similar change was made to the 12-week visit schedule. Only the names of the visits were changed, the timing of the visits remained the same.

   Rationale for change: To align this study with future CITADEL studies, many of which will be conducted at the same sites.

2. **Section 4.5, Overall Study Duration; Section 6.5, End of Study**

   Description of change: Clarified the timing of end of study and that subjects receiving study treatment at the time of the final analysis will continue to receive study treatment until withdrawal criteria are met.

   Rationale for change: Clarification.

3. **Section 6, Study Assessments (Tables 6 and 7); [redacted] Section 7.5.6.1, Chemistry and Hematology**

   Description of change: Added a line for *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis; added collections for serum chemistry, hematology, and serology; and made minor corrections. [redacted]

   Rationale for change: To ensure PJP prophylaxis is appropriately administered and blood samples are taken as required.

4. **Section 5.2.1.2, Supply, Packaging, and Labeling; Section 5.2.2.2, Supply, Packaging, and Labeling**

   Description of change: Replaced text describing how PJP prophylactic drugs will be procured by site.

   Rationale for change: To provide additional details about how PJP prophylactic drugs will be procured.

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

   Description of change: Modified the HBV and HCV exclusion criteria.

   Rationale for change: Based on emerging data from INCB 50465-101, INCB050465 does not appear to cause liver toxicity. The HBV and HCV exclusion criteria have been made consistent with criteria used for other PI3K inhibitors, which generally allows enrollment of subjects that have been infected with HBV or HCV, but excludes subjects with an active infection based on DNA or RNA tests, respectively.

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