Clinical Study Protocol

INCB 50465-202 / NCT02998476

A Phase 2, Multicenter, International, Open-Label, Safety and Efficacy Study of INCB050465 in Subjects With Relapsed or Refractory Diffuse Large B-Cell Lymphoma (CITADEL-202)

Product:	**INCB050465**
IND Number:	**121,474**
EudraCT Number:	**2016-002205-19**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation 1801 Augustine Cut-Off Wilmington, DE 19803**
Date of Protocol:	**26 MAY 2016**
Date of Amendment (Version) 1:	**30 AUG 2016**
Date of Amendment (Version) 2:	**09 NOV 2016**
Date of Amendment (Version) 3:	**23 FEB 2017**
Date of Amendment (Version) 4:	**05 NOV 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 50465-202 Protocol Amendment 4 (dated 05 NOV 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, International, Open-Label, Safety and Efficacy Study of INCB050465 in Subjects With Relapsed or Refractory Diffuse Large B-Cell Lymphoma	
Protocol Number: INCB 50465-202	**Study Phase:** 2
Indication: Diffuse large B-cell lymphoma	

Primary Objective:

- To assess the efficacy of INCB050465 in terms of objective response rate (ORR) in subjects with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in Group A.

Secondary Objectives:

- To assess the duration of response (DOR) in Group A.
- To assess progression-free survival (PFS) in Group A.
- To assess overall survival (OS) in Group A.
- To characterize the safety of INCB050465 in Group A and Group B.

[redacted]

Primary Endpoint:

- Objective response rate in Group A, defined as the percentage of subjects with a complete response/complete metabolic response (CR/CMR) or partial response/partial metabolic response (PR/PMR) as defined by revised response criteria for lymphomas, as determined by an Independent Review Committee (IRC).

Secondary Endpoints:

- Duration of response in Group A, defined as the time from first documented evidence of CR/CMR or PR/PMR 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.
- Progression-free survival in Group A, defined as the time from the date of the first dose of study drug until the earliest date of disease progression, as determined by radiographic disease assessment provided by an IRC, or death from any cause.
- OS in Group A, defined as the time from the date of the first dose of study drug until death by any cause.
- Safety as measured by clinical assessments, including vital signs and physical examinations, 12-lead electrocardiograms (ECG), chemistry and hematology laboratory values, and adverse events (AEs).

[redacted]

Overall Study Design: This is a Phase 2, multicenter, international, open-label study designed to evaluate the safety and efficacy of INCB050465 20 mg once daily for 8 weeks followed by 20 mg once weekly, administered orally to subjects with relapsed or refractory DLBCL (see Section 1.4 for dose rationale). The study consists of 2 groups: Group A and Group B. In Group A, 100 subjects who were not previously treated with a Bruton's tyrosine kinase (BTK) inhibitor (eg, ibrutinib) will be enrolled. In Group B, up to 20 subjects who were previously treated with a BTK inhibitor (eg, ibrutinib) will be enrolled. Subjects will be evaluated for ORR by an independent review committee (IRC) and followed for DOR, PFS, and OS. Subjects may receive treatment until disease progression, death, unacceptable toxicity, or consent withdrawal.

An interim futility analysis is planned when the first 40 subjects in Group A have been treated and have been evaluated for response or have permanently discontinued study treatment because of disease progression, withdrawal of consent, or death. Group A of the study will be terminated for futility if ≤ 13 of the 40 subjects have responded (ie, CR/CMR or PR/PMR) 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. No formal futility analysis will be conducted for Group B.

Note: With Amendment 4, Protocol-required procedures have been reduced for ongoing subjects.

Study Population: Subjects with histologically confirmed relapsed or refractory DLBCL who have received 2 to 5 prior therapies.

Key Inclusion Criteria:

- Men and women, aged 18 years or older (except in South Korea, aged 19 or older).
- Relapsed or refractory DLBCL, which has been histologically documented, defined as having received at least 2 but no more than 5 prior treatment regimens (eg, an anti-CD20 antibody, an anti-CD20 antibody with or without chemotherapy, or chemotherapy alone) and ineligible for high-dose chemotherapy supported by autologous stem cell transplant.
- Must have ≥ 1 measurable (≥ 2 cm in longest dimension) or ≥ 1 measurable extranodal lesion (> 1 cm in longest dimension) lesion on computed tomography (CT) scan or magnetic resonance imaging (MRI).
- Subjects must be willing to undergo an incisional or excisional lymph node biopsy of accessible adenopathy or provide the most recent, available archived tumor biopsy.
- Eastern Cooperative Oncology Group performance status 0 to 2.

Key Exclusion Criteria:

- Primary mediastinal (thymic) large B-cell lymphoma.
- Known brain or central nervous system metastases or history of uncontrolled seizures.
- Allogeneic stem cell transplant within the last 6 months, or active graft versus host disease following allogeneic transplant, or autologous stem cell transplant within the last 3 months.
- Use or expected use during the study of any prohibited medications, including potent cytochrome P450 3A4 inhibitors or inducers within 14 days or 5 half-lives (whichever is longer) before the first dose of study drug.
- Prior treatment with the following:
  - Group A: Prior treatment with a selective phosphatidylinositol 3-kinase (PI3K) δ inhibitor (eg, idelalisib), a pan-PI3K inhibitor, or a BTK inhibitor (eg, ibrutinib).
  - Group B: Prior treatment with a selective PI3Kδ inhibitor (eg, idelalisib) or a pan-PI3K inhibitor.

INCB050465/Study Drug, 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 to subjects in a fasted state. Subjects may have dose reductions or interruptions based upon clinical and laboratory assessments.

Reference Therapy, Dosage, and Mode of Administration: Not applicable.

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: During screening and every 21 days from the date of first study drug administration (Day 1), a study visit will be conducted that includes a physical examination, clinical laboratory tests, and an assessment of AEs. [redacted]

During screening, subjects will have an objective assessment of disease status performed by fluorodeoxyglucose (FDG) positron emission tomography (PET) and diagnostic quality CT scan or MRI. Subjects will also have a bone marrow biopsy performed at screening unless the subject has FDG-avid disease or has undergone a recent bone marrow biopsy. Disease status will be subsequently assessed by PET-CT/MRI at Weeks 9, 18, 27, and every 18 weeks thereafter until disease progression. On-study bone marrow biopsies will be required only if needed to confirm a CR/CMR.

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, or death (whichever occurs first).

Subjects withdrawn from study treatment because of disease progression will be followed approximately every 12 weeks for subsequent anticancer therapies and survival.

Note: With Amendment 4, Protocol-required procedures have been reduced for ongoing subjects.

Estimated Duration of Participation: Subject participation through safety follow-up is expected to average approximately 11 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 9 months).
- A safety follow-up period lasting 30 to 35 days.

Subjects will be followed for approximately 12 months after the safety follow-up period.

Estimated Number of Subjects: The target enrollment for this study is 100 to 120 subjects.

Principal Coordinating Investigator: [redacted], MD, [redacted]

Statistical Methods: Data from Group A and Group B will be analyzed separately. Response data will be analyzed when all subjects have received at least 1 postbaseline disease assessment, or have progressed, withdrawn from the study, or died. There will not be any statistical comparison between the 2 groups.

Sample Size:

Group A: 100 subjects will be enrolled. If the true ORR is 0.50, then there is about 90% probability of observing the lower bound of the 95% confidence interval of ORR $\geq$ 35%.

Group B: Up to 20 subjects will be enrolled. There is 87% probability of observing $\geq$ 6 responders in 20 subjects[redacted].

Primary Analysis: Group A only: The ORR as determined by the IRC and its 95% exact binomial confidence intervals (CIs) will be calculated. The ORR as determined by the investigators and its 95% CI will be provided as a sensitivity analysis.

Secondary Analyses:

Group A: The Kaplan-Meier estimation of median DOR and PFS (per IRC) and OS will be presented with respective 95% CIs.

All safety data, including AEs, laboratory data, vital signs, and ECGs, will be summarized descriptively.

[redacted]

Level of Significance: There will not be any statistical comparison between the 2 groups. Within each group, 2-sided 95% CIs will be reported for all analyses when appropriate.

Interim Analysis: An interim futility analysis is planned for Group A. The analysis will be conducted when 40 subjects have been treated and evaluated for response or have permanently discontinued study treatment because of disease progression, withdrawal of consent, or death. Group A will be terminated for futility if $\leq$ 13 of the 40 subjects responded (ie, CR/CMR or PR/PMR) based on assessments provided by the IRC. The futility boundary is calculated using a spending function of HSD(-4). No formal futility analysis will be conducted for Group B.

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
5PS	5-point scale
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
BTK	Bruton's tyrosine kinase
CFR	Code of Federal Regulations
CL/F	oral dose clearance
CLL	chronic lymphocytic leukemia
CMR	complete metabolic response
CMV	cytomegalovirus
CR	complete response
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
eCRF	electronic case report form
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FL	follicular lymphoma
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus

Abbreviation	Definition
HCV	hepatitis C virus
HDC	high-dose chemotherapy
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent Data Monitoring Committee
IEC	independent ethics committee
IN	Investigator Notification
IPI	International Prognostic Index
irAE	immune-related adverse event
IRB	institutional review board
IRC	independent review committee
IV	intravenous
IWRS	interactive web response system
LDi	longest transverse diameter of lesion
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NHL	Non-Hodgkin Lymphoma
ORR	objective response rate
OS	overall survival
pAKT	phosphorylated protein kinase B
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PI3K	phosphatidylinositol 3-kinase
PJP	*Pneumocystis jirovecii* pneumonia
PK	pharmacokinetic
PMD	progressive metabolic disease

Abbreviation	Definition
PMR	partial metabolic response
PPD	cross-product of the longest transverse diameter and perpendicular diameter
PR	partial response
QD	once daily
RNA	ribonucleic acid
SAE	serious adverse event
SDi	shortest axis perpendicular to the longest transverse diameter
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
V/F	volume of distribution

1. INTRODUCTION

1.1. Diffuse Large B-Cell Lymphoma

Non-Hodgkin lymphoma (NHL) is the most common hematologic malignancy, with over 385,000 new cases diagnosed in 2012 (Torre et al 2015). Incidence rates of NHL tend to be higher in North America, Western Europe, Northern Europe, and Australia compared with the rest of the world; it has been estimated that over 80,000 new cases of NHL and approximately 20,000 deaths due to NHL occurred in the United States in 2015 (Siegel et al 2015). Between 1975 and 2011, the incidence of new cases of NHL in the United States has nearly doubled from 11 to 20 cases per 100,000 people, but the proportion of deaths has slowly decreased (National Cancer Institute [NCI] 2014).

Diffuse large B-cell lymphoma (DLBCL) is a subtype of NHL. Diffuse large B-cell lymphoma is an aggressive form of NHL and is the most common NHL subtype, accounting for approximately 30% of all cases. The incidence is higher in men than women and generally increases with age, with the median age at onset generally occurring within the sixth decade (Swerdlow et al 2008). Diffuse large B-cell lymphoma can develop as a transformation from a less aggressive form of lymphoma or as a first occurrence of lymphoma (called *de novo*). Prognosis varies across patients with DLBCL. Subtype, patient characteristics, disease burden, and prior response to therapy affect clinical outcome, but all subtypes are considered aggressive and fatal if left untreated (Martelli et al 2013). Despite significant progress in the management of patients with DLBCL, an unmet need still exists (Foon et al 2012).

1.2. Treatment for Relapsed/Refractory DLBCL

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

1.3. INCB050465

Refer to the INCB050465 IB for current information on INCB050465.

Phosphatidylinositol 3-kinases (PI3Ks) 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 Investigator's Brochure [IB; 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. [redacted] Inhibition of tumor growth and suppression of PI3K/protein kinase B signaling was observed at plasma concentrations that approximated the IC_{90} (77 nM) for pAKT inhibition of Pfeiffer cells in human whole blood (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, Forero-Torres et al 2016). As of 02 SEP 2016, data were available for 46 subjects who received INCB050465 administered orally at once daily QD) doses of 5 mg (n = 1), 10 mg (n = 3), 15 mg (n = 3), 20 mg (n = 15), 30 mg (n = 20), and 45 mg (n = 4). The median duration of treatment was 104 days. Adverse events (AEs) observed in ≥ 20% of subjects were nausea, diarrhea, vomiting, neutropenia, fatigue, hypokalemia, and fever. No ≥ Grade 3 treatment-related AEs were reported in ≥ 10% of subjects. Serious AEs (SAEs) that occurred in ≥ 2 subjects included colitis (n = 3), diarrhea (n = 3), and pyrexia, pneumonia, dehydration, exfoliative dermatitis, and hypotension (n = 2 each). Eleven of the 46 subjects (24%) discontinued study treatment due to the following AEs: colitis, diarrhea, pneumonitis, rash, exfoliative dermatitis, psoriasis, neutropenia, fatigue, pneumonia, and hypercalcemia. All but 1 of these events occurred after the 9-week disease assessment. No liver function test abnormalities > Grade 1 were reported while subjects were receiving study treatment. No dose-limiting toxicities were identified, and the maximum tolerated dose was not reached.

As of 02 SEP 2016, 20 objective responses as reported by investigators were observed at doses ≥ 10 mg QD in 41 evaluable subjects with DLBCL, follicular lymphoma (FL), Hodgkin lymphoma, marginal zone lymphoma, chronic lymphocytic leukemia (CLL), and mantle cell lymphoma. These results include 3 complete metabolic responses (CMRs) and 2 partial metabolic responses (PMRs) observed among the 14 evaluable subjects with DLBCL. Objective responses for these 5 subjects occurred by the time of the 9-week disease assessment. The duration of treatment for these 5 subjects ranged from approximately 13 to 45 weeks, with 1 subject remaining on study treatment at the time of the data cutoff. [redacted]

1.4. Study Rationale

Aberrant activation of PI3Kδ has been associated with increased malignant B-cell proliferation and survival. Another PI3Kδ inhibitor, idelalisib, received approval from the FDA for the treatment of patients with relapsed CLL, in combination with rituximab, and also received accelerated approval from the FDA for the treatment of patients with relapsed follicular B-cell non-Hodgkin lymphoma (FL) or relapsed small lymphocytic lymphoma. Idelalisib was also approved by the European Medicines Agency for patients with chronic CLL who have received at least 1 prior therapy or in certain first-line settings and for FL that is refractory to at least 2 lines of treatment. The approvals were based on objective response rate (ORR) and demonstrate that inhibition of PI3Kδ can be an effective strategy in the treatment of some B-cell malignancies.

INCB050465 is a potent and selective inhibitor of PI3Kδ in enzyme and B-cell proliferation assays. Based on emerging safety, efficacy, [redacted] data from the ongoing Study INCB 50465-101 (see Section 1.3), subjects with relapsed or refractory DLBCL who have received 2 to 5 prior regimens and who are ineligible for HDC/ASCT will receive INCB050465 administered orally at a dose of 20 mg QD for 8 weeks followed by 20 mg once weekly. This dose was chosen based on emerging efficacy and safety data from the ongoing Study INCB 50465-101 (see Section 1.3). [redacted]
Furthermore, 20 mg QD has demonstrated efficacy in DLBCL (2 CMRs in 2 subjects) and in other types of non-Hodgkin lymphomas (9 objective responses in 9 subjects with non-Hodgkin lymphoma). However, 24% (n = 11) of all subjects in study INCB 50465-101 discontinued study treatment due to an AE. All but 1 of these events occurred after the 9-week disease assessment. Among the subjects with an objective response (n = 20), 7 (35%) discontinued study treatment due to an AE. Consequently, after administration of 20 mg QD for 8 weeks, the dosing regimen will be reduced to 20 mg once weekly. This once-weekly regimen is proposed to maintain response while providing time off from pathway inhibition, which may reduce the frequency of AEs. [redacted] This once-weekly regimen is similar to

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

The primary objective of this study is to evaluate the efficacy of INCB050465 in this patient population. The ORR is an acceptable primary endpoint in this single-arm, Phase 2 study evaluating subjects who have received 2 to 5 prior lines of therapy and in which no comparator exists.

1.5. Potential Risks and Benefits of the Treatment Regimen

Nonclinical data supported an initial dose of 5 mg QD in the first-in-human study (INCB 50465-101) based on adequate exposure margins and the lack of findings in recovery animals after drug withdrawal (INCB050465 IB). Potential risks with administration of INCB050465 based on preclinical findings include lymphoid depletion (INCB050465 IB). This may result in infections, fever, or cytokine release resulting in fever, chills, hypotension, wheezing, and/or rash.

Pneumonitis and colitis have been reported in subjects treated with the PI3Kδ inhibitor idelalisib (Gopal et al 2014), and these events have been observed for another PI3Kδ, INCB040093 (INCB040093 IB). In March 2016, several studies evaluating idelalisib administered in combination with several lymphoma standard-of-care therapies (eg, anti–CD20-containing regimens) were terminated because of an increased risk of death and SAEs due to infections and respiratory disorders in subjects administered the idelalisib combinations. The relevance of these findings with respect to INCB050465 administered as a monotherapy is currently unknown. To reduce the risk of infection with *Pneumocystis jiroveci* pneumonia (PJP), all subjects taking INCB050465 must also take a prophylactic antibiotic (see Section 5.6.1).

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

2.1. Study Objectives

2.1.1. Primary Objective

- To assess the efficacy of INCB050465 in terms of ORR in subjects with relapsed or refractory DLBCL in Group A.

2.1.2. Secondary Objectives

- To assess the duration of response (DOR) in Group A.
- To assess progression-free survival (PFS) in Group A.
- To assess OS in Group A.
- To characterize the safety of INCB050465 in Group A and Group B.

2.2. Study Endpoints

2.2.1. Primary Endpoint

- Objective response rate in Group A, defined as the percentage of subjects with a CR/CMR or PR/PMR as defined by revised response criteria for lymphomas (Cheson et al 2014), as determined by an Independent Review Committee (IRC).

2.2.2. Secondary Endpoints

- Duration of response in Group A, defined as the time from first documented evidence of CR/CMR or PR/PMR 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.
- Progression-free survival in Group A, defined as the time from the date of the first dose of study drug until the earliest date of disease progression, as determined by radiographic disease assessment provided by an IRC, or death from any cause.
- OS in Group A, defined as the time from the date of the first dose of study drug until death by any cause.

- Safety as measured by clinical assessments, including vital signs and physical examinations, 12-lead electrocardiograms (ECG), chemistry and hematology laboratory values, and AEs.

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. Men and women, aged 18 years or older (except in South Korea, aged 19 or older).
2. Relapsed or refractory DLBCL, which has been histologically documented, defined as having received at least 2 but no more than 5 prior treatment regimens (eg, an anti-CD20 antibody, an anti-CD20 antibody with or without chemotherapy, or chemotherapy alone) and ineligible for HDC/ASCT.
3. Group B only: Must have received prior Bruton's tyrosine kinase (BTK) inhibitor therapy (eg, ibrutinib).
4. Subjects must be willing to undergo an incisional or excisional lymph node biopsy of accessible adenopathy or provide the most recent, available archived tumor biopsy.
5. Must have ≥ 1 measurable nodal lesion (≥ 2 cm in longest dimension) or ≥ 1 measurable extranodal lesion (> 1 cm in longest dimension) on computed tomography (CT) scan or magnetic resonance imaging (MRI).
6. ECOG performance status 0 to 2 (see Table 10).
7. Adequate hematologic, hepatic, and renal function (values must not be achieved with growth factors):
   a. Absolute neutrophil count (ANC) ≥ 1.0×10^9/L.
   b. Hemoglobin ≥ 8.0 g/dL.
   c. Platelet count ≥ 50×10^9/L.
   d. Total bilirubin ≤ 1.5 × upper limit of normal (ULN).

e. Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤ 3.0 × 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.

8. 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 at least 55 years of age).
   b. Woman of childbearing potential who has a negative serum pregnancy test at screening 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.
9. Ability to comprehend and willingness to sign an informed consent form (ICF).

3.2. Subject Exclusion Criteria

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

1. Primary mediastinal (thymic) large B-cell lymphoma.
2. Known brain or central nervous system metastases or history of uncontrolled seizures.
3. Allogeneic stem cell transplant within the last 6 months, or active graft versus host disease following allogeneic transplant, or autologous stem cell transplant within the last 3 months before the date of the first dose of study drug.
4. Use of immunosuppressive therapy within 28 days of the date of study drug 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 study drug administration.
5. Prior treatment with the following:
   a. Group A: Prior treatment with a selective PI3Kδ inhibitor (eg, idelalisib), a pan-PI3K inhibitor, or a BTK inhibitor (eg, ibrutinib).
   b. Group B: Prior treatment with a selective PI3Kδ inhibitor (eg, idelalisib) or a pan-PI3K inhibitor.

6. Receipt of anticancer medications or investigational drugs within the following intervals before the date of the first dose of study drug:
    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.
7. Prior treatment-related toxicities that have not resolved to ≤ Grade 1 before the date of study drug administration date except for stable chronic toxicities (≤ Grade 2) not expected to resolve (eg, stable Grade 2 peripheral neurotoxicity).
8. Concurrent anticancer therapy (eg, chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, hormonal therapy, investigational therapy, or tumor embolization).
9. Use or expected use during the study of any prohibited medications, including potent cytochrome P450 (CYP) 3A4 inhibitors or inducers (see Appendix B) within 14 days or 5 half-lives (whichever is longer) before the date of study drug administration.
10. Significant concurrent, uncontrolled medical condition including, but not limited to, renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, neurological, cerebral, or psychiatric disease.
11. 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.
12. History of stroke or intracranial hemorrhage within 6 months of the date of study drug administration.
13. Chronic or current active infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment, and exposure to a live vaccine within 30 days ofstudy drug administration.
14. 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 enrolled in the United States will be excluded.
15. Liver disease:
    a. Evidence of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection or risk of reactivation: HBV DNA and HCV RNA must be undetectable. Subjects cannot be positive for hepatitis B surface antigen (HBsAg) or anti–hepatitis B core antibody. Subjects who have positive anti-HBs as the only evidence of prior exposure may participate in the study provided that there is both 1) no known history of HBV infection, and 2) verified receipt of hepatitis B vaccine.
16. Clinically significant cardiac disease, including unstable angina, acute myocardial infarction, and or cardiac conduction issues within 6 months of the date of study drug administration.

17. Current New York Heart Association Class II to IV congestive heart failure or uncontrolled arrhythmia.
18. 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.
19. Unable to swallow 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.
20. Known hypersensitivity or severe reaction to INCB050465 or its excipients (INCB050465 IB).
21. Currently pregnant or breastfeeding.
22. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

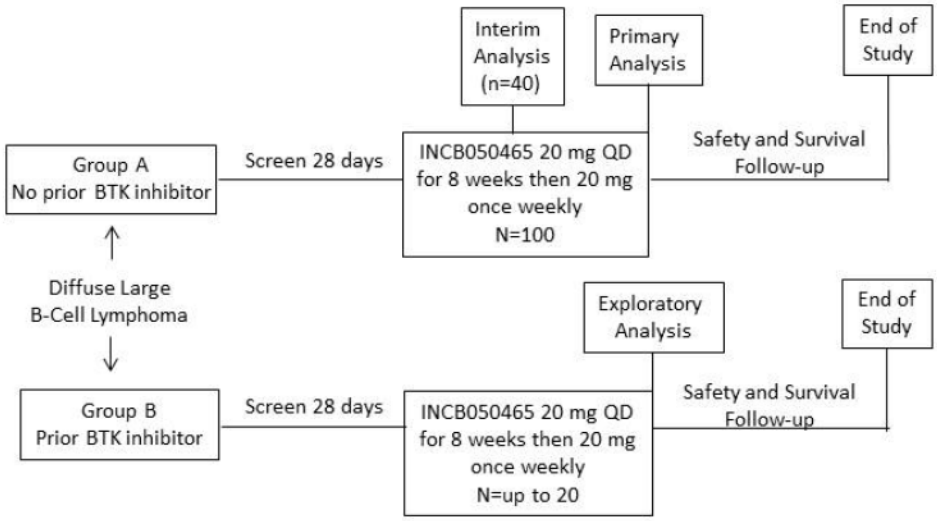
This is a Phase 2, multicenter, international, open-label study designed to evaluate the safety and efficacy of INCB050465 20 mg QD for 8 weeks followed by 20 mg once weekly. The study drug will be administered orally to subjects with relapsed or refractory DLBCL (see Figure 1). The study consists of 2 groups: Group A and Group B. In Group A, 100 subjects who were not previously treated with a BTK inhibitor (eg, ibrutinib) will be enrolled. In Group B, up to 20 subjects who were previously treated a BTK inhibitor (eg, ibrutinib) will be enrolled. Subjects will be evaluated for ORR by an independent review committee (IRC) and followed for DOR, PFS, and OS. Subjects may receive treatment until disease progression, death, unacceptable toxicity, or consent withdrawal. An interim futility analysis is planned when the first 40 subjects in Group A have been treated and have been evaluated for response or have permanently discontinued study treatment because of disease progression, withdrawal of consent, or death. Group A of the study will be terminated for futility if $\leq$ 13 of the 40 subjects have responded (ie, CR/CMR or PR/PMR) 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. No formal futility analysis will be conducted for Group B.

Subjects who have relapsed or refractory, histologically confirmed DLBCL will be screened for eligibility. Those who meet the eligibility criteria will be administered study drug (see Section 5.2). Subjects will be monitored for safety and efficacy periodically until disease progression, death, unacceptable toxicity, or withdrawal of informed consent. An independent Data Monitoring Committee (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. The study will be closed no later than 2 years after the first dose of INCB050465 is administered to the last patient enrolled, at which point an analysis of OS will be conducted.

Note: With Amendment 4, Protocol-required procedures have been reduced for ongoing subjects.

Figure 1: Study Design



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 and Sites

The study will enroll 100 to120 subjects across approximately 80 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 21-day

intervals. If the subject discontinues INCB050465, the treatment period will end, and the subject will enter the 30-day safety follow-up period after which the subject will enter the survival follow-up period (see Section 6.4). Study participation, excluding survival follow-up, is expected to average approximately 11 months per subject. Survival follow-up may average approximately 12 months.

4.5. Overall Study Duration

The study begins when the first subject signs the ICF. It is estimated that the study will take approximately 1.5 years to accrue 120 subjects and that the study will be closed no later than 2 years after the first dose of INCB050465 is administered to the last subject enrolled.

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.

Upon study closure, subjects who are still receiving study treatment will have the option to transition to Study INCB 50465-214, in which they may continue to receive study treatment.

5. TREATMENT

5.1. Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

Study sites will enter subject demographic and baseline data into the interactive web response system (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 drug assignment. The investigator or designee will select the assigned bottles of study drug from their stock that correspond to the number provided by the IWRS and dispense the study drug to the subject. All subsequent dispensing of study drug should follow this process. Refer to the IWRS manual for detailed information.

If a subject is mistakenly given a bottle of study drug 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 drug must be documented by the study site and reported to the IRB/IEC.

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

5.1.2. Randomization and Blinding

Not applicable.

5.2. INCB050465

5.2.1. Description and Administration

The dose and regimen of INCB050465 is 20 mg QD for 8 weeks followed by 20 mg once weekly. INCB050465 will be taken orally with water in a fasted state except on mornings of [redacted] clinic visits (see Table 11). Subjects should refrain from food consumption for 2 hours before and 1 hour after administration of INCB050465. The dosage strengths and form are 5 mg and 20 mg tablets (see Table 1).

Table 1: Description and Administration

Compound name	INCB050465
Dosage Strengths	5 mg and 20 mg
Form	Tablet
Active compound	INCB050465
Route of administration	Oral
Dose and Regimen	20 mg QD for 8 weeks followed by 20 mg once weekly
Instructions	INCB050465 will be taken orally with water in a fasted state except on mornings of [redacted] clinic visits (see Table 11). Subjects should refrain from food consumption for 2 hours before and 1 hour after administration of INCB050465.

5.2.2. Supply, Packaging, and Labeling

INCB050465 will be provided as 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.

Pneumocystis jirovecii pneumonia prophylaxis is required as coadministration with INCB050465; the prophylactic agents will be provided by Incyte. Incyte will determine the most appropriate manner in which to supply a prophylactic agent per country based on regulatory considerations. Further details are available in the study pharmacy manual.

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 study drug as follows:

- To store study drug at room temperature.
- To remove from the study drug 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 drug 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 INCB040465 will be calculated by the sponsor based on the drug accountability documented by the site staff and monitored by the sponsor/designee (tablet counts). Subjects will be instructed to bring all study drugs with them to the study visits for site personnel to conduct tablet counts to assess study drug accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

5.4. 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.

Because subjects may enter the study with extensive pretreatment and/or severe bone marrow infiltration by the primary disease, guidelines for dose interruption for hematologic AEs (see Table 2) are provided. The starting dose and dose reduction levels of INCB050465 are provided (see Table 3). 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 drug and the subject's underlying condition. Adverse events that have a clear alternative explanation or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose-reduction guidelines.

Table 2: Guidelines for Interruption and Restarting Study Drug

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 ANC with an oral temperature of at least 38.5°C OR with ≥ Grade 3 infection. • Platelet count is Grade 4 (< 25 × 10^9/L).	**Step 1:** Interrupt INCB050465 up to 14 days until the toxicity has resolved ≤ Grade 1. (For Grade 4 ANC, monitor ANC at least weekly.) **Step 2:** Restart INCB050465 at same dose. If assessed as related to INCB050465, restart at next lower dose. Monitor as clinically indicated.
Other toxicities	
• Diarrhea/colitis (Grade 1)	**Step 1:** Treat with antimotility agents (eg, 4 mg loperamide followed by 2 mg every 4 hours or after every unformed stool) and initiate supportive care (see Section 5.4.2). If not improved after 48 hours, treat per guidance for Grade ≥ 2.
• Diarrhea/colitis (Grade ≥ 2)	**Step1:** Interrupt INCB050465. Perform work-up for infection (including CMV, *C. difficile*, etc). Initiate or continue supportive care (see Section 5.4.2). Consider colonoscopy with biopsy for Grade ≥ 3. **Step 2:** If infection is ruled out, start oral steroids, or consider IV steroids if subject is being given IV fluids. If no improvement with oral steroids, switch to IV steroids. When diarrhea resolves to Grade ≤ 1, continue supportive care and taper steroids over 4 weeks. When taper is complete and diarrhea is Grade ≤ 1, restart INCB050465 at next lower dose with approval of the medical monitor. If Grade ≥ 2 diarrhea reoccurs, permanently discontinue INCB050465.
• Pneumonitis (Grade 1)	**Step 1:** Interrupt INCB050465 until the toxicity has resolved. **Step 2:** Restart INCB050465 at next lower dose. Monitor as clinically indicated.
• Pneumonitis (Grade ≥ 2)	Permanently discontinue INCB050465.

Table 2: Guidelines for Interruption and Restarting Study Drug (Continued)

ADVERSE EVENT	ACTION TAKEN
• 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 study treatment 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 study drug administration and follow-up per Protocol. Exceptions require approval of sponsor.
• Any other Grade 4 toxicity.	Discontinue study drug administration and follow-up per Protocol. Exceptions require approval of sponsor.

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

Table 3: Dose Levels for INCB050465

Timepoint	Dose
Starting dose	20 mg once daily for 8 weeks
Week 9, Day 1	20 mg once weekly
First dose reduction	10 mg once weekly
Second dose reduction	5 mg once weekly

Note that the first dose reduction is applicable for subject receiving either 20 mg QD or 20 mg once weekly.

5.4.2. Supportive Care Guidelines for Diarrhea/Colitis

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

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

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

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

5.4.3. Definition for Immune-Related Adverse Events

Adverse events of a potential immunologic etiology, or immune-related AEs (irAEs), may be defined as an AE consistent with an immune phenomenon associated with study drug exposure after all other etiologies have been eliminated. Immune-related AEs may be expected based on previous experience with INCB050465 and other drugs (eg, idelalisib) that inhibit PI3Kδ. 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 drug 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 2 and Section 5.4.2. 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 phase will be considered complete, and the follow-up phases will begin.

5.5.1. Criteria for Study Treatment Discontinuation

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

- The subject has experienced an unacceptable toxicity defined as follows:
  - Occurrence of an AE that is related to treatment with the study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest.
  - 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 INCB050465.
- 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: Informed consent withdrawn means that the subject can no longer receive study treatment **and** can no longer be followed.
- 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 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. (Note: Not applicable in Canada.)
- If a subject is noncompliant with study procedures or study drug 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 end-of-treatment (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 drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

If a subject actively withdraws from study treatment, then the subject will continue in the safety and survival follow-up periods of the study. The study monitor or sponsor must be notified if a subject actively withdraws from study treatment or withdraws the informed consent. If a subject withdraws informed consent, then the subject will have completed the study, and no additional data collection should occur.

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 drug 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.

5.6.2. Supportive Care Measures

Supportive care should be administered to subjects as per the institutional policy at the site for the standard therapy that the subject will receive. Additional information may be available in the appropriate package inserts. This includes the use of prophylactic growth factors, which should be based on American Society of Clinical Oncology guidelines for the use of white blood cell growth factors (Smith et al 2006) and the investigator's clinical judgment.

5.6.3. Restricted Medications

- Use of systemic corticosteroid doses ≤ 10 mg/day prednisone (or equivalent) is permitted but discouraged from the screening visit through the EOT visit.
- Use of weak or moderate inducers or inhibitors of CYP3A4 (Appendix B) is discouraged, and investigators should seek other options where possible.
- 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).

5.6.4. Prohibited Medications and Therapies

- Use of potent inducers and inhibitors of CYP3A4 are prohibited (Appendix B). Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole.
- Use of any anticancer medications other than the study medication as described (see Section 3.2) through the 30-day follow-up is prohibited.
- Use of systemic corticosteroid doses > 10 mg/day prednisone (or equivalent) is not permitted from the screening visit through the EOT visit.
- Radiation therapy.

6. STUDY ASSESSMENTS

See the schedule of assessments (Table 4) and schedule of laboratory assessments (Table 5) 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. 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.

Note: Upon implementation of Protocol Amendment 4, only study assessments indicated in Table 6 and Table 7 will be performed.

Table 4: Schedule of Assessments

Note: Upon implementation of Protocol Amendment 4, only the schedules of assessments in Table 6 and Table 7 should be followed.

Procedure	Section	Screening	Treatment				EOT	Safety Follow-Up	Disease Follow-Up	Survival Follow-Up
		Day -28 to -1	Day 1	Day 15 (± 3 Days)	Every 3 Weeks (± 3 Days)	Every 12 Weeks (± 3 Days)		EOT + 30-35 Days		Every 12 Weeks (± 1 Week)
Informed consent	7.1	X								
Contact IWRS	7.2	X	X		X		X			
Inclusion & exclusion criteria	3.1 3.2	X	X							
Demography and medical history	7.3.1	X								
Prior/concomitant medications	7.3.1.1	X	X	X	X		X	X		
Comprehensive physical exam	7.4.2	X[a]					X			
Disease-specific physical exam	7.4.2.1		X	X	X			X		
Vital signs	7.4.3	X	X	X	X		X	X		
12-lead ECG	7.4.4	X	X	X		X	X	X		
ECOG status	7.5.6	X	X		X		X	X		
AE assessment	7.4.1	X	X	X	X		X	X		
FDG-PET/CT scan	7.5.1 7.5.2	X	Every 9 weeks (± 1 week) through Week 27, then every 18 weeks (± 1 week) thereafter.[b]							
Bone marrow exam	7.5.3	X[c]								
Study drug dispensing	5.1		X		X[d]					
Study drug accountability	5.3		X		X		X			
INCB050465 administration	5.2.1		X	X	X					
Disease follow-up	6.4.2								X[e]	
Survival follow-up	6.4.3									X[f]

FDG = fluorodeoxyglucose; PET = positron emission tomography.

[a] Height required at screening only.

[b] If the PET-CT is of diagnostic quality, then a separate CT does not need to be performed. 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.

[c] Required at baseline except for reasons provided in Section 7.5.3. Also required if needed to confirm CR/CMR.

[d] Study drug will be dispensed at Weeks 1, 4, 7, and 10, and every 12 weeks thereafter.

[e] Only for subjects who discontinue study treatment for reasons other than disease progression.

[f] May be conducted by phone or email.

Table 5: Schedule of Laboratory Assessments

Note: Upon implementation of Protocol Amendment 4, only the schedules of assessments in Table 6 and Table 7 should be followed.

Laboratory Tests	Section	Screening	Treatment				EOT	Safety Follow-Up
		Day -28 to -1	Day 1	Day 15 (± 3 Days)	Every 3 Weeks (± 3 Days)	Other		EOT + 30-35 Days
Serum chemistries	7.4.5.1	X	X[a]	X	X		X	X
Hematology	7.4.5.1	X	X[a]	X	X		X	X
Serology	7.4.5.3	X				X[b]		
Serum pregnancy	7.4.5.2	X[c]					X	
Urine pregnancy	7.4.5.2				X[d]			
HIV testing	7.4.5.4	X[e]						
[redacted]								

[a] Day 1 tests may be omitted if the screening tests occurred in the preceding 7 days. If needed, Day 1 blood draws should be performed before dose administration.
[b] Samples for CMV DNA analysis only will be collected every 3 weeks for 10 weeks (Day 1 of Weeks 4, 7, and 10) and then every 12 weeks thereafter.
[c] Only for female subjects of childbearing potential; negative pregnancy test must be obtained within 14 days before administration of study drug.
[d] Only for females of childbearing potential.
[e] Optional for subjects enrolled in the United States.

[redacted]

Table 6: Schedule of Assessments for Ongoing Subjects in All Cohorts Upon Implementation of Protocol Amendment 4

Procedure	Section	At Least Every 12 Weeks in Clinic[a]	EOT	Follow-Up	Notes
				EOT + 30-35 Days	
Prior/concomitant medications	7.3.1.1	X	X	X	Review to ensure no prohibited medications are being used. Provide data to sponsor in regard to SAEs only.
Study drug dispensing	5.1	X			
Study drug accountability	5.3	X	X		
Distribute reminders	7.8.2	X	X		
Laboratory tests	Table 7	X	X	X	Performed at each site as per standard of care and monitored per investigator discretion.
AEs/SAEs	7.4.1	X	X	X	AEs that lead to the discontinuation of study treatment and all SAEs must be recorded in the CRFs, regardless of the causal relationship.
FDG-PET/CT scan	7.5.1 7.5.2				Performed per standard-of-care guidelines.

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

Table 7: Schedule of Laboratory Assessments for Ongoing Subjects in All Cohorts Upon Implementation of Protocol Amendment 4

Local Laboratory Tests	Section	At Least Every 12 Weeks in Clinic	EOT	Follow-Up	Details
				EOT + 30-35 Days	
Serum chemistries	N/A	X	X	X	Performed at each site as per standard of care and monitored per investigator discretion.
Hematology	N/A	X	X	X	Performed at each site as per standard of care and monitored per investigator discretion.

Table 8: Laboratory Tests: Required Analytes (Not Applicable After Implementation of Protocol Amendment 4)

Serum Chemistries	Hematology	Serology	Other
Albumin	Hemoglobin	HBsAg	**Pregnancy Test**
Alkaline Phosphatase	Hematocrit	Anti-HBsAg	Female subjects of childbearing potential require serum pregnancy and urine pregnancy tests (see Table 5).
ALT	Platelet count (absolute)	Anti-HB core IgG	
AST	Red blood cell count	HCV antibody	
Bicarbonate	White blood cell count	HCV-RNA	
Blood urea nitrogen	Differential cell count:	HBV-DNA	
C-reactive protein	Basophils %	CMV DNA	
Calcium	Eosinophils %	HIV antibody (immunoassay)[b]	
Chloride	Lymphocytes (absolute)		
Creatinine	Monocytes		
Glucose	Neutrophils (absolute)		
Lactate dehydrogenase			
Phosphate			
Potassium			
Sodium			
Total bilirubin			
Direct bilirubin[a]			
Indirect bilirubin[a]			
Total serum protein			
Total cholesterol			

Note: Additional laboratory tests may be required, as agreed by investigator and sponsor, based on emerging safety data.
[a] Only required if total bilirubin is > ULN.
[b] Optional for subjects enrolled in the United States.

6.1. Screening

Screening is the interval between signing the ICF and the date that the study treatment is first administered (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, serology, and serum pregnancy will be used to determine eligibility.

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 day that the subject receives the first dose of study drug (Day 1). This day must be no more than 28 days after the subject has signed the ICF. Dates for subsequent study visits will be determined based on this day and should occur within the visit windows outlined in the schedule of assessments (see Table 4) 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 effort should be made to have the subject return for the follow-up visit and report any AEs that may occur during this phase.

If a subject is scheduled to begin a new anticancer therapy before the end of the safety follow-up period, 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 per the schedule of assessments (see Table 4). 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.
- 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 study will continue up to 2 years after the first dose of study treatment is administered to the last subject enrolled, at which point the study will be closed.

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

Subjects ongoing after implementation of Protocol Amendment 4 will only have assessments performed as indicated in Table 6 and Table 7 and at a frequency determined by the investigator as guided by the standard of care. **Unless noted below, procedures listed in this section are not required to be performed or collected in the CRF after implementation of Amendment 4.**

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 study entry to obtain the treatment assignment, throughout the study as indicated to update the study drug supply (see Table 4), and at the EOT visit.

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 DLBCL, histology, current staging, sites of disease, prior surgery, radiation, and other details related to the disease under study will be collected.

7.3.1.1. 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.

Upon implementation of Amendment 4, use of concomitant medications should be monitored to verify that subjects are not taking any concomitant medication prohibited per Protocol (Section 5.6.4). A concomitant medications is required to be entered in the SAE form if considered associated with an SAE or the eCRF if the concomitant medication led to study drug discontinuation.

7.4. Safety Assessments

Upon implementation of Amendment 4, only safety assessments (including laboratory analytes) that are consistent with standard of care and monitoring should be performed per the investigator's discretion. Subjects must be taken off study treatment if, in the opinion of the investigator, an unacceptable toxicity develops.

7.4.1. Adverse Events

Adverse events will be monitored from the time the subject signs 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. 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.

Upon implementation of Amendment 4, AEs that lead to the discontinuation of study treatment and all SAEs must be recorded in the CRFs, regardless of the assumption of a causal relationship with the study drug.

7.4.2. 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; and 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).

7.4.2.1. 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.

7.4.3. Vital Signs

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

7.4.4. Twelve-lead 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 done 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 INCB050465 on Day 15. 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 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.

7.4.5. Laboratory Assessments

Blood draws for laboratory assessments will occur at study visits indicated (see Table 5). Blood draws will be completed before the subject receives the daily dose of INCB050465. Specific laboratory assessments are provided (see Table 8).

All laboratory assessments will be performed at a central laboratory. If a local laboratory assessment is deemed necessary by the investigator and results in a change in patient management (eg, dose modification) or an SAE, then the assessment data and reference ranges must be recorded in the subject's eCRF.

Upon implementation of Amendment 4, laboratory assessments (Table 7) only need to be performed in accordance with standard of care at each investigational site and monitored as per the investigator’s discretion. Laboratory results do not need to be reported in the CRF, but all laboratory results corresponding with an SAE must be reported on the SAE form.

7.4.5.1. Chemistry and Hematology

All chemistry and hematology assessments (see Table 5 and Table 8) will be performed from blood samples collected using institutional best practices.

7.4.5.2. Pregnancy Testing

A serum pregnancy test will be performed at screening and EOT. Urine pregnancy test will be performed per Table 5; positive results must be confirmed with a serum pregnancy test. Pregnancy testing will only be required for women of childbearing potential.

7.4.5.3. Serology

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

7.4.5.4. 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.

7.5. Efficacy Assessments

Subjects will have an objective assessment of disease status using PET and diagnostic quality CT scan or MRI.

7.5.1. FDG-PET or Combined PET-CT

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

Scheduled assessments should always be calculated from the first dose of study treatment. Imaging should not be delayed for delays in treatment.

Note: Subjects who discontinue study treatment for any reason other than disease progression or withdrawal of consent will be followed according to the disease assessment schedule until either disease progression, the start of a new anticancer therapy, or death, whichever occurs first.

Upon implementation of Amendment 4, FDG-PET or combined PET-CT assessments are only required to be performed as per standard of care guidelines and monitored. Subjects must be taken off study if, in the opinion of the investigator, the disease has progressed and the subject is no longer having clinical benefit from the study treatment.

7.5.2. Computed Tomography Scan or Magnetic Resonance Imaging

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

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. Scheduled assessments should always be calculated from the first dose of study treatment. Imaging should not be delayed for interruption of study treatment.

Upon implementation of Amendment 4, CT or MRI assessments are only required to be performed as per standard of care guidelines and monitored. Subjects must be taken off study if, in the opinion of the investigator, the disease has progressed and the subject is no longer having clinical benefit from the study treatment.

7.5.3. 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 of the first dose of study drug.
- Subject had a bone marrow examination performed after the last treatment for NHL and the results showed lymphoma involvement of the bone marrow.
- Baseline PET scan shows that the subject does have FDG-avid disease in the bone marrow (PET + bone marrow).

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

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.

7.5.4. Independent Review Committee

All imaging (PET and 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 PET CT–based response criteria of the Lugano Classification (Cheson et al 2014) by independent reviewers as described in the Imaging Charter.

7.5.5. Response Criteria – The Lugano Classification

Sites will use the PET-CT–based response criteria of the Lugano Classification (Cheson et al 2014) to assess response to treatment locally. Details regarding response assessment per the Lugano Classification are provided (see Table 9). Positron emission tomography is required and therefore the criteria for PET-based response should be applied in most circumstances. Computed tomography/MRI–based response criteria are provided for those subjects with PET scans that cannot be interpreted or who do not have FDG-avid disease. Response per the PET-CT and CT/MRI criteria will be collected in the eCRF.

Table 9: Lugano Classification for Response Assessment

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

Table 9: Lugano Classification for Response Assessment (Continued)

Site	PET-Based Response	CT-Based Response
	Progressive metabolic disease	**Progressive disease (requires at least 1 of the following)**
Individual target nodes/nodal lesions	Individual target nodes/nodal lesions: • Score 4 or 5[a] with an increase in intensity of uptake from baseline and/or • New FDG-avid foci consistent with lymphoma at interim or EOT assessment Extranodal lesions: • New FDG-avid foci consistent with lymphoma at interim or EOT assessment New lesions: • New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered Bone marrow: • New or recurrent FDG-avid foci	PPD progression: • An individual node/lesion must be abnormal with all of the following: – LDi > 1.5 cm – Increase by ≥ 50% from PPD nadir – Increase in LDi or SDi from nadir: o 0.5 cm for lesions ≤ 2 cm o 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

5PS = 5-point scale; LDi = longest transverse diameter of lesion; 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.

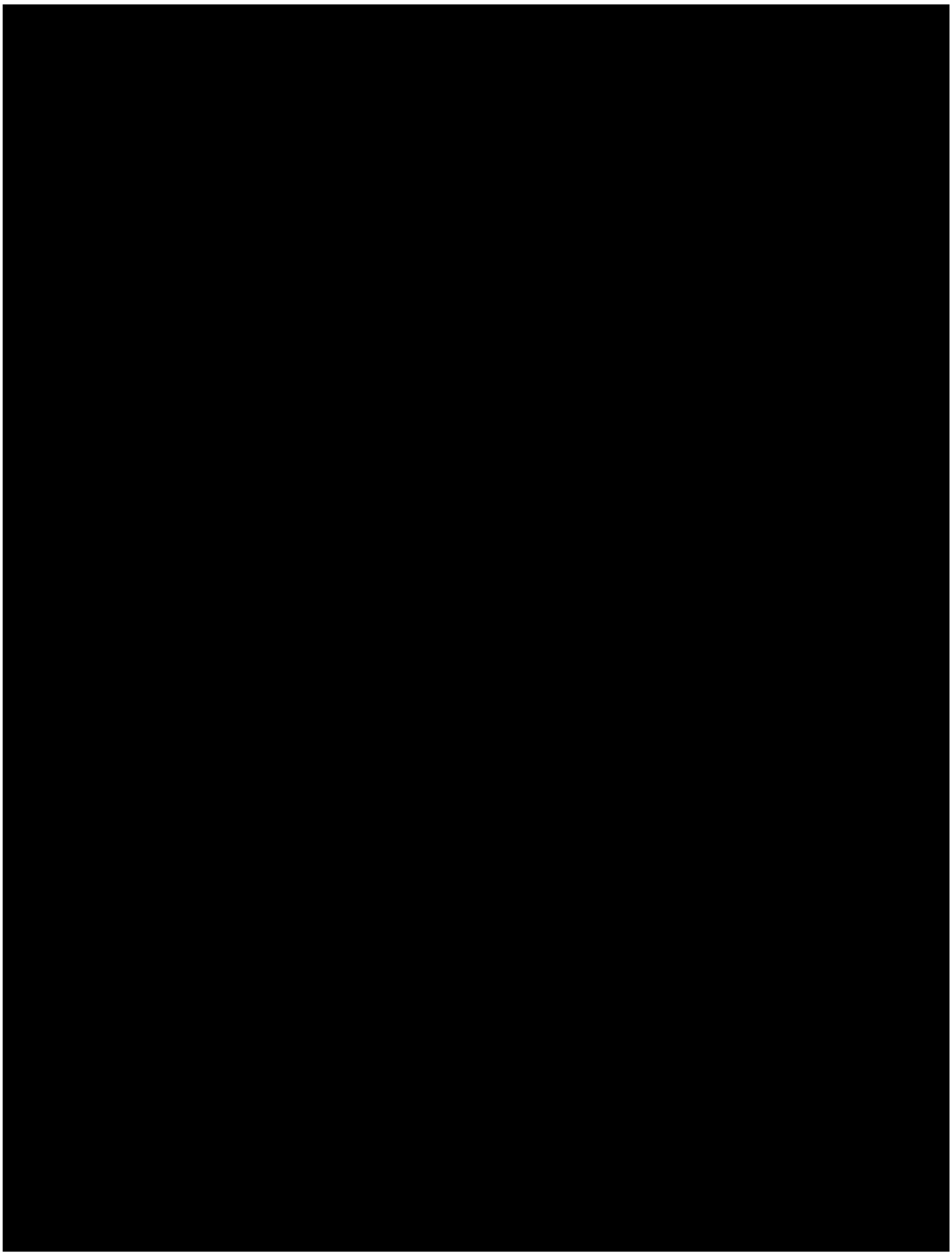
[a] PET 5-point scale: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

7.5.6. ECOG Performance Status

Eastern Cooperative Oncology Group performance status (Oken et al 1982; Table 10) will be assessed (see Table 4). Performance status must be assessed by a medically-qualified individual and recorded in the eCRF.

Table 10: 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



[redacted]

7.8. Other Study Procedures

7.8.1. Administration of Study Drug

See Section 5.2.1 for complete details regarding study drug administration.

After implementation of Amendment 4, subjects will be dispensed the appropriate amount of medication to self-administer study drug as per protocol until their next scheduled visit (scheduled no more than 12 weeks later). Subjects will continue to self-administer study medication, and compliance will continue to be assessed.

7.8.2. 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 7.6). The reminder cards for the Day 15 visit will have an area on which the date and time of the last dose taken (from the previous day) and the time of their last meal before the visit should be recorded.

After implementation of Amendment 4, subjects will receive reminder cards that will include the date and time of the next visit and instructions for study drug administration.

7.8.3. Data Collection for Survival Follow-Up

For subjects having entered the survival follow-up period of the study, the site will collect data as described (see Section 6.4.3).

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions

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

8.1.2. Reporting

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

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

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

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

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

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

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

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

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

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

Upon implementation of Amendment 4, AEs leading to treatment discontinuation and all SAEs regardless of causal relationship must be reported on the AE form in the eCRF.

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 (severe) AE does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1. A dose modification for the laboratory abnormality may be required (see Section 5.4) and should not contribute to the designation of a laboratory test abnormality as an SAE.

8.3. Serious Adverse Events

8.3.1. Definitions

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

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

8.3.2. Reporting

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

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

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

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

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

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

Upon implementation of Amendment 4, all SAEs regardless of causal relationship will be reported as described above.

8.4. Adverse Events of Special Interest

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities. These events (regardless of seriousness) will be reported per the SAE reporting timelines (see Section 8.3.2).

- 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

8.5. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed 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 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.

8.6. 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 (INCB050465 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.

8.7. Independent Data Monitoring Committee

An IDMC will be formed and 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.

8.8. Product Complaints

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

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

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

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

9. STATISTICS

9.1. Study Populations

The 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 per protocol (PP) population includes all subjects in the full analysis set who were sufficiently compliant with the Protocol. The following procedures will be performed to identify those subjects who are to be excluded from the PP population before the database freeze:

- Clinical review of Protocol deviations/violations
- Clinical review of concomitant medications as defined in Section 5.6 of the Protocol
- Clinical review of the dose administration and drug accountability listing

The determination of subjects being considered for exclusion from the PP population by the clinical team will be prepared and signed before database freeze.

The safety population includes all subjects enrolled in the study who received at least 1 dose of INCB050465. This population will be used for all safety analyses.

[redacted]

9.2. Selection of Sample Size

The study will enroll 100 subjects into Group A. If the true ORR is 0.50, then there is approximately 90% probability of observing the lower bound of the 95% CI of the ORR $\geq$ 35%.

[redacted]

9.3. Level of Significance

There will not be any statistical comparison between the 2 groups. Within each group, 2-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

Objective response rate is defined as the percentage of subjects with a CR/CMR or PR/PMR as determined by revised response criteria for DLBCL (Cheson et al 2014).

The ORR as determined by the IRC and its 95% exact binomial CIs will be calculated for subjects in Group A. This is considered the primary efficacy analysis of the study.

The ORR as reported by the investigator and its 95% exact binomial CIs will also be calculated for subjects in Group A.

Response data will be analyzed when all subjects have received at least 1 postbaseline disease assessment, or have progressed, withdrawn from the study, or died.

9.4.1.2. Secondary Efficacy Analyses

Duration of response is defined as the time from first documented evidence of CR/CMR or PR/PMR until disease progression or death due to any cause among subjects who achieve an overall response (ie, CR/CMR or PR/PMR) as determined by revised response criteria for lymphomas (Cheson et al 2014). 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/PMD before the discontinuation or the start of the new anticancer treatment.

Progression-free survival is defined as the time from the date of first dose of the study drug to the first documented disease progression as determined by revised response criteria for lymphomas (Cheson et al 2014), 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/PMD 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.

The Kaplan-Meier estimation of median DOR and PFS as determined by the IRC and its 95% CIs will be provided for subjects in Group A.

The Kaplan-Meier estimation of median DOR and PFS as reported by the investigator and its 95% CIs will also be provided for subjects in Group A.

Overall survival is defined as the time from the date of 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 subjects is last known to be alive. The Kaplan-Meier estimation of median OS and its 95% CIs will be provided for subjects in Group A.

[redacted]

9.4.2. Safety Analyses

9.4.2.1. Adverse Events

A treatment-emergent adverse event (TEAE) is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study drug administration. 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 using Grades 1 through 4.

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

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

Number (%) of subjects reporting any TEAEs, any SAEs, any Grade 3 or 4 TEAEs, any treatment-related TEAEs, any treatment-related SAEs, any treatment-related Grade 3 or 4 TEAEs, any fatal TEAE, and any TEAEs leading to treatment interruption/dose reduction/discontinuation will be tabulated by system organ class and preferred term.

9.4.2.2. Clinical Laboratory Tests

Laboratory data will be classified into Grades 1 through 4 using CTCAE v4.03 when applicable. The following summaries will be produced for the laboratory data:

- Descriptive statistics of the value and change from baseline at each assessment time will be provided.
- For laboratory parameters that have CTC grading, shift tables will be provided showing change in CTC grade from baseline to the worst grade postbaseline.
- For laboratory parameters where CTC grades are not defined, shift tables from baseline to the worst postbaseline value will be produced using the low/normal/high classifications based on laboratory reference ranges.

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

9.4.2.3. Vital Signs

Descriptive statistics and mean change from baseline will be summarized for vital signs (weight, blood pressure, pulse, respiratory rate, and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities (see Table 12), and subjects

exhibiting clinically notable vital sign abnormalities will be listed. A value will also be considered an "alert" value if it is outside the established range and shows a > 25% change from baseline. The abnormal values for subjects exhibiting alert vital sign abnormalities will be listed

Table 12: 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	> 38°C	< 35°C
Respiratory rate	> 24/min	< 12/min

9.4.2.4. Electrocardiograms

Descriptive statistics and mean change from baseline will be summarized for the ECG parameter at each assessment time. Average of all values before the first dose of study drug will be used as the baseline value. Criteria for clinically notable ECG abnormalities are defined (see Table 13). The abnormal values for subjects exhibiting clinically notable ECG abnormalities will be listed. Alert ECG values are defined as an absolute value outside the defined range and absolute percentage change > 25% (30% for QRS) interval. The abnormal values for subjects exhibiting alert ECG abnormalities will be listed. Outliers of QT, QTcB, and QTcF, defined as absolute values > 450 milliseconds or change from baseline > 30 milliseconds, will also be listed.

Table 13: Criteria for Clinically Notable Electrocardiogram Abnormalities

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

QTcF = Fridericia correction.

9.5. Analyses for the Independent 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 in Group A (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 40 subjects in Group A have been treated and have been evaluated for response or have permanently discontinued study treatment because of disease progression, withdrawal of consent, or death. Group A of the study will be terminated for futility if ≤ 13 of the 40 subjects have responded (ie, CR/CMR or PR/PMR) based on assessments provided by the IRC; otherwise the study will continue. The futility boundary is determined using a spending function of HSD(-4). 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 privacy laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that sensitive information is handled in accordance with local requirements (eg, HIPAA). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

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

records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

10.5. Financial Disclosure

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

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

10.6. Publication Policy

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

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

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

Such methods include:

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

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

Source: CTFG 2014.

APPENDIX B. CYTOCHROME P450 AND P-GLYCOPROTEIN INHIBITORS AND CYTOCHROME P450 INDUCERS

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

In Vivo CYP3A Inhibitors

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

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

[1] To allow better comparability, DDI studies with the probe substrate midazolam were selected first.
When no study with midazolam was available, the AUCratio of another probe or sensitive substrate is presented.
[2] 240 mL GFJ double-strength administered TID for 3 days

In Vivo CYP3A Inducers

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

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

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

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

APPENDIX C. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	30 AUG 2016
Amendment (Version) 2:	09 NOV 2016
Amendment (Version) 3:	23 FEB 2017
Amendment (Version) 3-CAN:	12 DEC 2017
Amendment (Version) 4:	05 NOV 2019

Amendment 4 (05 NOV 2019)

Overall Rationale for the Amendment: The primary purpose of this amendment is to reduce Protocol-required procedures for subjects who remain on study treatment. Subjects should be monitored per the standard of care for their condition as determined by the investigator.

1. **Synopsis; Section 4.1, Overall Study Design; Section 6, Study Assessments (including new Table 6 and Table 7); Section 7, Conduct of Study Assessments and Procedures; Section 7.3.1.1, Prior and Concomitant Medications and Procedures; Section 7.4, Safety Assessments; Section 7.4.1, Adverse Events; Section 7.4.5, Laboratory Assessments; Section 7.5.1, FDG-PET or Combined PET-CT; Section 7.5.2, Computed Tomography Scan or Magnetic Resonance Imaging; Section 7.8.1, Administration of Study Drug; Section 7.8.2, Distribution of Subject Reminder Cards**

   Description of change: The sections were updated to include information on reduced Protocol-required assessments for subjects who are ongoing in the study.

   Rationale for change: To reduce the burden of unnecessary procedures for the ongoing remaining subjects and the sites.

2. **Synopsis**

   Description of change: The coordinating PI for the study was added ([redacted] MD, [redacted]).

   Rationale for change: To identify the study's coordinating PI.

3. **Section 1.3, INCB050465**

   Description of change: Added a statement to refer to the IB for current information on INCB050465.

   Rationale for change: The IB has been updated and is a better source for this information.

4. **Section 4.6, Study Termination**

   Description of change: Statement added indicating that upon study closure, subjects who are still receiving study treatment will have the option to transition to Study INCB 50465-214, in which they may continue to receive study treatment.

Rationale for change: To include a crossover option for subjects to continue treatment after study closure.

5. **Section 7.4.1, Adverse Events; Section 8.1.2, Reporting; Section 8.3.2, Reporting**

   Description of change: Serious adverse events (SAEs) and adverse events leading to discontinuation from study treatment will be collected by the sponsor.

   Rationale for change: Collection of all SAEs and AEs leading to discontinuation is sufficient for safety monitoring of the study treatment at this point in the study.

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.

Amendment 3-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 3 (23 FEB 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 50465-202 Amendment 2 (09 NOV 2016) summarized below. A redline version of the amendment depicting updated and previous text is also provided.

1. **Synopsis; Section 1.4, Study Rationale; Section 3.1, Subject Inclusion Criteria**

   Description of change: Change the minimum number of allowed prior systemic therapies from 1 to 2 and provide types of prior therapies.

   Rationale for change: Requested by European Regulatory Agency.

2. **Synopsis; Section 1.5, Potential Risks and Benefits of the Treatment Regimen; Section 5.2.2, Supply, Packaging, and Labeling; Section 5.6.1, *Pneumocystis Jirovecii* Prophylaxis**

   Description of change: Require that all subjects receive prophylaxis against *Pneumocystis jirovecii* pneumonia.

   Rationale for change: Requested by European Regulatory Agency.

3. **Section 1.4, Study Rationale**

   Description of change: The dose rationale was moved from Section 1.5, Potential Risks and Benefits of the Treatment Regimen, to Section 1.4, Study Rationale.

   Rationale for change: To relocate the dose rationale to the appropriate section of the Protocol.

4. **Section 1.5, Potential Risks and Benefits of the Treatment Regimen**

   Description of change: A paragraph was added stating that subjects should avoid sun/ultraviolet light.

   Rationale for change: Requested by European Regulatory Agency.

5. **Section 3.1, Subject Inclusion Criteria; Section 6, Study Assessments (Table 5)**

   Description of change: The amount of time that men should avoid fathering a child was increased to 93 days in inclusion criterion 8c; an administrative error was corrected by removing the pregnancy test on Day 1 in inclusion criterion 8b. Pregnancy test for women of childbearing potential was added at each 3-week visit in Table 5.

   Rationale for change: Requested by European Regulatory Agency.

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

   Description of change: Exclusion criterion 13 was modified to exclude subjects that had exposure to a live vaccine within 30 days of study drug administration.

   Rationale for change: Requested by European Regulatory Agency.

7. **Section 3.2, Subject Exclusion Criteria (criterion 14); Section 6, Study Assessments (Tables 5 and 6); Section 7.4.5.4, HIV Screening Test**

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

   Rationale for change: Requested by European Regulatory Agency.

8. **Section 5.4.1, Criteria and Procedures for Dose Interruptions and Reductions of INCB050465 (Table 2)**

   Description of change: Provide guidance that all subjects with Grade 3 ANC ($< 1.0 \times 10^9$/L) should have INCB050465 administration interrupted.

   Rationale for change: Requested by European Regulatory Agency.

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

Amendment 2 (09 NOV 2016)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to change the dose of INCB050465.

This amendment includes the changes to Protocol INCB 50465-202 Amendment 1 (30 AUG 2016) summarized below. A redline version of the amendment depicting updated and previous text is also provided.

1. **Synopsis; Section 1.4, Study Rationale; Section 4.1, Overall Study Design; Section 5.2.1, Description and Administration**

   Description of change: The dose of INCB050465 has been changed from 30 mg once daily to 20 mg once daily for 8 weeks followed by 20 mg once weekly.

   Rationale for change: As of 02 SEP 2016, among all subjects (n = 46) in study INCB 50465-101, 11 (24%) have discontinued study drug due to an adverse event (AE). Among the subjects with an objective response (n = 20), 7 (35%) discontinued study treatment due to an AE. The dose has been changed in an effort to reduce the frequency of AEs that lead to study drug discontinuation.

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

   Description of change: Inclusion criterion 1 was modified to allow only subjects aged 19 years or older to enroll in South Korea.

   Rationale for change: The legal adult age in South Korea is 19 years.

3. **Section 1.3, INCB050465**

   Description of change: Safety and efficacy data have been updated based on a data cut of 02 SEP 2016.

   Rationale for change: These changes were made to provide the most recent emerging data to support the need for a dose change and the new dose rationale.

4. **Section 1.5, Potential Risks and Benefits of the Treatment Regimen**

   Description of change: The potential risks and benefits of the treatment regimen were updated based on the 02 SEP 2016 data cut, and the dose rationale was provided.

   Rationale for change: The changes were made to provide a current interpretation based on the most recent data. The dose rational was changed to support the new dose.

5. **Section 5.4, Treatment Interruptions and Adjustments**

   Description of change: Table 2 (Guidelines for Interruption and Restarting Study Drug) and Table 3 (Dose Levels for INCB050465) were updated, and the term "immune-related adverse event" was defined.

   Rationale for change: New guidance was provided for AEs that have caused treatment discontinuation in Study INCB 50465-101 to assist physicians manage these AEs. The term "immune-related adverse event" was defined so investigators can consistently answer the following question in the eCRF: "Is this event an immune-related adverse event?"

6. **Section 6, Study Assessments (Table 4: Schedule of Assessments)**

   Description of change: The frequency of drug dispensing was altered.

   Rationale for change: Because the dose schedule changed from daily to weekly at Week 9, the dose dispensing schedule was changed to reduce the amount of drug that would otherwise be discarded.

7. **Section 8.4, Adverse Events of Special Interest**

   Description of change: Rash ≥ Grade 2 was added to the list of adverse events of special interest, and diarrhea was changed to ≥ Grade 2.

   Rationale for change: Rash was added because this is an AE that has led to study treatment discontinuation and has occurred with some frequency in Study INCB 50465-101. The change in diarrhea reporting was made to reduce the amount of expedited reporting for this event.

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 1 (30 AUG 2016)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to fulfill a request from the FDA to 1) add an Independent Data Monitoring Committee and 2) Conduct an interim analysis for futility in Group A.

This amendment includes the changes to Protocol INCB 50465-202 (26 MAY 2016) summarized below. A redline version of the amendment depicting updated and previous text is also provided.

1. **Synopsis; Section 4.1, Overall Study Design; Section 9.2, Selection of Sample Size; Section 9.6, Interim Analysis**

   Description of change: An interim futility analysis has been added. The analysis is planned when the first 40 subjects in Group A have been treated and have been evaluated for response or have permanently discontinued study treatment because of disease progression, withdrawal of consent, or death. Group A of the study will be terminated for futility if ≤ 13 of the 40 subjects have responded (ie, complete response [CR]/complete metabolic response [CMR] or partial response [PR]/partial metabolic response [PMR]) based on assessments provided by the independent review committee; otherwise the study will continue. A timely assessment of response will be performed to avoid the risk of overenrollment. No formal futility analysis will be conducted for Group B.
   Section 9.2 (Selection of Sample Size) was updated to be consistent with the numbers used in the added interim analysis.

   Rationale for change: Requested by the FDA.

2. **Synopsis; Section 4.1, Overall Study Design; Section 4.6, Study Termination; Section 8.7, Independent Data Monitoring Committee; Section 9.5, Analyses for the Independent Data Monitoring Committee**

   Description of change: An independent Data Monitoring Committee (IDMC) was included in the study to review safety and perform the futility analysis.

   Rationale for change: Requested by the FDA.

3. **Synopsis; Section 2, Study Objectives and Endpoints**

   Description of change: The primary objective was updated to clarify that efficacy will be assessed in terms of objective response rate (ORR) in Group A, and study endpoints were updated to indicate Group A or Group B where applicable.

   Rationale for change: For clarity and to make the objectives and endpoints consistent.

4. **Synopsis; Section 2.2, Study Endpoints; Section 4.1, Overall Study Design; Section 5.5.1, Criteria for Study Treatment Discontinuation; Section 6, Study Assessments; Section 7.5.3, Bone Marrow Examination; Section 7.5.5, Response Criteria – The Lugano Classification; Section 9.4.1, Efficacy Analyses**

   Description of change: Complete response (CR), partial response (PR), and progressive disease (PD) were changed throughout the document to complete response/complete metabolic response (CR/CMR), partial response/partial metabolic response (PR/PMR), and progressive disease/progressive metabolic disease (PD/PMD).

Rationale for change: The change was made to be consistent with the endpoints of the Lugano Criteria, which are being used to evaluate the disease assessments.

5. **Section 5.4.1, Criteria and Procedures for Dose Interruptions and Reductions of INCB050465 (Table 2); Section 5.4.2, Supportive Care Guidelines for Diarrhea/Colitis; Section 11, References**

   Description of change: Guidance for management of diarrhea and colitis was added, and guidance for ALT/AST elevation and Grade 3 toxicities was modified.

   Rationale for change: To support investigators whose subjects experience diarrhea/colitis, which has been observed in the ongoing INCB050465 Phase 1 study.

[redacted]

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.

Signature Manifest

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