Official Title: **A Phase 2, Open-Label Study of INCB050465 in Participants With Autoimmune Hemolytic Anemia**

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Clinical Study Protocol

INCB 50465-206

A Phase 2, Open-Label Study of INCB050465 in Participants With Autoimmune Hemolytic Anemia

Product:	**INCB050465**
IND Number:	**121,474**
EudraCT Number:	**2017-003652-22**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation 1801 Augustine Cut-Off Wilmington, DE 19803**
Original Protocol (Version 0):	**07 NOV 2017**
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Amendment (Version) 3:	**01 FEB 2019**
Amendment (Version) 4:	**31 OCT 2019**
Amendment (Version) 5:	**02 NOV 2020**

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study Protocol, Good Clinical Practices as defined in Title 21 of the US Code of Federal Regulations Parts 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 50465-206 Protocol Amendment 5 (Version 5 dated 02 NOV 2020) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

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LIST OF ABBREVIATIONS

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

Abbreviation	Definition
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AIHA	autoimmune hemolytic anemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC_{0-t}	area under the concentration-time curve from time = 0 to the last measureable concentration at time = t
BMI	body mass index
CAD	cold agglutinin disease
CBC	complete blood count
CFR	Code of Federal Regulations
CL/F	apparent oral dose clearance
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration over the dose interval
CNS	central nervous system
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DAT	direct antiglobulin test
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EOT	end of treatment
ECG	electrocardiogram
eCRF	electronic case report form
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	full analysis set
Fc	fragment crystallizable

Abbreviation	Definition
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
IC_{50}	concentration that results in 50% inhibition
IC_{90}	concentration that results in 90% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IL	interleukin
IN	Investigator Notification
IRB	institutional review board
IRT	interactive response technology
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NK	natural killer
[redacted]	[redacted]
PD	pharmacodynamic
PD-1	programmed cell death protein 1
PI3Kδ	phosphatidylinositol 3-kinase enzymes delta isoform
PIP2	phosphatidylinositol-4,5-bisphosphate
PIP3	phosphatidylinositol-3,4,5 trisphosphate
PJP	*Pneumocystis jiroveci* pneumonia
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy

Abbreviation	Definition
PR	partial response
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
TEAE	treatment-emergent adverse event
t_{max}	time to maximum concentration
Treg	regulatory T cell
ULN	upper limit of normal
wAIHA	warm-type autoimmune hemolytic anemia
WBC	white blood cell

1. PROTOCOL SUMMARY

Protocol Title: A Phase 2, Open-Label Study of INCB050465 in Participants With Autoimmune Hemolytic Anemia

Protocol Number: INCB 50465-206

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate the efficacy of INCB050465 in the treatment of participants with AIHA.	• Proportion of participants attaining a CR (defined as hemoglobin > 12 g/dL not attributed to transfusion effect* and the normalization of hemolytic markers) at any visit from Week 6 to Week 12. • Proportion of participants attaining a PR (defined as hemoglobin 10-12 g/dL or ≥ 2 g/dL increase from baseline not attributed to transfusion effect and the normalization of hemolytic markers) at any visit from Week 6 to Week 12. *No transfusion effect definition: >1 week since last transfusion.
To evaluate the safety of INCB050465 administered as repeat doses in participants with AIHA.	Safety and tolerability will be assessed by monitoring AEs, measuring vital signs and ECGs, and conducting clinical laboratory blood and urine sample assessments.

Overall Design:

Study Phase	Phase 2
Clinical Indication	AIHA
Population	Men and women, aged 18 years or older with primary AIHA without evidence of a lymphoproliferative malignancy.
Number of Participants	Approximately 25
Study Design	Open-label, multicenter study
Estimated Duration of Study	Treatment duration will vary among participants. The initial study period will be 28 weeks in duration. For participants who are eligible for an extension of treatment based on their clinical response, the treatment duration may be extended with sponsor approval.
Safety Review Committee	Yes (internal)

Treatment Groups and Duration:

Participation is 28 weeks for participants who are not eligible for an extension based on clinical response and includes the following:

- Screening: up to 28 days
- Treatment: up to 12 weeks
- Extension period: For participants receiving benefit from study drug, further participation may continue with sponsor approval until the drug is available through another clinical study, or is commercially available, or the sponsor stops the study or the study drug development.
- Follow-up: up to 12 weeks (3 months)

Cohort 1: INCB050465 1 mg QD for up to 12 weeks. At Week 6, participants who fulfill dose increase criteria (see definition below) will be offered INCB050465 2.5 mg QD for up to 6 weeks. If there are any tolerability issues in individual participants who received 2.5 mg, the dose may be decreased to 1 mg.

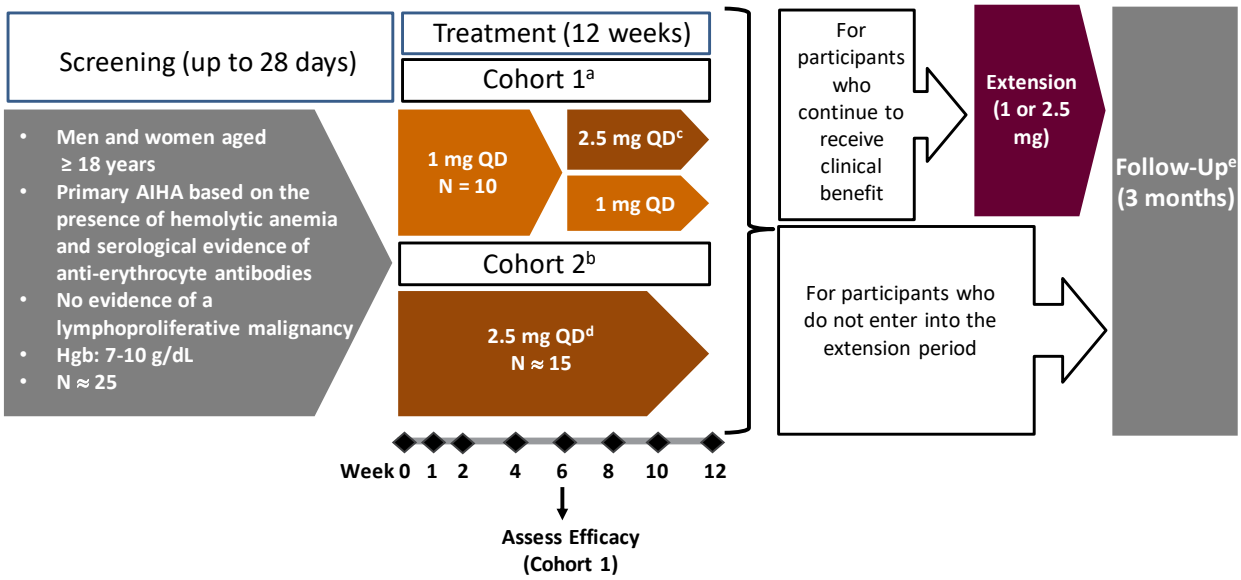
Cohort 2: INCB050465 2.5 mg QD for up to 12 weeks. If there are any tolerability issues in individual participants, the dose may be decreased to 1 mg.

Criteria for dose increase: (1) Continue to require transfusions by Week 6 visit, or (2) do not attain a meaningful clinical response (at least a stabilization ≥ 2 g/dL increase in hemoglobin from baseline to Week 6). *Dose increases require sponsor preapproval (see Section 6.6).*

Participants who complete the 12-week treatment period and continue to receive clinical benefit from study drug may enter into an extension period with sponsor approval to continue receiving INCB050465 until the drug is available through another clinical study, or is commercially available, or the sponsor stops the study or the study drug development.

The study design is shown in Figure 1 below.

Figure 1: Study Design Schema



[a] Cohort 1: N = 10; no more than 3 CAD or mixed-type AIHA participants.
[b] Cohort 2: N = approximately 15, with approximately 5 CAD AIHA and up to 8 wAIHA participants; the remainder can be wAIHA, CAD, or mixed-type AIHA participants.
Participants in Cohort 2 may begin enrollment after enrollment of a minimum of 6 wAIHA participants in Cohort 1 and review of safety and efficacy through Week 6.
[c] (1) At Week 6, participants who receive 1 mg QD study drug and who fulfill dose increase criteria* may have their dose increased to 2.5 mg QD of INCB050465 until Week 12.
(2) If there are any tolerability issues in individual participants who received 2.5 mg, the dose may be decreased to 1 mg.
[d] If there are any tolerability issues in individual participants who received 2.5 mg, the dose may be decreased to 1 mg.
[e] If relapse of AIHA occurs within this period, PD and clinical laboratory markers of hemolysis will be assessed, and the participants will be treated based on investigators' decision.
* Criteria for dose increase in individual participants in Cohort 1 (see Section 6.6):
(1) Continue to require transfusions by Week 6 visit, or
(2) Do not attain a meaningful clinical response (at least a stabilization ≥ 2 g/dL increase in hemoglobin from baseline to Week 6).

Table 1: Schedule of Assessments

Procedure	Protocol Section	Screening	Treatment								Follow-Up[a]		
		Days -28 to -1	Day 1	Wk 1 ± 3 days	Wk 2 ± 3 days	Wk 4 ± 3 days	Wk 6[b] ± 3 days	Wk 8 ± 3 days	Wk 10 ± 3 days	Wk 12 ± 3 days (EOT)	Month 1 + 5 days	Month 2 ± 5 days	Month 3 ± 5 days (EOS)
Administrative procedures													
Informed consent	8.1.1	X											
Contact IRT	8.1.3	X	X	X	X	X	X	X	X	X	X	X	X
Review inclusion and exclusion criteria	5.1, 5.2	X	X										
Demography and medical history	8.1.4	X											
Prior/concomitant medications	8.1.5	X	X	X	X	X	X	X	X	X	X	X	X
Study drug accountability and assess compliance	6.5			X	X	X	X	X	X	X			
Study drug dispensing	6.1		X			X		X					
Prophylactic treatment for PJP	6.7.1.1		X	X	X	X	X	X	X	X	X	X	X
Safety procedures/assessments													
Physical examination[c]	8.3.2	X[c]	X[c,d]	X	X	X		X		X			X[c]
Vital signs[e]	8.3.3	X	X	X	X	X	X	X	X	X			X
Serology[f]	8.3.5.7	X											
D-Dimer	8.3.5.5	X				X		X		X			
Vitamin B12/folic acid	8.3.5.2	X											
FSH[g]	8.3.5.6	X											
Serum pregnancy[h]	8.3.5.6	X											
Urine pregnancy[h]	8.3.5.6		X	X	X	X	X	X	X	X			
Urinalysis	8.3.5.4	X								X			
Serum chemistries[i]	8.3.5.1 8.3.5.3	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[j]	8.3.4	X			X			X		X			
AE assessment	8.3.1	X	X	X	X	X	X	X	X	X	X	X	X

Table 1: Schedule of Assessments (Continued)

Procedure	Protocol Section	Screening	Treatment								Follow-Up[a]		
		Days -28 to -1	Day 1	Wk 1 ± 3 days	Wk 2 ± 3 days	Wk 4 ± 3 days	Wk 6[b] ± 3 days	Wk 8 ± 3 days	Wk 10 ± 3 days	Wk 12 ± 3 days (EOT)	Month 1 + 5 days	Month 2 ± 5 days	Month 3 ± 5 days (EOS)
Efficacy assessments													
Hematology	8.2.1	X	X	X	X	X	X	X	X	X	X	X	X
Hemolysis markers[k]	8.2.1	X	X	X	X	X	X	X	X	X	X[k]	X[k]	X[k]
DAT and cold agglutinin levels	8.2.2	X								X			
Complement assessment (CH50, C3, and C4)	8.2.1		X							X			
FACIT-Fatigue sub-scale	8.2.3		X				X			X	X	X	X
PK plasma sampling[l]	8.4			X	X[m]			X[m]		X			
[redacted]													

[a] For participants who are not eligible to enter into the extension period.
[b] Dose modification.
[c] Comprehensive physical examination at screening, Day 1, and EOS; targeted physical examination at all other time points.
[d] Height and body weight will only be assessed at Day 1.
[e] Vital signs will include body temperature, respiratory rate, blood pressure, and pulse.
[f] Serology includes HIV, hepatitis, anti-Streptolysin antibody, and anti-phospholipid antibody tests.
[g] For women of nonchildbearing potential only (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR postmenopausal, defined by last menstrual period > 12 months before screening and confirmed by FSH).
[h] For women of childbearing potential only.
[i] Ferritin, iron, and total iron-binding capacity will be tested at screening for all participants and at Week 6 if the participant has ongoing transfusions requirements during the study.
[j] Single ECG. At screening, in the event that a single QTcF is > 470 milliseconds for males or > 480 milliseconds for females, triplicate ECG measurements may be performed.
[k] Hemoglobin, haptoglobin, LDH, reticulocyte count, total bilirubin and direct/indirect bilirubin are hemolytic markers will be measured. During follow-up, these hemolytic markers should be assessed if a participant becomes symptomatic or starts new treatment; relevant biomarkers should also be included.
[l] Plasma for PK analysis will be collected predose and 1, 2, and 4 hours postdose at Weeks 2 and 8. Predose PK will be collected at Weeks 1 and 12.
[m] No food intake 4 hours predose and 1 hour postdose on Weeks 2 and 8.
[redacted]

Table 2: Schedule of Assessments for the Extension Period

Procedure	Protocol Section	Extension Period	EOT Extension Period	Follow-Up		
		At Least Every 8-12 Weeks in Clinic		Month 1 + 5 days	Month 2 ± 5 days	Month 3 ± 5 days (EOS)
Prior/concomitant medications	8.1.5	X	X	X	X	X
Study drug dispensing	6.1	X				
Study drug accountability and assess compliance	6.5	X	X			
AE assessment	8.3.1	X	X	X	X	X
Prophylactic treatment for PJP	6.7.1.1	X	X	X	X	X
Hematology[a,b]	8.2.1	X	X	X	X	X
Hemolysis markers[a]	8.2.1	X	X	X	X	X
Serum chemistries [a]	8.3.5.1	X				

[a] Performed at each site as per the standard of care for participant's condition and monitoring at the investigator's discretion. Frequency to be determined by the investigator if it is necessary to monitor any other ongoing clinical condition.
[b] Hematology panel will be performed at local laboratory.

2. INTRODUCTION

INCB050465 is an inhibitor of the Class IA PI3K enzymes, with selectivity for the delta isoform (PI3Kδ) that is proposed for development for treatment of hematological malignancies and solid tumors. Uncontrolled B-cell and T-cell proliferation and differentiation are strongly implicated in the pathogenesis of hematological malignancies and autoimmune diseases. PI3Kδ serves a critical signal for B-cell and T-cell development. Over-activated PI3Kδ signaling would compromise the normal immune functions. Therefore, PI3Kδ inhibition represents a potential therapeutic strategy in the treatment of hematological malignancies and autoimmune diseases, including AIHA.

2.1. Epidemiology of Autoimmune Hemolytic Anemia

Autoimmune hemolytic anemia is a rare acquired disorder in which autoantibodies directed against RBC membrane antigens lead to their accelerated destruction. The estimated incidence of AIHA in adults is 0.8 to 3 per 100,000 per year, with a mortality rate of 11% (Zanella and Barcellini 2014). The disease can be distinguished on the basis of the autoantibody Ig class and thermal characteristics in wAIHA (IgG-mediated) and CAD (IgM-mediated). Mixed-type AIHA (7%-8% of all AIHA) coexists of warm autoantibodies and high-titer cold agglutinins. Autoimmune hemolytic anemia is also classified as primary (idiopathic), in which hemolysis dominates the clinical picture in the absence of any other coexisting disorder, and secondary forms, which accompany and are complications of an underlying disease (eg, lymphoproliferative disease, infections, immunodeficiency, and tumors). Warm AIHA accounts for 70% to 80% of all cases in adults, and at least half of the wAIHA cases are associated with an underlying disease. Acute CAD is mainly secondary to infections, whereas chronic CAD is frequently associated with lymphoproliferative or neoplastic diseases (Oken and Garratty 2004).

2.2. Mechanisms of Erythrocyte Destruction in Autoimmune Hemolytic Anemia

There are several immunologic mechanisms are involved in the pathogenesis of wAIHA that include ADCC, phagocytosis, and direct complement-mediated lysis (Barcellini 2015). The most frequent autoantibodies against RBCs are IgG, which mainly determine extravascular hemolysis through the ADCC. Cytotoxic CD8+T cells and NK cells that carry membrane receptors for the Fc portion of IgG directly lyse RBCs in the reticuloendothelial system (spleen and liver). Phagocytosis by macrophages is another way RBCs are destroyed. The macrophage surface expresses receptors for the Fc region of IgG, which enables trapping and ingestion of opsonized RBCs that are coated with IgG, primary in the spleen. Moreover, for RBCs heavily coated with IgG, the amount of antigen-antibody complex can be sufficient for binding complement protein complex C1 and thus activate the classical complement pathway. Upon complement activation in wAIHA, phagocytosis of C3b-opsonized erythrocytes by Kupffer cells in the liver is responsible for most of the RBC destruction.

In contrast to wAIHA, in CAD, most RBC destruction does not occur in the spleen. Immunoglobulin M-cold autoantibody binds complement C1 and initiates the classical complement pathway, which results in the cleavage of C3 to C3a and C3b. When RBCs in the peripheral circulation at cooler temperatures return to the central circulation with higher temperature, the IgM antibody detaches from the cell surface, while C3b remains bound. A proportion of the C3b-coated RBCs is sequestered by macrophages in the liver, whereas the other RBCs are lysed through the activation of C5 by C3b. C5 complement activation results in membrane attack complex formation and intravascular hemolysis that results in severe acute exacerbations and profoundly hemolytic patients (Berentsen et al 2015).

2.3. Current Treatment and Unmet Need in Autoimmune Hemolytic Anemia

Currently there is no approved and effective targeted therapy for treatment of AIHA. For wAIHA, corticosteroids remain the first-line therapy; however high initial doses are required, responses are often achieved slowly, and only a minority of patients (< 20%) achieve a lasting response (< 20%; Barcellini et al 2014). Since most RBC destruction occurs in the spleen in wAIHA, it is not surprising that splenectomy is a reasonably efficient second-line treatment with a sustained response rate of 60% to 70%. In the third-line situation, immunosuppressive drugs such as danazol, azathioprine, cyclophosphamide, or cyclosporine are used, although response rates are poorly documented, and most publications are single case reports or small retrospective studies. In contrast to wAIHA, only 14% of CAD patients have responses to corticosteroids, and other unspecific immunosuppressive drugs have little efficacy. As CAD is usually not a primary disease, recommended first-line therapy is to treat the underlying disease.

Rituximab is a chimeric monoclonal antibody that targets CD20 antigen on B lymphocytes. By binding to CD20, it induces apoptosis of CD20-positive B cells. Rituximab has recently been licensed in rheumatoid arthritis and is also widely used off-label in various autoantibody-mediated autoimmune diseases, such as immune thrombocytopenic purpura and systemic lupus erythematosus. Recently, rituximab has been considered as second-line therapy for wAIHA and first-line therapy for CAD. Second-line treatment with rituximab leads to response rates similar to splenectomy (~70%), but rituximab-induced responses seem less sustained, and relapses are frequent. Major concerns regarding the adverse effects from rituximab are related to long-lasting B-cell suppression and include increased risk of infection including hepatitis B reactivation (Artz et al 2010) and possibly PML (Carson et al 2009).

In recent years, several complement inhibitors have become available in the clinic, some with proven efficacy in AIHA. Eculizumab is a humanized monoclonal antibody that binds to the C5 component and inhibits terminal complement activation. There have been 2 case reports describing patients with CAD who were successfully treated with eculizumab (Röth et al 2009, Gupta and Wang 2014). However, in these 2 reports, it was only effective in AIHA patients with intravascular hemolysis, and also increases the risk of meningococcal infection. A monoclonal antibody (TNT009) targeting C1 to inhibit the classical complement pathway is also under study. Other complement inhibition drugs that target either C3 or the classical pathway have only been reported in experimental and preclinical studies or in few clinical observations.

2.4. Phosphatidylinositol 3-Kinase Delta in Autoimmune Diseases

Phosphatidylinositol 3-kinases belong to a family of lipid signaling kinases that phosphorylate phosphoinositides of the inositol ring (Cantley 2002). Phosphatidylinositol 3-kinase enzymes 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 PIP2, giving rise to PIP3. PIP3 functions as a second messenger that controls a number of cellular processes, including growth, survival, adhesion, and migration.

The delta isoform of PI3K is expressed primarily in hematopoietic cells and plays an essential role in B-cell development and function. Aberrant PI3Kδ signaling activates and proliferates self-reactive B cells that produce autoantibodies, act as antigen-presenting cells presenting self-antigen to autoreactive T cells, and produce pro-inflammatory cytokines, and therefore has been strongly linked to autoimmunity (Puri and Gold 2012). Indeed, PI3Kδ inhibitors such as IC87114, have now been shown to reduce the incidence and severity of autoimmune arthritis, asthma, experimental autoimmune encephalomyelitis, and systemic lupus erythematosus in mouse models. Clinical studies are now evaluating the potential of PI3Kδ inhibitors for the treatment of a variety of inflammatory diseases including allergic rhinitis and chronic obstructive pulmonary disease. The ability of PI3Kδ inhibitors to reduce the severity of these inflammatory diseases may be due not only to their actions on B cells, but also to inhibitory effects on other immune cells that contribute to autoimmune disease such as T cells, mast cells and neutrophils (Fung-Leung 2011). Given the fact that in addition to B cells, several T cell subsets, including Treg, Th17, and Th1 cells, are also involved in AIHA pathogenesis, inhibition of PI3Kδ signaling could have benefit in the treatment of patients with current unmet need in AIHA and other autoimmune diseases.

A preclinical study indicated that IL-2 knockout mice developing AIHA improved RBC counts, hematocrit, and hemoglobin and reduced anti-RBC reactivity (eg., decreased auto-IgM antibodies) after being treated with a PI3Kδ inhibitor (INCB040093, 100 mg/kg BID PO; Incyte unpublished data). This result strengthens the hypothesis that inhibition of PI3Kδ signaling may attenuate autoreactive antibody production that destroy RBCs and lead to AIHA.

2.5. INCB050465

INCB050465 is a potent inhibitor of PI3Kδ [redacted] with approximately [redacted] for the other PI3K family members (IB). B-cell proliferation triggered by anti–IgM-mediated cross-linking of the B-cell receptor is known to be PI3Kδ dependent. INCB050465 potently inhibits antibody-induced proliferation of human CD19+ B cells with an IC_{50} value of [redacted] nM. [redacted]. These effects were not due to INCB050465 mediated general cytotoxicity.

INCB050465 inhibited the production of IL-17, IFN-γ, and IL-13 by naive T cells cultured under Th17, Th1 and Th2 differentiation conditions, respectively. These data suggest that in addition to the effects of PI3Kδ inhibition on B cells, it may also potentially impact some aspects of T cell function.

Clinical experiences of INCB050465 are solely based on oncology studies in patients with cancer who received higher doses for longer periods of time. In a Phase 1/2, dose-escalation and expansion study, INCB050465 is being evaluated as a monotherapy for patients with B-cell malignancies. Sixty-nine participants (as of 30 MAR 2017) received INCB050465 administered orally at QD doses of 5, 10, 15, 20, and 45 mg. INCB050465 has been generally well-tolerated in participants with doses up to 45 mg. The median duration of treatment was 96 days. The most frequently reported treatment-related TEAE was diarrhea ([redacted]). Other treatment-related TEAEs occurring ≥ 10% included nausea ([redacted]), neutropenia (14.5%), and fatigue ([redacted]). Serious AEs occurred in [redacted] ([redacted]). The most frequent SAE reported was diarrhea ([redacted]). Serious AEs were observed in all dose cohorts. Ten participants ([redacted]) had SAEs that were considered related to INCB050465 by the investigators. Related SAEs that occurred in more than 1 participant were colitis, diarrhea, and dermatitis exfoliative ([redacted] each participant). No dose-limiting toxicities were identified, and the maximum tolerated dose was not reached. [redacted] The PD analyses demonstrated robust and sustained pathway inhibition at all dose levels tested (Phillips et al 2016). Refer to the IB for further details.

2.6. Study Rationale

Currently, there is no approved and effective targeted therapy for treatment of AIHA. Despite current treatment algorithms, there is a significant morbidity and mortality rate, and disease relapse remains an ongoing challenge for a significant number of patients with AIHA. Therefore, there remains an unmet need for new treatments for AIHA. In addition to showing efficacy in a number of B-cell–related cancers, treatment with INCB050465 has shown significant improvement in animal models of AIHA and lupus nephritis, as well as other antibody-mediated diseases. INCB050465 may represent an alternative treatment for participants who have failed at least 1 prior treatment. INCB050465 may be a more flexible intervention, as current therapy with rituximab results in profound and sustained depletion of circulating B cells.

The length of treatment in this study is 12 weeks with an observational follow-up of 12 weeks (3 months), as AIHA tends to follow a course of remission/relapse following conventional therapies. The length of treatment is expected to allow for recovery of hemoglobin and evaluation of hemolytic markers, as well as permit initial safety assessment. Participants with warm, cold (CAD), and mixed-type AIHA who have failed at least 1 prior treatment for AIHA will be eligible for enrollment. To mirror the relative incidence of warm, mixed, and cold (CAD) disease, which is about 80% warm AIHA patients and about 20% of mixed and CAD patients, a minimum of 7 patients with warm AIHA will be enrolled in Cohort 1, and the remaining patients may be CAD or mixed, or the cohort may be completed with warm AIHA patients as available. Cohort 2 ($n \approx 15$) distribution and increased number of participants are intended to better evaluate CAD AIHA patients and possible signal observed in Cohort 1, as well as account for higher baseline variability seen in the wAIHA subpopulation. Cohort 2 will have approximately 5 CAD AIHA participants and up to 8 wAIHA participants; the remainder can be wAIHA, CAD, or mixed-type AIHA. As corticosteroid treatment plays an important role in management of the disease, participants will be permitted to continue on a low dose (equivalent to ≤ 20 mg/day of prednisone) of corticosteroids or taper corticosteroids as appropriate. The

study is open-label, because the safety and efficacy of INCB050465 in AIHA is unknown, and an open-label design will allow careful monitoring in a serious disease that is rare and has a heterogeneous population.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the efficacy of INCB050465 in the treatment of participants with AIHA.	• Proportion of participants attaining a CR (defined as hemoglobin >12 g/dL not attributed to transfusion effect* and the normalization of hemolytic markers) at any visit from Week 6 to Week 12. • Proportion of participants attaining a PR (defined as hemoglobin 10-12 g/dL or at least ≥ 2 g/dL increase from baseline not attributed to transfusion effect and the normalization of hemolytic markers) at any visit from Week 6 to Week 12. *No transfusion effect definition: > 1 week since last transfusion.
To evaluate the safety of INCB050465 administered as repeat doses in participants with AIHA.	Safety and tolerability will be assessed by monitoring AEs, measuring vital signs and ECGs, and conducting clinical laboratory blood and urine sample assessments.
Secondary	
To further evaluate the efficacy of INCB050465 in the treatment of participants with AIHA.	• Proportion of participants attaining a CR during postbaseline visits. • Proportion of participants attaining a PR during postbaseline visits. • Proportion of participants attaining a ≥ 2 g/dL increase in hemoglobin from baseline. • Mean, change, and percentage change from baseline of hemoglobin. • Proportion of participants requiring transfusions. • Proportion of participants who achieve normalization of hemolytic markers. *(Hemolysis markers: hemoglobin, haptoglobin, LDH, reticulocyte count, total bilirubin, and direct/indirect bilirubin.)* • Change of daily usage of prednisone. • FACIT-F sub-scale assessment.
To evaluate the PK effects of INCB050465.	PK endpoints: C_{max}, t_{max}, C_{min}, AUC_{0-t}, and CL/F.
To evaluate the PD effects of INCB050465.	Change from baseline in PD markers: reticulocyte count, DAT for IgG and C3b, cold agglutinin levels, haptoglobin, total bilirubin, direct/indirect bilirubin, LDH, and complement assessment (CH50, C3, and C4).
[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, open-label study designed to evaluate the safety and efficacy of INCB050465 administered orally to participants with AIHA who have decreased hemoglobin and evidence of ongoing hemolysis that requires treatment intervention. Participants with primary warm, cold (CAD), and mixed-type AIHA without an underlying lymphoproliferative malignancy or autoimmune related hemolytic anemia and have failed at least 1 prior treatment for AIHA will be eligible for enrollment. Participants will be treated for 12 weeks. There are 2 cohorts in this study: Cohort 1, with up to 10 participants, with no more than 3 cold (CAD)/mixed-type AIHA participants to appropriately reflect response in the overall population, which is predominantly warm AIHA; and Cohort 2, with approximately 15 participants, with approximately 5 CAD AIHA, up to 8 warm AIHA, and the remainder from any of the 3 AIHA types. Cohort 2 distribution and increased number of participants are intended to better evaluate CAD AIHA patients and possible signal observed in Cohort 1, as well as account for higher baseline variability seen in the wAIHA subpopulation. The first cohort (Cohort 1, n = 10 participants) enrolled will initially receive INCB050465 1 mg QD. At Week 6, participants who continue to require transfusions or do not attain a meaningful clinical response (at least a stabilization ≥ 2 g/dL increase in hemoglobin from baseline to Week 6) may have their dose increased, with sponsor preapproval, to 2.5 mg QD of INCB050465 until Week 12 (see Section 6.6). If there are any tolerability issues in individual participants who received 2.5 mg, the dose may be decreased to 1 mg. Following enrollment of a minimum of 6 warm AIHA participants in the first cohort and review of safety and efficacy through Week 6, Cohort 2 may begin enrollment. Participants in Cohort 2 (n ≈ 15) will receive INCB050465 2.5 mg QD for 12 weeks. If there are any tolerability issues, the dose may be decreased to 1 mg. The investigator and sponsor should review and agree any dose increases or decreases. Following the last dose of INCB050465, participants will be eligible for a 12-week (3 months) follow-up for evaluation of the safety and durability of response.

An internal Safety Review Committee (see Section 9.6) will review clinical response and AE data. If there is no clinical response (CR or PR) by Week 12 in the first cohort of 10 participants, including those who receive dose escalation to 2.5 mg, the study will be stopped for futility. If there is a clear emerging signal from either Cohort 1 or Cohort 2, the committee may make recommendations as to the expanded study of either cohort to obtain additional safety and efficacy data at either dose level.

Participants who complete the 12-week treatment period and demonstrate clinical benefit from study drug may enter into an extension period with sponsor approval to continue receiving INCB050465 until the drug is available through another clinical study, or is commercially available, or the sponsor stops the study or the study drug development. Visits during the extension period will be conducted every 8 to 12 weeks to continue to monitor the effectiveness of the clinical response, as well as clinical safety laboratory assessments and adverse events.

4.2. Overall Study Duration

The study begins when the first participant signs the ICF. Participation through follow-up is expected to be approximately 28 weeks for participants who complete treatment at Week 12 and

enter the follow-up period. For participants that are eligible for the extension period, further participation may continue with sponsor approval until the drug is available through another clinical study, or is commercially available, or the sponsor stops the study or the study drug development. It is estimated that the study will take approximately 12 to 18 months to accrue approximately 25 participants, and that the final analysis will be performed 12 months after the last participant completes the follow-up visits. The end of the study will occur when all participants have completed all applicable follow-up assessments.

4.3. 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 IRB/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 if required by regulatory decision.

5. STUDY POPULATION

Participants with warm, cold (CAD), and mixed-type AIHA without an underlying lymphoproliferative malignancy compose the study population. Participants will be permitted to continue on a low dose (equivalent to ≤ 20 mg/day of prednisone) of corticosteroids or taper corticosteroids as appropriate.

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

5.1. Inclusion Criteria

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

1. Men or women, aged 18 years or older.
2. Diagnosis of AIHA based on the presence of hemolytic anemia and serological evidence of anti-erythrocyte antibodies, detectable by the DAT as follows:
    a. Warm: DAT positive for IgG only or IgG plus C3d
    b. Cold (CAD): DAT positive for C3d only, with cold agglutinins of I specificity
    c. Mixed: DAT positive for IgG and C3d, with coexistence of warm autoantibodies and high titer cold agglutinins
3. Participants who have disease progression after treatment with standard therapies that are known to confer clinical benefit or who are intolerant to treatment. There is no limit to the number of prior treatment regimens.
4. Hemoglobin 7 to 10 g/dL (as determined by local laboratory).
5. No evidence of a lymphoproliferative malignancy or other autoimmune-related underlying conditions (eg, systemic lupus erythematosus, Castleman's disease, Sjögren's syndrome, or other autoimmune diseases).

6. ECOG performance status score of 0 to 2 (see Appendix C and Oken et al 1982).
7. 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 postmenopausal, defined by last menstrual period > 12 months before screening and confirmed by FSH).
    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 at least 93 days after the last dose of study drug. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participant and her 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 drug. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participant and his understanding confirmed.
8. Able to comprehend and willing to sign an ICF.
9. Willingness to receive PJP prophylaxis during the study period.

5.2. Exclusion Criteria

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

1. Pregnant or breastfeeding women.
2. Concurrent conditions and history of other diseases:
    a. History or clinical manifestations of significant unstable metabolic, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, urological, neurological, or psychiatric disorders.
    b. Current or previous malignancy within 5 years of study entry, except basal or squamous cell skin cancer with removal considered to be curative, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in situ of the cervix, or other noninvasive or indolent malignancy without sponsor approval.
    c. 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.
    d. Current New York Heart Association Class II to IV congestive heart failure or uncontrolled arrhythmia.
3. Inadequate hematologic function defined as follows (as determined by local laboratory):
    a. ANC $< 1.5\times 10^9$/L.
    b. Platelet count $< 100 \times 10^9$/L.
4. Severely impaired liver function (Child-Pugh Class C) or ALT or AST $\geq 2 \times$ ULN on repeated assessment.
5. Impaired renal function with estimated creatinine clearance less than 45 mL/min.

6. Anti-phospholipid antibodies positive or elevated anti-streptolysin antibodies.
7. Hepatitis B (HBV) or hepatitis C (HCV) infection: Participants who are positive for the hepatitis B surface antibody or hepatitis B core antibody will be eligible if they are negative for HBV-DNA; these participants should be considered for prophylactic antiviral therapy. Participants who are positive for the anti-HCV antibody will be eligible if they are negative for HCV-RNA.
8. Known HIV infection or positivity on immunoassay. Note: HIV screening test is optional for participants enrolled in the United States, but participants with known HIV infection enrolled in the United States will be excluded.
9. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. Participants with screening QTc interval > 470 milliseconds for males and > 480 milliseconds for females (corrected by Fridericia) are excluded. In the event that a single QTcF is > 470 milliseconds for males or > 480 milliseconds for females, the participant may enroll if the average QTcF for 3 ECGs is < 470 milliseconds for males or < 480 milliseconds for females.
10. Use of the following medications:
    a. Treatment with rituximab within 3 months of the baseline visit.
    b. Use of immunosuppressive therapy within 28 days of the baseline visit. Immunosuppressive therapy includes, but is not limited to, cyclosporine A, tacrolimus, or high-dose corticosteroids. Participants receiving corticosteroids must be at a dose level ≤ 20 mg/day (prednisone or equivalent corticosteroid dose) within 14 days of the baseline visit.
    c. Chronic or current active infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment or exposure to a live vaccine within 28 days of the baseline visit.
    d. Use or expected use during the study of any prohibited medications, including potent CYP3A4 inhibitors or inducers within 14 days or 5 half-lives (whichever is longer) before the baseline visit.
    e. Current treatment or treatment within 30 days or 5 half-lives (whichever is longer) before the baseline visit with another investigational medication, or current enrollment in another investigational drug protocol.
    f. Use of any prohibited medications (see Section 6.7.3) within 14 days or 5 half-lives (whichever is longer) before the baseline visit.
11. Known hypersensitivity or severe reaction to INCB050465 or its excipients (IB).
12. 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.
13. Current alcohol or drug use that, in the opinion of the investigator, will interfere with the participant's ability to comply with the dose regimen and study evaluations.

14. Participants who, in the opinion of the investigator, are unable or unlikely to comply with the dose regimen and study evaluations.
15. 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 participant; or interfere with interpretation of study data.

5.3. Lifestyle Considerations

Not applicable.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Participants may be rescreened for the study if there is a change in their medical status that would affect their eligibility such as discontinuation of a prohibited medication or short intercurrent illness that has resolved. Clinical laboratory abnormalities detected at screening may be repeated as part of screening and should not be considered criteria for re-screening.

5.5. Replacement of Participants

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

6. STUDY TREATMENT

6.1. Study Treatment Administered

The study will use an IRT system for management of study enrollment. The system will assign the participant study number, track participant visits, and manage of study drug inventory. See Table 3 for study drug information.

Extension Period:

Participants will be dispensed the appropriate amount of study drug until their next scheduled visit. Participants will continue to self-administer INCB050465 per the investigator's instruction with study drug compliance continuing to be assessed.

Table 3: Study Drug Information

Study Drug Name:	INCB050465
Dosage Formulation:	Tablet
Unit Dose Strength(s)/Dosage Level(s):	1 mg and 2.5 mg
Route of Administration:	Oral
Administration Instructions:	1 tablet QD. INCB050465 will be taken orally with water without regard to food except on mornings of PK clinic visits (see Table 1 and Table 6). Participants should not take their dose at home when they have a PK visit. INCB050465 should be taken at approximately the same time each day.
Packaging and Labeling:	INCB050465 will be provided as 1 mg and 2.5 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.
Storage:	Bottles of INCB050465 should be stored at ambient conditions (15°C-30°C or 59°F-86°F).

6.2. Instruction to Participants for Handling Study Drug

Participants must be instructed in the handling of INCB050465 as follows:

- Store study drug at room temperature (15°C-30°C or 59°F-86°F).
- Only remove the number of tablets needed from the study drug bottle at the time of administration.
- Do not remove doses in advance of the next scheduled administration.
- Make every effort to take doses on schedule.
- Report any missed doses.
- Keep study drug in a safe place and out of reach of children.
- Bring all used and unused study drug bottles to the site at each visit.

6.3. Preparation, Handling, and Accountability

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.
- Participant use of the study drug, including pill or unit counts from each supply dispensed.
- Return of study drug to the investigator or designee by participants.

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

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's standard operating procedure.

6.4. Measures to Minimize Bias: Randomization and Blinding

Not applicable.

6.5. Study Treatment Compliance

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

6.6. Dose Modifications

6.6.1. Criteria and Procedures for Dose Increases of Study Drug

At Week 6, participants may be eligible for a dose increase. Due to the need to receive clinical laboratory results and to consult with the sponsor as needed prior to increasing the dose, investigators may implement the dose increase either at an unscheduled drug dispensing visit between the Week 6 and Week 8 visits or at the scheduled Week 8 visit. Any other requests for dose increase at alternate times may be considered on an individual basis in consultation with the sponsor. Individual participants in Cohort 1 may increase from INCB050465 1 mg QD to 2.5 mg QD with sponsor preapproval in the following circumstances, provided that protocol eligibility criteria are met at the time of escalation:

- Dose increase criteria, defined as the following:
  - The participant continues to require transfusions by the Week 6 visit or
  - The participant does not attain a meaningful clinical response (at least a stabilization ≥ 2 g/dL increase in hemoglobin from baseline to Week 6).
- The investigator determines there has not been a clinically meaningful response in hemoglobin and other hemolysis parameters.
- The participant is otherwise tolerating the current dose and has not had any drug-related adverse events.
- In the opinion of the investigator, the participant does not have a concurrent condition or circumstance that would complicate the dose escalation or PK sampling, or pose an increased risk.

6.6.2. Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug

Individual decisions regarding dose interruptions and reductions 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 participant's underlying condition.

In all cases, investigators may employ any measures or concomitant medications, after discussion with the sponsor (whenever possible), necessary to optimally treat the participant.

Adverse events that have a clear alternative explanation or transient (≤ 72 hours) or abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose reduction guidelines. If there are any tolerability issues in individual participants who received 2.5 mg in Cohort 1, the dose may be decreased to 1 mg. For Cohort 2, dose reduction from 2.5 mg QD to 1 mg QD may occur if there are SAEs or AEs that are attributed to be related to INCB050465 (see Table 4 for the guidelines). Dose reduction may occur at any time during the 12 weeks of administration; however, consultation between the investigator and sponsor should occur if dose reduction is being considered for any participant.

Table 4: Guidelines for Interruption and Restarting of Study Drug

ADVERSE EVENT	ACTION TAKEN
Chemistry	
AST and/or ALT is > 3.0 × ULN.	**Step 1:** Interrupt study drug up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1 except by approval of the medical monitor. **Step 2:** Restart study drug at same dose. If assessed as related to study drug, restart study drug at 1 mg if receiving 2.5 mg and monitor as clinically indicated.
Hematology	
• ANC ≤ 1.0 × 10^9/L, unless due to underlying disease. • Platelet count is 50 × 10^9/L to < 75 × 10^9/L, unless due to underlying disease.	**Step 1:** Interrupt study drug up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1 or pretherapy baseline. **Step 2:** Restart study drug at same dose and monitor as clinically indicated.
• Grade 4 ANC (< 0.5 × 10^9/L). • ≥ Grade 3 ANC with an oral temperature of at least 38.5°C OR with ≥ Grade 3 infection. • Platelet count is < 50 × 10^9/L.	Discontinue study drug administration and follow-up per Protocol. (Exceptions require approval of sponsor.)
Other toxicities	
Any Grade 1 or Grade 2 toxicity.	Continue study drug administration and treat the toxicity; monitor as clinically indicated.
Any Grade 3 toxicity, if clinically significant and not manageable by supportive care.	**Step 1:** Interrupt study drug up to 2 weeks (14 days), until toxicity resolves to ≤ Grade 1. **Step 2:** Restart study drug at same dose. If assessed as related to study drug, restart study drug at 1 mg if receiving 2.5 mg and monitor as clinically indicated.
Any recurrent Grade 3 toxicity after dose reduction.	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.

6.6.3. Criteria for Permanent Discontinuation of Study Drug

The occurrence of unacceptable toxicity not caused by the underlying disease will be presumed to be related to study drug treatment and will require that the study drug be permanently discontinued. Unacceptable toxicity is 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 participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.

6.7. Concomitant Medications and Procedures

All concomitant medications and treatments must be recorded in the eCRF. Any prior medication received up to 30 days before the baseline visit will be recorded in the eCRF.

Concomitant treatments and/or procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF.

6.7.1. Permitted Medications and Procedures

6.7.1.1. *Pneumocystis jirovecii* Pneumonia Prophylaxis

All participants will receive a PJP prophylaxis regimen determined by the investigator. Examples of standard PJP prophylaxis therapies include trimethoprim-sulfamethoxazole, atovaquone, dapsone with or without pyrimethamine, and pentamidine (National Comprehensive Cancer Network 2017). Due to reports of cross-sensitivity between sulfonamides and dapsone, all participants who have a known or suspected allergy to sulfonamides must receive either inhaled pentamidine or atovaquone for PJP prophylaxis. If inhaled pentamidine or atovaquone are not available, the participants should not be enrolled. Prophylaxis should be given while participants are receiving study drug and should continue for at least 2 to 6 months after the last dose of study drug.

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

6.7.1.2. Folic Acid, Vitamin B12, or Iron Deficiencies

Participants who are noted to be deficient in folic acid, vitamin B12, or iron should have replacement determined by the investigator as per current standard of care.

6.7.2. Restricted Medications and Procedures

Restricted medications and procedures include the following:

- Use of systemic corticosteroid doses ≤ 20 mg/day prednisone (or equivalent) is permitted from the 14 days before the baseline visit through the EOT visit. Prednisone (or equivalent) should remain stable and may be tapered if the investigator considers it appropriate based on the participant's clinical response.
- Short courses of systemic corticosteroid doses > 20 mg/day prednisone (or equivalent) are permitted (eg, for the treatment of severe or life-threatening AEs) but are otherwise discouraged from the screening visit through the EOT visit.
- Use of weak or moderate inducers or inhibitors of CYP3A4 or P-glycoprotein is discouraged, and investigators should seek other options where possible.

6.7.3. Prohibited Medications and Procedures

Prohibited medications and procedures include the following:

- Use of potent inducers and inhibitors of CYP3A4 is prohibited, with the exception of topical ketoconazole because of its low bioavailability.

- Apart from the study treatments, the use of any medications as described in the exclusion criteria (see Section 5.2) through the safety follow-up is prohibited.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

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

7.1.1. Permanent Discontinuation of Study Treatment

Participants **must** be withdrawn from study drug for the following reasons:

- The participant becomes pregnant.
- Consent is withdrawn.

  Note: Consent withdrawn means that the participant can no longer be followed. Participants may choose to discontinue study drug and remain in the study to be followed.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

A participant **may** be discontinued from study drug as follows:

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

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study drug, the EOT visit should be conducted. Reasonable efforts should be made to have the participant return for follow-up visits. These visits are described in Table 1. The last date of the last dose of study drug and the reason for discontinuation of study drug will be recorded in the eCRF.

If a participant is discontinued from study drug:

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

If the participant discontinues study drug and actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), then no additional data collection should occur; however, participants will have the option of withdrawing consent for study drug but continuing in the follow-up period of the study for safety/efficacy assessments (see Section 8.9).

7.2. Participant Withdrawal From the Study

A participant may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If a participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he or she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

See Table 1 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address

or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

Participants transitioning into the extension period of the study will have efficacy and safety assessments performed in accordance with the standard of care at each investigational site for the participant's condition and monitoring at the investigator's discretion and not less than every 8 to 12 weeks (see Table 2). Unless noted below, procedures listed in this section are not required to be performed in the extension period of the study.

8.1.1. Administration of Informed Consent Form

Valid informed consent must be obtained from the study participant 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 participant. 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 participant. The informed consent process for each participant must be documented in writing within the source documentation.

8.1.2. Screening Procedures

Screening is the interval between the signing of the ICF and the day that the participant is administrated the first dose of study drug (Day 1). Informed consent must be obtained before performing any study specific procedures. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

All information associated with eligibility requirements must be entered into the appropriate eCRF pages.

Results from the screening visit evaluations will be reviewed to confirm 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 treatment will be used to determine eligibility and entered into the eCRF. Treatment should start as soon as possible. Additionally, a participant who fails screening may repeat the screening process if the investigator believes there has been a change in eligibility status (eg, after recovery from an infection).

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of the site ID and participant number. Site staff should contact IRT to obtain the participant ID number during screening. IRT will be contacted at each regular study visit to update the study drug supply. Additional details are provided in the IRT Manual.

8.1.4. Demography and Medical History

8.1.4.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening.

8.1.4.2. Disease Characteristics and Treatment History

A disease-targeted medical and medication history, including date of diagnosis of AIHA, serological test, rituximab treatment history and other details related to the disease under study, will be collected at screening.

8.1.5. Prior and Concomitant Medications and Procedures

Prior and concomitant medications and procedures will be reviewed to determine participant eligibility. All concomitant medications and measures must be recorded in the eCRF, and any medication received or procedure performed within screening period before enrollment and up to the end of the follow-up period (see Table 1) 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 participant's medical condition during the study will also be recorded in the eCRF.

Extension Period

Use of concomitant medications should be monitored as described in Table 2 for participants in the extension period of the study to verify that participants are not taking any concomitant medication prohibited per Section 6.7.3.

8.2. Efficacy Assessments

Efficacy assessments are conducted at the visits noted in Table 1.

8.2.1. Hemoglobin Level, Hemolysis Markers, Direct Antiglobulin Test, and Complement Assessment

Participants will undergo hematology, serum chemistries, hemolysis markers, DAT, and complement assessment (CH50, C3, and C4) to evaluate type of AIHA diagnosis and disease status (see Table 5).

Note: For the purpose of participants' enrollment eligibility and safety and efficacy assessments, blood samples for hematology panels, including CBC and differential count, will sent to a local laboratory for analysis (see Table 5). All other Protocol-required blood samples aside from hematology panels will be sent to the central laboratory for analysis. Local laboratory

hematology panel results and central laboratory results for all other assessments will be entered into the eCRF.

8.2.2. Direct Antiglobulin Test and Cold Agglutinin Test

Direct antiglobulin tests for the detection of IgG and complement bound to RBCs will be performed at a central laboratory or local laboratory at screening visit (see Table 1 and Section 5.1). If DAT was performed within 28 days before screening at the study site, the participant does not need to retest DAT at the screening visit. However, if DAT was performed greater than 28 days before screening or performed in a location other than the study site, the sponsor will review and make a recommendation if retesting DAT is required.

[redacted]

8.3. Safety Assessments

Safety assessments are conducted at the visits noted in Table 1 and Table 2.

Extension Period

Adverse events leading to treatment discontinuation, all AEs suspected to be TEAEs and all SAEs regardless of causality relationship will be reported on the AE eCRF during the extension period.

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF. Participants 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, participants 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 9.

8.3.2. Physical Examinations

Abnormalities that are considered clinical 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.

8.3.2.1. Comprehensive Physical Examination

At screening, Day 1, and EOS, a comprehensive physical examination should be conducted. The comprehensive physical examination will include assessment(s) of the following organ or body

systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes; as well as a brief neurological examination. Height and body weight will be assessed only at the Day 1 visit.

8.3.2.2. Targeted Physical Examination

At all other study visits except at screening, Day 1, and EOS, the targeted physical examination will be a symptom-directed evaluation. The targeted physical examination will include assessment(s) of the body systems or organs, as indicated by participant symptoms, AEs, or other findings.

8.3.3. Vital Signs

Vital sign measurements include blood pressure, pulse, respiratory rate, and body temperature. Blood pressure and pulse will be taken with the participant 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.

8.3.4. Electrocardiograms

All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after 5 minutes of rest. The 12-lead ECGs will be performed locally and be interpreted by the investigator at the site and used for immediate participant management. Interpretation of the 12-lead ECG will be used to determine eligibility at screening. An additional ECG will be performed at Week 2, Week 8, and the EOT visit (Week 12) or earlier, if the participant discontinues treatment). Throughout the study, a 12-lead ECG may be conducted if associated with an AE or other signs or symptoms. The decision to include or exclude a participant or discontinue his or her 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. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

8.3.5. Laboratory Assessments

Blood draws for laboratory assessments will occur at study visits indicated in the schedule of assessments (see Table 1). Specific laboratory assessments are provided in Table 5. Blood may be drawn in pediatric tubes to minimize blood loss from phlebotomy.

All laboratory assessments will be performed at a central laboratory, with the exception of the following, in which case the investigative site laboratory or an accredited local laboratory may be used:

- Hematology panels (see Table 5), including CBC and differential count, will be sent to a local laboratory for analysis (see Section 8.2.1).
- For local laboratory assessments deemed necessary by the investigator for participant management (ie, dose modification, SAE, or COVID-19 restrictions affecting travel to the site for extension visits). Note: Such assessment data and reference ranges must be recorded in the participant's eCRF.

Extension Period:

Laboratory assessments (see Table 5) including hematology panels and hemolysis markers need to be performed in accordance with standard of care at each investigational site for the participant's condition and monitoring at the investigator's discretion and not less than every 8 to 12 weeks. Any other clinical lab monitoring should be done per the investigator's judgment for monitoring any other clinical conditions. Laboratory results will need to be documented in the eCRF.

8.3.5.1. Chemistry and Hematology

All chemistry assessments (see Table 1 and Table 5) will be performed from blood samples collected using institutional best practices (refer to the Laboratory Manual). Hematology panels will be analyzed by local laboratories.

8.3.5.2. Vitamin B12 and Folic Acid

Vitamin B12 and folic acid will be tested at screening. Participants who are deficient in either folic acid or vitamin B12 will have replacement determined by the investigator as per standard of care.

8.3.5.3. Iron Clinical Assessment

All participants will have iron assessments (iron, total iron-binding capacity, ferritin) at screening. If elevated ferritin levels are present (> 200 ng/mL in women or > 250 ng/mL in men), additional testing and follow-up recommendations will be provided to the investigator in consultation with the medical monitor. These recommendations will include evaluation of the liver (serum transaminases and MRI) and for other causes of iron overload as indicated by the participant's medical history.

Iron assessments will be repeated during the study at Week 6 if the participant has ongoing transfusion requirements during the study.

8.3.5.4. Urinalysis

Urinalysis will be performed by a central laboratory at screening and EOT or if the participant discontinues treatment (see Table 1 and Table 5).

8.3.5.5. Coagulation

A D-dimer assessment (see Table 5) will be performed from blood samples collected using institutional best practices (refer to the Laboratory Manual).

8.3.5.6. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during screening. Urine pregnancy tests will be conducted as outlined in Table 1, as medically indicated, or per country-specific requirement. Urine pregnancy tests will be done locally. If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test, which may be performed locally.

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

8.3.5.7. Serology

Anti-Streptolysin antibody, anti-phospholipid antibody, hepatitis, and HIV tests will be performed at a central laboratory (see Table 1). Hepatitis and HIV tests will be conducted during the screening period. If participants are positive for active disease, they should not be enrolled per exclusion criteria. Note: HIV screening test is optional for participants enrolled in the United States, but participants with known HIV infection enrolled in the United States will be excluded.

Table 5: Required Laboratory Analytes

<table>
<tr><th>Serum Chemistries</th><th>Hematology[a,b]</th><th>Urinalysis With Microscopic Examination</th><th>Screening Serology</th><th>Coagulation</th></tr>
<tr><td rowspan="20">Albumin
Alkaline phosphatase
ALT
AST
Bicarbonate
Blood urea nitrogen
Calcium
Chloride
Creatinine
Ferritin (screening visit and repeat at Week 6 if participant has ongoing transfusion requirements)
Folic acid (screening visit)
Glucose
Haptoglobin
Iron (screening visit and repeat at Week 6 if participant has ongoing transfusion requirements)
LDH
Phosphate
Potassium
Sodium
Total bilirubin[c]
Total protein
Total iron-binding capacity (screening visit and repeat at Week 6 if participant has ongoing transfusion requirements)
Uric acid</td><td rowspan="20">CBC, including:
• Hemoglobin
• Hematocrit
• Platelet count
• RBC count
• WBC count

Differential count, including:
• Basophils
• Eosinophils
• Lymphocytes
• Monocytes
• Neutrophils

Absolute values must be provided for WBC differential laboratory results:
• Lymphocytes
• Neutrophils</td><td>Color and appearance
pH and specific gravity
Bilirubin
Glucose
Ketones
Leukocytes
Nitrite
Occult blood
Protein
Urobilinogen</td><td rowspan="2">Hepatitis B surface antigen
Hepatitis B surface antibody
Hepatitis B core antibody
Hepatitis C virus antibody
Hepatitis C virus-RNA (only performed if antibody positive)
HIV antibody
Anti-streptolysin antibody
Anti-phospholipid antibody</td><td rowspan="2">D-Dimer</td></tr>
<tr><td>Hemolysis Markers[b]</td></tr>
<tr><td colspan="3">Haptoglobin (will be measured in serum chemistry panel)
LDH (will be measured in serum chemistry panel)
Reticulocyte count (will be measured in hematology panel)
Hemoglobin (will be measured in hematology panel)
Total bilirubin[c] (will be measured in serum chemistry panel)</td></tr>
<tr><td colspan="3">DAT and Cold Agglutinin Test</td></tr>
<tr><td colspan="3">DAT for IgG and C3d*
Cold agglutinin levels*
* Baseline and EOT</td></tr>
<tr><td colspan="3">Other Assessments</td></tr>
<tr><td colspan="3">Urinalysis
FSH
Urine pregnancy test (at site)
Serum pregnancy test
Complement assessment (CH50, C3, and C4)*
* Baseline and EOT
Vitamin B12 (screening visit)</td></tr>
</table>

Note: Additional tests may be required, as agreed upon by the investigator and sponsor, based on emerging safety data.

[a] Hematology parameters will be managed in real-time by local laboratory assessments.

[b] Hematology panels and hemolysis markers need to be performed in accordance with the standard of care at each investigational site for the participant's condition and monitoring at the investigator's discretion.

[c] If total bilirubin is elevated above ULN, direct/indirect bilirubin will be measured.

8.4. Pharmacokinetic Assessments

8.4.1. Blood Sample Collection

Pharmacokinetic samples will be obtained at the visits and collection times shown (see Table 6) for all participants receiving INCB050465.

The exact date and time of the PK blood draws, the date and time of the last dose of study drug preceding the blood draw (if applicable), and the time of the previous meal will be recorded in the eCRF.

Instructions for sample preparation and shipping will be provided in the Laboratory Manual. Participants will receive reminder cards in advance of the study visit providing instruction to hold the dose of study drug on the day of the visit and a place to record the time of the prior dose of study drug and time of the most recent meal or snack consumed.

Pharmacokinetic sampling will occur on 4 separate days. If the PK plasma sample collection is missed for a visit, then the sample collection should be performed at the next visit. On the PK visit days, participants must refrain from taking study drug before arriving at the research unit. Participants should not have consumed any food within 4 hours before arriving at the research unit. A predose (trough) PK sample should be collected at each of the PK visits. Following collection of the predose PK sample, INCB050465 will be administered, and subsequent timed samples will be collected (see Table 6). The participants may have a light meal following the 1 hour postdose PK sampling at Weeks 2 and 8.

Table 6: Sample Collection Time Windows for Pharmacokinetic Assessments for INCB050465

	Timing of Sample Relative to Study Drug			
Study Visit	**Predose**	**1 h ± 10 min**	**2 h ± 10 min**	**4 h ± 30 min**
Week 1	X			
Week 2[a]	X	X	X	X
Week 8[a]	X	X	X	X
Week 12	X			

Note: In case of dose interruption, the new timing of PK sampling should be discussed with sponsor.
[a] No food intake 4 hours predose and 1 hour postdose on Weeks 2 and 8. The participants may have a light meal following the 1 hour postdose PK sampling at Weeks 2 and 8.

[redacted]

8.6. 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.

8.7. End of Treatment

When the participant permanently discontinues study drug, then the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The participant should be encouraged to return for the safety follow-up visits.

8.8. Extension Period

In the extension period of the study, participants will be required to visit the clinic per standard of care but no less frequently than every 8 to 12 weeks for dispensing of study drug (see Table 2). Safety assessments (including laboratory analytes) that are consistent with the standard of care for the participant's condition should be performed per the investigator's discretion using a local laboratory (see Section 8.3.5). All SAEs, AEs leading to treatment discontinuation, and TEAEs will continue to be collected by the sponsor. Disease status will continue to be monitored by laboratory tests including hematology panels and hemolysis markers as appropriate at a frequency consistent with the standard of care for the participant's disease.

8.9. Follow-Up

8.9.1. Safety Follow-Up

For participants who do not enter extension period, the safety follow-up period is the interval between the EOT visit (Week 12) and the scheduled follow-up visits, 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 visits, or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant return for the follow-up visits and report any AEs that may occur during this period. If the participant cannot return to the site for the safety follow-up visits, the participant should be contacted by telephone for assessment of AEs and SAEs. Sites should be instructed to document this contact in the source.

8.9.2. Additional Follow-Up Period

Participants will have additional follow-up assessments for 12 weeks (3 months) after EOT. Safety follow-up is included in this 12-week (3 months) additional follow-up period. The following information will be collected:

- The start date of new AIHA therapy.
- Type of therapy.
- Marker for hemolysis.

If the participant withdraws consent for study drug but continues in the follow-up period of the study, the above information will also be collected.

The site will also use continuing participant records to supply data on subsequent treatment regimens and disease activities in the eCRF.

For participants who receive study drug in the extension period, the safety follow-up is included in the 12-week (3-month) additional follow-up period and should occur 30 to 35 days after the last dose of study drug.

9. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

9.1. Adverse Events

9.1.1. Definitions

For the purposes of this Protocol, an 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 participant 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, or require changes in the study drug.

Anemia and transfusions should not be reported as AEs unless it represents a clinically meaningful decrease from baseline in hemoglobin.

9.1.2. 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. 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 9.3.2. 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 v5.0 Grades 1 through 4. The CTCAE v5.0 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 participant 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 participant 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 drug: 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 SAE definition provided in Section 9.3.1.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements (see Section 9.3.2).

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 participant 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.

9.2. Laboratory Test Abnormalities

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

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 AE does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 9.3.1. A dose modification for the laboratory abnormality may be required (see Section 6.6) and should not contribute to the designation of a laboratory test abnormality as an SAE.

9.3. Serious Adverse Events

9.3.1. 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 participant'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 participant or may require medical or surgical intervention to prevent 1 of the outcomes listed above.

9.3.2. Reporting

Every SAE, regardless of suspected causality (eg, relationship to study drug(s) or study procedure or disease progression), occurring after the participant 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 drug. 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 drug: 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 participant 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 IN to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions 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.

9.4. 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 participant during maternal or paternal exposure to study drug, the following procedures should be followed in order to ensure participant safety:

- The study drug must be discontinued immediately.
- 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.

9.5. 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 IB. Additional safety information collected between IB updates will be communicated in the form of INs. Any important new safety information should be discussed with the participant during the study, as necessary. If new significant risks are identified, they will be added to the ICF and participants will resign the ICF.

9.6. Data Monitoring Committee

There will be no formal Data Monitoring Committee. However, a Safety Review Committee, which will include the sponsor's medical monitor, pharmacovigilance representative, and statistician, as well as the investigators, will conduct meetings via teleconference on a regular basis to review emerging safety and clinical response data and dose modifications. Recommendations from this committee may include the option to expand study of Cohort 1, pending review of the efficacy response and adverse event data.

If there is no clinical response (CR or PR) by Week 12 in the first cohort of 10 participants, including those who receive dose escalation to 2.5 mg, the study will be stopped for futility.

9.7. 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 or 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 9.1.2 of this Protocol.

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

10. STATISTICS

10.1. Sample Size Determination

The sample size was based on the precedent of other studies and was not based on statistical power calculations (Go et al 2017, Hill et al 2017, Lechner and Jäger 2010). The study is not powered for statistical comparison of efficacy endpoints; the sample size is based on the demonstration of preliminary findings of clinical response. It is anticipated that a sample size of approximately 25 participants will permit sufficient data to warrant further investigation. Also, the sample size depends on the occurrence of safety findings. Approximately 10 participants will be enrolled in Cohort 1, and approximately 15 in Cohort 2, which will provide > 89% chance of detecting at least 1 AE of interest (eg, colitis, exfoliative dermatitis, infections) if the underlying AE rate is 20% for Cohort 1 and > 96% chance for Cohort 2.

10.2. Populations for Analysis

Full Analysis Set: All participants enrolled in the study who receive at least 1 dose of study drug. The FAS will be used for the summary of demographics, baseline characteristics, participant disposition, and analyses of all efficacy and safety data.

Pharmacokinetic/Pharmacodynamic Evaluable: All participants who receive at least 1 dose of study drug and provide at least 1 postdose blood sample for PK or biomarker assessment. The study pharmacokineticist will review data listings of participant administration and sample records to identify participants to be excluded from the analysis.

10.3. Level of Significance

No formal efficacy hypotheses will be tested.

10.4. Statistical Analyses

Both efficacy and safety analyses will be conducted using the FAS. The baseline value for a variable will be defined as the last nonmissing value for this variable before or on Day 1, unless otherwise specified.

10.4.1. Efficacy Analyses

10.4.1.1. Primary Efficacy Analyses

Efficacy assessments of primary endpoint will be summarized using descriptive statistics at each visit. For categorical measurements, summary statistics will include sample size, frequency, and percentages. For continuous measurements, summary statistics will include sample size, mean, median, standard deviation, standard error of the mean, minimum, and maximum. Summary statistics for continuous measures will be provided for baseline, the actual measurements at each visit, and the change and percentage change from baseline at each visit, if applicable. All analyses will be implemented using SAS® software (SAS Institute Inc., Cary, NC; v9.1 or higher).

10.4.1.2. Secondary Efficacy Analyses

The secondary endpoints will be analyzed using the similar method as specified in the primary analysis.

10.4.1.3. Other Efficacy Analyses

The other efficacy endpoints will be summarized using descriptive statistics.

10.4.2. Safety Analyses

10.4.2.1. Adverse Events

A treatment-emergent adverse event 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 v5.0 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, the AE will be considered treatment-related. The incidence of AEs and treatment-related AEs will be tabulated.

10.4.2.2. Clinical Laboratory Tests

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

10.4.2.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time.

10.4.2.4. Electrocardiograms

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time.

10.4.3. Pharmacokinetic Analysis

The PK parameters of C_{max}, t_{max}, C_{min}, AUC_{0-t}, and CL/F (INCB050465) will be calculated from the blood plasma concentrations of INCB050465 using standard noncompartmental (model-independent) PK methods. Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as WinNonlin®. Nominal times will be used in all cases, except when the difference between the actual time and nominal time is greater than 10 minutes for samples collected up to 4 hours after administration and greater than 30 minutes for samples collected more than 4 hours after administration; in these cases, actual time will be used for PK analysis. Refer to Section 8.4 for a detailed list and description of the PK parameters.

If there is a sufficient amount of plasma concentration data from this study, the data will be analyzed by standard population PK methods using appropriate software (eg, NONMEM).

[redacted]

10.5. Interim Analysis

Not applicable.

10.6. Analyses for the Data Monitoring Committee

Not applicable.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. 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 participant 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 participants.
  - 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 participants' questions have been answered and the participants 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 participant. 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 participant 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 participants 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.

11.2. Data Management

Data management will be performed in a validated database via an 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 participant. 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 participant'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.

11.3. 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.

Participant names will not be supplied to the sponsor or its designee, if applicable. Only the participant number and participant's initials (participant's initials will only be recorded if allowable by local regulations) will be recorded in the eCRF, where permitted; if the participant'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 participants 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.

11.4. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies subject to FDA Regulation Title 21 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 participants, 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.

11.5. 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 Participants 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]
- Vasectomized partner[2,3]
- Sexual abstinence[4]

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide[5]
- cap, diaphragm or sponge with spermicide[5]
- tubal ligation

[1] Hormonal contraception may be susceptible to interaction with the study drug, 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] Vasectomized partner is a highly effective method provided of avoiding pregnancy that partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized 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 participant.
[5] A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.
Source: Clinical Trial Facilitation Group 2014.

APPENDIX B. FACIT FATIGUE SUB-SCALE (VERSION 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

APPENDIX C. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS 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.

APPENDIX D. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	11 JAN 2018
Amendment (Version) 1-FRA:	23 MAY 2018
Amendment (Version) 2:	20 JUN 2018
Amendment (Version) 3:	01 FEB 2019
Amendment (Version) 4:	31 OCT 2019
Amendment (Version) 5:	02 NOV 2020

Amendment 5 (02 NOV 2020)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to allow participants in the open-label extension period to continue receiving treatment until the drug is available through another clinical study, or is commercially available, or the sponsor stops the study or the study drug development. In addition, due to the impact of the COVID-19 pandemic on study enrollment, and the rare occurrence of patients with CAD, Cohort 2 will change the enrollment of CAD AIHA to approximately 5 CAD AIHA participants.

1. **Section 1, Protocol Summary (Treatment Groups and Duration); Section 4.1, Overall Design; Section 4.2, Overall Study Duration**

   Description of change: Extended the extension period to allow participants receiving benefit from study drug to continue receiving INCB050465 until the drug is available through another clinical study, or is commercially available, or the sponsor stops the study or the study drug development.

   Rationale for change: To allow participants with limited treatment options to continue receiving treatment until the drug is available through another clinical study, or is commercially available, or the sponsor stops the study or the study drug development.

2. **Section 1, Protocol Summary (Figure 1: Study Design Schema footnote); Section 2.6, Study Rationale; Section 4.1, Overall Design**

   Description of change: Changed the number of CAD participants from "at least" 5 CAD AIHA to approximately 5 CAD AIHA participants.

   Rationale for change: Approximately 20% of all patients with AIHA have CAD, and this will allow completion of enrollment while maintaining the representative mix of type for patients with AIHA.

3. **Section 5.3, Lifestyle Considerations**

   Description of change: Removed instruction to avoid excess sun exposure.

   Rationale for change: Parsaclisib is not phototoxic.

4. **Section 8.3.5, Laboratory Assessments; Section 8.8, Extension Period**

   Description of change: Specified that laboratory assessments may be conducted at a local laboratory due to COVID-19 restrictions affecting travel to the site for extension visits.

   Rationale for change: To facilitate remote safety assessments during the pandemic.

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

Amendment 4 (31 OCT 2019)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to increase the number of participants in Cohort 2 (from 10 to approximately 15) and change the proportion of CAD and warm AIHA patients. These changes are based on the recommendations from the internal Safety Review Committee meeting (18 SEP 2019).

1. **Section 1, Protocol Summary (Overall Design table; Figure 1: Study Design Schema); Section 2.6, Study Rationale; Section 4.1, Overall Design; Section 4.2, Overall Study Duration; Section 10.1, Sample Size Determination**

   Description of change: Increased the number of participants in Cohort 2 (from 10 to approximately 15) and changed the proportion of CAD and warm AIHA patients (at least 5 CAD AIHA and up to 8 wAIHA participants; the remainder can be wAIHA, CAD, or mixed-type AIHA).

   Rationale for change: To confirm clinical response signal with a slightly larger patient population and allow a better evaluation of the CAD AIHA subpopulation.

2. **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 (01 FEB 2019)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to add an extension period for participants who are receiving clinical benefit from the study treatment and to provide guidance for hematology panel collection.

1. **Section 1, Protocol Summary (Figure 1, Study Design Schema and Table 2, Schedule of Assessments for the Extension Period); Section 4.1, Overall Design; Section 6.1, Study Treatment Administered; Section 8.1, Administrative and General Procedures; Section 8.1.5, Prior and Concomitant Medications and Procedures; Section 8.3, Safety Assessments; Section 8.3.5, Laboratory Assessments; Section 8.8, Extension Period; Section 8.9, Follow-Up**

   Description of change: Added an extension period for participants who are receiving clinical benefit from the study treatment per the investigator's discretion up to the time all enrolled participants complete the study.

   Rationale for change: To continue to provide study treatment to participants who are receiving clinical benefit.

3. **Section 2.8.1, Potential Risks of INCB050465 Based on Preclinical Safety**

   Description of change: Added 3- and 9-month preclinical toxicity results in rats and in dogs.

   Rationale for change: To support adding an extension period for participants who are receiving clinical benefit from study treatment.

4. **Section 5.2, Exclusion Criteria; Section 6.7.2, Restricted Medications and Procedures; Section 6.7.3, Prohibited Medications and Procedures; Appendix B, Cytochrome P450 3A4 and P-Glycoprotein Inhibitors and Cytochrome P450 3A4 Inducers**

   Description of change: Deleted CYP lists and corresponding references to the CYP lists.

   Rationale for change: No longer providing CYP lists in protocols.

5. **Section 5.1, Inclusion Criteria; Section 5.2, Exclusion Criteria; Section 8.2.1, Hemoglobin Level, Hemolysis Markers, Direct Antiglobulin Test, and Complement Assessment; Section 8.3.5, Laboratory Assessments (Table 5, Required Laboratory Analytes)**

   Description of change: Clarified that blood samples for hematology panels, including CBC and differential count, will be sent to a local laboratory for analysis.

   Rationale for change: To provide real-time management of participants' enrollment eligibility and safety and efficacy assessments.

6. **Section 6.6.1, Criteria and Procedures for Dose Increases of Study Drug**

   Description of change: Added unscheduled drug dispensing visit between the Week 6 and Week 8 visits or at the regularly scheduled Week 8 visit for participants who may be eligible for a dose increase.

   Rationale for change: To allow for clinical laboratory assessments and consultation with the sponsor as needed prior to increasing the dose.

7. **Section 5.2, Exclusion Criteria**

   Description of change: In exclusion criterion #7, clarified that participants with positive results for hepatitis B surface antigen or hepatitis B core antibody will be eligible if they are negative for HBV-DNA and that these participants should be considered for prophylactic antiviral therapy. Participants who are positive for the anti-HCV antibody will be eligible if they are negative for HCV-RNA.

   Rationale for change: Participants who were previously infected with HBV or who have received the HBV vaccine can test positive for the hepatitis B surface antigen or hepatitis B core antibody. The exclusion criterion was revised to allow participants who were previously infected with HBV or who have received the HBV vaccine to enroll in the study. The study will only exclude current active infection or chronic infection of participants with HBV.

8. **Section 9.1.2, Reporting; Section 10.4.2.1, Adverse Events**

   Description of change: Updated CTCAE version from v4.03 to v5.0.

   Rationale for change: To align with the most recent version of CTCAE.

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 (20 JUN 2018)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to clarify that the AIHA population enrolled in this study does not include treatment-naive participants and to provide further information on sample size determination.

1. **Section 5.1, Inclusion Criteria**

   Description of change: Removed participants who refuse standard treatment.

   Rationale for change: To address the request of the France Competent Authority to remove treatment-naive participants.

2. **Section 5.1, Inclusion Criteria**

   Description of change: New inclusion criterion #9 was added to indicate that participants should be willing to receive PJP prophylaxis.

   Rationale for change: All participants in this study are required to receive PJP prophylaxis. If a participant is not willing to receive PJP prophylaxis or if PJP prophylaxis regimens are not available at a study site, the participant should not be enrolled.

3. **Section 8.2.2, Direct Antiglobulin Test and Cold Agglutinin Test**

   Description of change: Language was added to allow participants for whom DAT was performed within 28 days before screening at the study site not to retest DAT at the screening visit.

   Rationale for change: Direct antiglobulin test is a diagnostic test for AIHA. It does not tend to have significant fluctuation week to week. This study allows a previous DAT result to be used as a screening value if it was performed within 28 days before screening.

4. **Section 10.1, Sample Size Determination**

   Description of change: Language was added to further address that current sample size will permit sufficient data to warrant further investigation.

   Rationale for change: To address the request of the Italy Coordinating Ethics Committee to further clarify sample size determination.

5. **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-FRA (23 MAY 2018)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to clarify that the AIHA population enrolled in this study does not include treatment-naive participants.

1. **Section 5.1, Inclusion Criteria**

   Description of change: Removed participants who refuse standard treatment.

   Rationale for change: To address the request of the France Competent Authority to remove treatment-naive participants.

2. **Section 8.2.2, Direct Antiglobulin Test and Cold Agglutinin Test**

   Description of change: Language was added to allow participants for whom DAT was performed within 28 days before screening at the study site not to retest DAT at the screening visit.

   Rationale for change: Direct antiglobulin test is a diagnostic test for AIHA. It does not tend to have significant fluctuation week to week. This study allows a previous DAT result to be used as a screening value if it was performed within 28 days before screening.

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

Amendment 1 (11 JAN 2018)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The primary purpose of this amendment is to limit the AIHA population to participants who have disease progression after treatment with standard therapies and to add a stopping rule for futility.

1. **Section 1, Protocol Summary (Table 1, Schedule of Assessments); Section 6.7.1.2, Folic Acid, Vitamin B12, or Iron Deficiencies; Section 8.3.5, Laboratory Assessments (Table 4, Required Laboratory Analytes); Section 8.3.5.2, Vitamin B12; Section 8.3.5.3, Iron Clinical Assessment**

   Description of change: Added assessment of ferritin and iron at Week 6 for participants who receive transfusions during the study and assessment of vitamin B12 levels at screening. A subsection was created (Section 6.7.1.2) for permitted medications for folic acid, vitamin B12, or iron deficiencies.

   Rationale for change: Week 6 assessments were added to monitor for the potential risk for iron overload in participants who continue to receive transfusions during the study. The vitamin B12 assessment was added to avoid the potential risk of neurologic issues in participants receiving folic acid supplementation.

2. **Section 4.1, Overall Design; Section 9.6, Data Monitoring Committee**

   Description of change: Language was added to provide guidance regarding the Protocol stopping rules for futility.

   Rationale for change: To address the FDA's request to include guidance for stopping rules for futility.

3. **Section 1, Protocol Summary (Table 1, Schedule of Assessments); Section 5.1, Inclusion Criteria; Section 5.2, Exclusion Criteria**

   Description of change: Revised Inclusion criterion 3 to remove language describing prior treatments and adding language to describe eligible patients as those who have disease progression after treatment with standard therapies. Exclusion criterion 9 was revised to reflect that a subject may enroll if the average QTcF for 3 separate ECGs is within the upper limit (ie, < 470 milliseconds for males and < 480 milliseconds for females); footnote "i" in Table 1 was updated to indicate triplicate ECG may be performed at screening. In exclusion criterion 10b, the corticosteroid dose level limit was revised to include "prednisone or equivalent corticosteroid dose" language.

   Rationale for change: In response to FDA comments, the language in inclusion criterion 3 has been revised to reflect that this study population is limited to participants who have no other standard treatment options. Exclusion criteria 9 was clarified for circumstances in which a participant with a history of elevated QTcF would be eligible for the study. Exclusion criterion 10b was revised to clarify the dose limit for corticosteroids.

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

Signature Page for VV-CLIN-000602 v8.0

Approval	[redacted] Approver 02-Nov-2020 12:48:49 GMT+0000
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