Clinical Study Protocol

INCB 50465-207

An Open-Label Phase 2 Study of INCB050465 in Participants With Primary Sjögren's Syndrome

Product:	**INCB050465**
IND Number:	[redacted]
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol (Version 0):	**12 JUN 2018**

INVESTIGATOR'S AGREEMENT

I have read the INCB 50465-207 Protocol (Version 0 dated 12 JUN 2018) 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

Abbreviations and Special Terms	Definition
AE	adverse event
AECG	American–European Consensus Group
ALT	alanine aminotransferase
ANC	absolute neutrophil count
[redacted]	[redacted]
[redacted]	[redacted]
AST	aspartate aminotransferase
AUC	area under the plasma or serum concentration curve
BTK	Bruton's tyrosine kinase
CAML	calcium-modulating ligand
CD	cluster of differentiation
C_{min}	minimum observed plasma or serum concentration
CTCAE	Common Terminology Criteria for Adverse Events
CXCL13	CXC motif chemokine ligand 13
CYP	cytochrome P450
DLT	dose-limiting toxicity
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOT	end of treatment
EQ-5D	European Quality Of Life 5 Dimensions questionnaire
ESSDAI	EULAR Sjögren's Syndrome Disease Activity Index
ESSPRI	EULAR Sjögren's Syndrome Patient Reported Index
EULAR	European League Against Rheumatism
FAS	full analysis set
FSFI	Female Sexual Function Index
FSH	follicle-stimulating hormone
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	concentration that results in 50% inhibition

Abbreviations and Special Terms	Definition
IC_{90}	concentration that results in 90% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
[redacted]	[redacted]
IL	interleukin
IRB	institutional review board
IRT	interactive response technology
IV	intravenous
JAK	Janus kinase
MedDRA	Medical Dictionary for Regulatory Activities
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamic
PGIC	Patient Global Impression of Change questionnaire
PI3Kδ	phosphatidylinositide 3-kinase delta isoform
PJP	*Pneumocystis jirovecii* pneumonia
[redacted]	[redacted]
PROMIS	Patient-Reported-Outcomes Measurement Information System
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
RA	rheumatoid arthritis
RNA	ribonucleic acid
SGUS	salivary gland ultrasound
SLE	systemic lupus erythematosus
SoA	schedule of activities
SS	Sjögren's syndrome
T3, T4	triiodothyronine and thyroxine (thyroid hormones)
TB	tuberculosis
TEAE	treatment-emergent adverse event, AEs reported for the first time or worsening of a pre-existing event after first dose of study treatment
TNF	tissue necrosis factor
Treg	regulatory T cell
ULN	upper limit of normal

1. PROTOCOL SUMMARY

Protocol Title: An Open-Label Phase 2 Study of INCB050465 in Participants With Primary Sjögren's Syndrome

Protocol Number: INCB 50465-207

Objectives and Endpoints:

Table 1 presents the primary and key secondary objectives and endpoints.

Table 1: Primary and Key Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the impact of INCB050465 on salivary gland echostructure	• Proportion of participants with a 1 point or greater improvement on the SGUS score for parotid and submandibular glands at Week 4 and Week 12
Key Secondary	
To assess the impact of INCB050465 on salivary CXCL13	• Change and percent change from baseline in salivary CXCL13 levels at Week 4 and Week 12
To evaluate the safety and tolerability of INCB050465	• Frequency, duration, and severity of AEs, clinical laboratory test results, vital sign results, ECGs, and physical examination findings

Overall Design:

Table 2 presents the key study design elements. Further study details are presented after the table.

Table 2: Key Study Design Elements

Study Phase	Phase 2
Clinical Indication	Primary SS, moderate to severe in intensity
Population	Adults aged ≥18 years diagnosed with moderate to severe primary SS
Number of Participants	12
Study Design	This is a single group, open-label study of the impact of the PI3Kδ inhibitor INCB050465 on signs and symptoms of SS. Twelve participants meeting the inclusion criteria and none of the exclusion criteria will be enrolled. Participants will receive treatment with INCB050465 1 mg QD for 12 weeks and undergo ultrasound measurement of salivary glands, measurements of salivary flow, collection of symptom questionnaires, and PD [redacted] blood sampling to allow studies of cytokine levels [redacted] and other PD markers.

Table 2: Key Study Design Elements (Continued)

Estimated Duration of Study Participation	Screening: Up to 28 days Baseline: Day 1 Study drug administration: 12 weeks Follow up: 30 days (+ 7 days) after last dose of study drug Total: Up to 21 weeks
Data Monitoring Committee	No

Treatment Groups and Duration:

This is an open-label, Phase 2 study to assess the impact of PI3Kδ inhibitor INCB050465 on signs and symptoms of SS. A single group of 12 participating adults, ≥ 18 years old, who meet the inclusion criteria, will be enrolled for a duration of 12 weeks (with a 30-day safety follow-up period) and receive treatment with INCB050465 1.0 mg QD. Participants will undergo ultrasound measurement of salivary glands, measurements of salivary flow, collection of symptom questionnaires, and PD [redacted] blood sampling to allow studies of cytokine levels, gene expression levels, and other PD markers.

The study design is shown in Figure 1.

[redacted]

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Table 3 provides the SoA for the study, and Table 4 provides a Schedule of Laboratory Assessments.

Table 3: Schedule of Activities

	Screening (Day -28 to Day -1)	Day 1	Week 2 (± 3 Days)	Week 4 (± 7 Days)	Week 8 (± 7 Days)	Week 12/ EOT (± 7 Days)	Safety Follow-Up (30 Days [+7 Days] After Last Dose of Study Drug)	Comments
Administrative Procedures								
Informed consent	X							
Contact IRT	X	X	X	X	X	X		
Inclusion/exclusion criteria	X	X						
Medical and medication history	X							
Concomitant medications	X	X	X	X	X	X	X	
Dispense reminder card		X	X	X	X			
Administer study drug during visit		X	X	X	X			
Dispense study drug		X	X	X	X			
Drug accountability and compliance assessment			X	X	X	X		
Administer PJP prophylaxis if needed*		X	X	X	X	X	X	From Day 1 to at least 30 days after last dose of study drug. *See Section 6.6.1.1.
Safety Assessments								
AE assessment	X	X	X	X	X	X	X	
Comprehensive physical examination	X						X	
Targeted physical examination		X	X	X	X	X		Body systems with symptoms should be physically examined.
Vital signs	X	X	X	X	X	X	X	Measure height at screening only.
12-lead ECG	X	X	X			X	X*	*Standard ECG.
Efficacy Assessments								
Ultrasound of parotid and submandibular salivary glands		X*		X		X		*Schedule ultrasound 2 weeks before Day 1 to ensure results availability.
Measurement of total unstimulated salivary flow	X	X		X	X	X		
Measurement of total stimulated salivary flow	X*	X		X	X	X		*Documented measurement within 12 weeks before screening visit.
Questionnaire for dryness of eyes, mouth, and (females only) vagina	X	X		X	X	X		
ESSDAI assessment	X	X		X	X	X		
ESSPRI questionnaire	X	X		X	X	X		
PGIC questionnaire	X	X		X	X	X		
FSFI questionnaire	X	X		X	X	X		Female participants only.
PROMIS Fatigue questionnaire	X	X		X	X	X		
EQ-5D questionnaire	X	X		X	X	X		

Table 4: Schedule of Laboratory Assessments

	Screening (Day -28 to Day -1)	Day 1	Week 2 (± 3 days)	Week 4 (± 7 Days)	Week 8 (± 7 Days)	Week 12/EOT (± 7 Days)	Safety Follow-Up (30 Days [+ 7 Days] After Last Dose of Study Drug)	Comments
Clinical Laboratory Assessments								
Serum chemistries	X	X	X	X	X	X	X	
Hematology	X	X	X	X	X	X	X	
Serum pregnancy test	X						X	All female participants of childbearing potential.
FSH	X							To document hormonal menopause defined as amenorrhea of at least 12 months before screening
Urine pregnancy test		X	X	X	X	X		Female participants of childbearing potential only.
Thyroid function	X							
Serology – HIV, HBV, and HCV, viral load reflex if required	X							
TB test	X							QuantiFERON-TB Gold test or T-spot.TB.
Urinalysis	X					X	X	
[redacted]								

2. INTRODUCTION

INCB050465 is an inhibitor of the Class IA PI3K enzymes, with selectivity for the delta isoform (PI3Kδ), and is in development for treatment of hematologic malignancies, solid tumors, and autoimmune diseases. Uncontrolled B-cell and T-cell proliferation and differentiation are strongly implicated in the pathogenesis of hematologic malignancies and autoimmune diseases. PI3Kδ serves a critical signal for B-cell and T-cell development. Overactive PI3Kδ signaling leads to uncontrolled B-cell and T-cell proliferation and differentiation, which are strongly implicated in the pathogenesis of autoimmunity. [redacted]

2.1. Background

2.1.1. Sjögren's Syndrome

Sjögren's syndrome is a chronic autoimmune exocrinopathy, an inflammatory disease affecting the glands that produce tears, saliva, and vaginal and bronchial secretions. Thus, persistent dryness of the mouth and eyes caused by functional and structural impairment of the salivary and lachrymal glands are the hallmarks of the disease. Sjögren's syndrome is primarily a disorder of women in their sixth and seventh decade, although men and younger women can be affected. Sjögren's syndrome is found worldwide, with reported clinical characteristics similar in China, Japan, and California (Kang et al 1993).

Estimates of the incidence and prevalence of SS are difficult given the variety of criteria used in the various studies, with a range of 0.01% to 0.09% (Risselada et al 2014, Theander et al 2011, Vitali 2003). It would appear that only about 10% of all people with documented dry eyes have SS. In a population-based study from Olmsted County, MN, using the 1993 European SS criteria, the annual incidence of SS was approximately 4 per 100,000 people (Pillemer et al 2001). Of incident cases, 70% had primary SS. A 2014 meta-analysis of population-based studies found the incidence of SS to be approximately 7 per 100,000 people (Qin et al 2015), with the highest incidence rates in studies from Europe and Asia. The prevalence in the meta-analysis was estimated at 43 per 100,000 (0.043%).

The major clinical manifestations are dryness of the eyes and mouth caused by decreased lacrimal and salivary gland function (eg, decreased lacrimal and salivary gland function), causing dryness of the eyes and mouth (Pertovaara et al 1999, Ramos-Casals et al 2005). Isolated keratoconjunctivitis sicca is the form of ocular dryness that led Henrik Sjögren, in 1933, to initially describe clinical and histologic findings of the syndrome named after him. Keratoconjunctivitis sicca represents a deficiency in production of the aqueous phase of the tear layer due to damage of the lacrimal glands; the term "dry eye syndrome" refers to the broad spectrum of disorders leading to ocular dryness.

In addition to the glandular/exocrine features noted above (which can also include significant swelling of the parotid salivary glands), there can also be significant extraglandular features affecting multiple organ systems, including inflammatory joint disease, interstitial pneumonitis, hematologic abnormalities and lymphoproliferative changes (non-Hodgkin lymphoma).

Sjögren's syndrome also affects nonexocrine organs (Carsons and Bhimji 2017). Sjögren's syndrome can be a primary process (unassociated with an underlying inflammatory process) or secondary, most often associated with RA (25%-35% of patients with RA have SS) or SLE. Other diseases or treatments can cause many or most of the clinical manifestations of SS (eg, prior head and/or neck irradiation, infection with HCV or HIV, lymphoma, sarcoidosis, graft-versus-host disease, and recent use of medications with anticholinergic properties). Serological abnormalities include the presence of autoantibodies (antinuclear antibodies, RF, and antibodies to Ro/SS-A and La/SS-B), hypocomplementemia, and cryoglobulinemia; vasculitis can also occur.

2.1.2. Diagnosis of Sjögren's Syndrome

The diagnosis of SS is a challenge as it shares multiple clinical and immunologic features with other autoimmune connective tissue disorders. Hence, there is no single diagnostic test for SS; the diagnosis is made based on appropriate clinical findings and laboratory results, after excluding other potential causes of ocular and/or oral dryness. The diagnosis should be considered in any individual with persistent dry eyes and/or mouth, especially if parotid gland enlargement or increase in dental caries are present. The diagnosis of SS can be made in individuals with an objective finding of ocular and/or oral dryness for whom there is substantive evidence of an underlying autoimmune basis targeting the exocrine glands and thereby causing dysfunction. A variety of classification criteria have been developed, but these are not appropriate for use as diagnostic criteria.

The variety of criteria and clinical, serologic, and histologic markers makes study of SS difficult and comparison of outcomes challenging. For the purposes of studies, the assured diagnosis is most often based on 2002 AECG criteria, which include the concurrent presence of various signs and symptoms represented in the 6 diagnostic standards (Vitali et al 2002):

1. Oral symptoms
2. Ocular symptoms
3. Evidence of oral signs
4. Evidence of ocular dryness
5. [redacted]
6. Positive gland biopsy

[redacted]

A biopsy of a minor salivary gland on the inner aspect of the mouth remains an important diagnostic test, the degree of abnormality predicting the risk of developing lymphoma; additionally, extant primary lymphoma can be detected (Foulks et al 2015, Saraux et al 2016). A positive lip biopsy (showing focal lymphocytic sialadenitis with a focus score ≥ 1) is found in 66% to 89% of patients with SS classified by the 2002 AECG criteria, with a sensitivity of about 80%.

[redacted]

(magnetic resonance imaging and ultrasound identify inhomogeneity within the glandular parenchyma; scintigraphy and contrast sialography are less commonly used). Between 2013 and 2015, 5 studies of imaging techniques found that ultrasonography had a sensitivity of 55% to 66% and specificity of 93% to 98% for a diagnosis of SS (Brito-Zeron and Ramos-Casals 2014, Fazaa et al 2014, Ramos-Casals et al 2010, Ramos-Casals et al 2012, Thanou-Stavraki and James 2008).

2.2. Current Treatment and Unmet Needs for Sjögren's Syndrome

There is no disease-modifying treatment available for SS. The goals of current forms of therapy are to decrease symptoms of dryness in the eyes, mouth, and other affected areas (eg, vagina), prevent complications of mucosal dryness (eg, dental decay, corneal ulceration), detect and manage systemic manifestations of SS, and prevent progression of glandular disease to a lymphoproliferative state; these therapies do not address the underlying disease.

Current approaches have been summarized (Foulks et al 2015, Vivino et al 2016) as follows. Initial therapy for all patients should be nonpharmacologic and preventive, which should include expert ophthalmologic and dental care, education, and assurance that all vaccinations are up-to-date. Secretagogues may be useful in patients for whom artificial tears and saliva do not suffice. Especially in secondary SS, interventions may be needed to address extraglandular manifestations (eg, skin, joint, blood vessel, pulmonary, and renal damage). These treatments are usually similar to those used for the underlying disorders (eg, SLE or RA) and can include nonsteroidal anti-inflammatory drugs, glucocorticosteroids, antimalarials (hydroxychloroquine), and nonbiologic disease-modifying antirheumatic drugs (eg, methotrexate, leflunomide, azathioprine, sulfasalazine, mycophenolic acid, and cyclosporine). For lymphoproliferative disease and the more severe extraglandular features of SS (eg, cryoglobulinemic vasculitis, interstitial lung disease, pulmonary hypertension, interstitial nephritis, glomerulonephritis, primary biliary cirrhosis, mononeuritis multiplex), other, more potent agents may be required (eg, cyclophosphamide or rituximab).

2.3. PI3Kδ in Autoimmune Diseases

PI3Ks belong to a family of lipid signaling kinases that phosphorylate phosphoinositides of the inositol ring (Cantley 2002). PI3K 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 phosphatidylinositol 4,5-bisphosphate, giving rise to phosphatidylinositol (3,4,5)-trisphosphate, which 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 proinflammatory cytokines, and therefore has been strongly linked to autoimmunity (Puri and Gold 2012). [redacted]

[redacted]

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, autoreactive CD4+ T cells are involved in SS pathogenesis (Kasperkiewicz et al 2017), inhibition of PI3Kδ signaling could have benefit in the treatment of patients with current unmet need in SS and other autoimmune diseases.

2.3.1. PI3Kδ in Sjögren's Syndrome

Germinal center-like ectopic lymphoid structures are thought to play an important role in local chronic B-cell activation and clonal expansion, autoantibody production, and Ig class switching in SS (Bombardieri et al 2017, Salomonsson et al 2003). Importantly, a strong association between SS and polymorphisms in the CXCR5 locus has been reported (Lessard et al 2013). CXCR5 is the receptor for CXCL13 and is critical for the migration of B cells and T follicular helper cells into secondary lymphoid tissues. T follicular helper cells have been detected in the salivary glands of patients with primary SS within germinal center-like structures (Maehara et al 2012, Szabo et al 2014,) and are more frequent in the peripheral blood of SS patients compared with healthy controls (Jin et al 2014).

Genetic deletion or pharmacologic inhibition of PI3Kδ leads to defective B-cell activation, reduced proliferation, and functional suppression (Bilancio et al 2006, Henley et al 2008, Vigorito et al 2004). The formation of T follicular helper cells and the production of key effector molecules is critically dependent on PI3Kδ activity (Rolf et al 2010). Finally, CXCR5 receptor downstream signaling is partially PI3Kδ-dependent, resulting in diminished chemotaxis and disrupted germinal center organization (Reif et al 2004).

[redacted]

[redacted]

2.4. Study Rationale

2.4.1. Scientific Rationale for Study Design

Currently, there is no approved therapy for SS that acts to improve all symptoms of this disease. Treatment is palliative and symptom-specific, and therefore there remains a significant unmet medical need for new treatments for SS. [redacted]

2.4.2. Nonclinical Toxicology and Safety Margins

A series of nonclinical toxicity studies were completed to support human clinical studies with INCB050465. The toxicologic and toxicokinetic profiles of INCB050465 were characterized in single and repeat oral dose studies of up to 3 months in duration in rats and dogs. The most prominent findings observed included lymphoid depletion, most notably B-cell regions of multiple lymphoid organs, including lymph nodes, spleen, thymus, and GALT, at all doses. [redacted] Reversibility of the effects on lymphoid system was clearly demonstrated.

[redacted]

[redacted]

Refer to the INCB050465 IB for additional details regarding the safety margins.

2.4.3. Justification for Dose

[redacted]

Refer to the INCB050465 IB for further details.

[redacted]

The most prominent findings following repeat-dose exposure to INCB050465 in both rats and dogs were lymphoid depletion, most notably B-cell regions, of multiple lymphoid organs, including lymph nodes, spleen, thymus, and gut-associated lymphoid tissue, at all doses. Lymphoid depletion was considered a DLT. Effects on the lymphoid system are an expected result of immunomodulatory effects of PI3Kδ inhibition (Marone et al 2008, Pillai and Cariappa 2009). Reversibility of the effects on the lymphoid system was clearly demonstrated and would be expected to occur in a clinical setting.

INCB050465 was evaluated in 1-month (28 days) and 3-month (91 days) toxicology studies in Sprague Dawley rats and beagle dogs. In the rat studies, INCB050465 was administered daily for 1 month at doses of 10, 30, or 100 mg/kg per day or daily for 3 months at doses of 3, 7.5, or 15 mg/kg per day. In the dog studies, INCB050465 was administered daily for 1 month at doses of 1, 3, or 15 mg/kg per day or daily for 3 months at doses of 0.3, 0.75, or 1.5 mg/kg per day. Recovery was evaluated after a 4-week (1-month study) or 6-week (3-month study) recovery period in both species.

The primary effect observed in 1-month and 3-month studies in both rats and dogs was dose-dependent immunosuppression (evident as minimal to marked depletion of lymphoid tissues, including thymus, lymph nodes, spleen, and gut-associated lymphoid tissue), which was attributed to the pharmacologic activity of INCB050465. All lymphoid effects showed evidence of reversibility at the end of the study recovery periods.

[redacted]

[redacted]

The potential risk associated with INCB050465 clinical administration is expected to be low based on the proposed dose of 1 mg, adequate exposure margins, the demonstrated lack of findings in recovery animals following drug withdrawal, and comprehensive evaluation of safety and PK.

For more detailed information about the known and expected risks and reasonably expected AEs of INCB050465, refer to the IB.

[redacted]

[redacted]

2.5.3. Potential Benefits of INCB050465 in Sjögren's Syndrome

Participants may experience clinically meaningful improvements in their SS signs and symptoms during the study and may additionally benefit from the comprehensive safety assessments conducted as part of the study (eg, clinical laboratory tests, physical examinations, ECGs).

Participants will also contribute to the process of developing a novel anti-inflammatory agent for SS, a condition with high unmet need that is severely debilitating to participants' well-being and daily functioning.

2.5.4. Overall Risk/Benefit Statement

[redacted]

3. OBJECTIVES AND ENDPOINTS

Table 5 presents the objectives and endpoints.

Table 5: Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the impact of INCB050465 on salivary gland echostructure.	• Proportion of participants with a 1 point or greater improvement on the SGUS score for parotid and submandibular glands at Week 4 and Week 12.
Secondary	
To assess the impact of INCB050465 on salivary CXCL13	• Change and percent change from baseline in salivary CXCL13 levels at Week 4 and Week 12.
To assess the efficacy of INCB050465	• Change and percent change in stimulated and unstimulated whole salivary flow from baseline at Weeks 4, 8, and 12. • Change and percent change in ESSDAI at Week 12. • Change and percent change in ESSPRI at Weeks 4, 8, and 12. • Change and percent change in symptom scores for dryness of eyes, mouth, and vagina at Weeks 4, 8, and 12. • Proportions of participants in each PGIC category at Weeks 4, 8, and 12. • Change and percent change in PROMIS Fatigue short form at Weeks 4, 8, and 12. • Change and percent change in FSFI at Weeks 4, 8, and 12 (female participants only). • Change and percent change in EQ-5D at Weeks 4, 8, and 12.
To evaluate the safety and tolerability of INCB050465	• Frequency, duration, and severity of AEs, clinical laboratory test results, vital sign results, ECGs, and physical examination findings.
[redacted]	

Table 5: Objectives and Endpoints (Continued)

[redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a single group, open-label study of the impact of PI3Kδ inhibitor INCB050465 on signs and symptoms of SS. Twelve participants meeting the inclusion criteria and none of the exclusion criteria will be enrolled. Participants will receive treatment with INCB050465 [redacted] QD for 12 weeks and undergo ultrasound measurement of salivary glands, measurements of salivary flow, collection of symptom questionnaires, and PD [redacted] blood sampling to allow studies of cytokine levels, gene expression levels, and other PD markers.

Participants will have regularly scheduled study visits at screening, Day 1 (baseline; first day of dose administration), and at the end of Weeks 4, 8 and 12, where laboratory and other assessments will be performed. There will also be a laboratory-only visit at the end of Week 2 to collect safety laboratory assessments [redacted]. Participants will complete questionnaires regarding signs and symptoms of disease at each study visit.

Ultrasound measurement of the parotid and submandibular glands will be performed on Day 1 (before the first dose) and after 4 and 12 weeks of treatment. Ultrasound of glands will be performed in the longitudinal and transverse planes with participants in a supine position. The ultrasound images will be evaluated for quality then transmitted to a central vendor for reading and data summarization.

The echostructure of each gland on B-mode images will be graded on a 5-point scale (0 to 4):

- Grade 0: normal homogeneous gland.
- Grade 1: small hypoechoic areas with hyperechoic bands.
- Grade 2: multiple hypoechoic areas less than 2 mm.
- Grade 3: multiple hypoechoic areas 2 to 6 mm.
- Grade 4: multiple hypoechoic areas larger than 6 mm.

For each timepoint, 4 grades will be obtained, one for each parotid and submandibular gland. The SGUS score is the numeric sum of the 4 individual grades (maximum score of 16). Instructions for conducting and transmitting ultrasound measurements will be provided in the Study Manual.

Stimulated and unstimulated salivary flow will be performed at baseline and after 4, 8, and 12 weeks of treatment. Instructions for performing salivary flow measurements will be provided in the Study Manual.

PJP prophylaxis: Prior treatment with prednisone or equivalent may represent a risk factor for PJP in combination with other immunosuppressants. Participants who have received prednisone ≥ 20 mg per day (or equivalent) within 60 days before baseline are excluded. Participants receiving ≥ 10 mg to < 20 mg of prednisone (or equivalent) may be at increased risk for PJP, and prophylaxis should be considered for these participants, particularly if they have a history of PJP or have recently received any immunosuppressive therapy that may represent and increased risk. Participants receiving < 10 mg of prednisone or equivalent have some potential risk. PJP prophylaxis is not required for these participants but should be considered by the investigator only in exceptional circumstances in consultation with the medical monitor as needed.

Examples of standard PJP prophylaxis therapies include trimethoprim-sulfamethoxazole, atovaquone, dapsone with or without pyrimethamine, and pentamidine (Baden et al 2012). 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. Prophylaxis should be given while participants are receiving study drug and should continue for at least 30 days after the last dose of study drug.

In addition to these study visits, there will be laboratory-only visits at the end of Week 2 to collect safety laboratory assessments [redacted].

Week 12 will correspond to the EOT. A safety follow up visit will occur 30 (+7) days after the last dose of study drug.

4.2. Overall Study Duration

Individual participants will participate for a duration of up to 21 weeks (4 weeks screening, 12 weeks treatment, 4-5 weeks safety follow-up; see Figure 1).

The study begins when the first participant signs the ICF. The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed all study visits, including the follow-up visit.

The investigator will be expected to monitor for and report any SAEs, AEs of special interest, and pregnancies as detailed in Section 9. The remaining participants are considered to be on study until a discontinuation criterion is met and written notification is provided to the sponsor.

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 agency. If the study is terminated prematurely, the sponsor or designee will notify the investigators, the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study.

5. STUDY POPULATION

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. Prospective approval of Protocol deviations to recruitment and enrollment criteria, also known as Protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Ability to comprehend and willingness to sign a written ICF for the study.
2. Age ≥ 18 years at the time of signing the ICF.
3. Primary SS diagnosed according to the revised AECG criteria (Vitali et al 2002), defined as presence of any 4 of the 6 items below, with at least items d) and f), or the presence of any 3 of items c), d), e) and f):
   a. Ocular dryness symptoms.
   b. Oral dryness symptoms.
   c. Schirmer's test ≤ 5 mm/5 min.
   d. Focus score ≥ 1 focus/4 mm^2 on minor salivary gland biopsy.
   e. Unstimulated whole salivary flow ≤ 0.1 mL/min.
   [redacted].
4. Minimum score of 2 on the SGUS score for parotid and submandibular glands.
5. ESSDAI score ≥ 5.

[redacted]

7. Symptomatic oral dryness score of at least 5 on patient questionnaire.
8. Willingness to avoid pregnancy or fathering children based on the criteria below:
   a. Woman of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea and at least 50 years of age, and FSH levels > 30 IU/L).
   b. Woman of childbearing potential who has a negative serum pregnancy test at screening and negative urine pregnancy test before the first dose on Day 1 and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up visit. 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) or from sperm donation from screening through 93 days after treatment with INCB050465. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participant and his understanding confirmed.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Diagnosis of secondary SS according to the revised AECG criteria (eg, the presence of a previously diagnosed or a present diagnosis of RA, SLE, systemic sclerosis, mixed connective tissue disease, polymyositis, dermatomyositis, immunoglobulin G4-related disorder, sarcoidosis, or any other defined autoimmune rheumatologic disorder).
    a. NOTE: Nonrheumatologic autoimmune disorders (eg, Hashimoto thyroiditis, alopecia, vitiligo, Type 1 diabetes mellitus) do not constitute an exclusion; the medical monitor should be consulted if there are questions regarding a specific participant's disease history or diagnosis.
2. Concurrent conditions and history of other diseases:
    a. History or clinical manifestations of significant unstable metabolic, hepatic, renal, hematologic, pulmonary, cardiovascular, gastrointestinal, urological, neurological, or psychiatric disorders.
    b. Clinically significant cardiac disease, including unstable angina, acute myocardial infarction, and or cardiac conduction issues within 180 days of the date of study drug administration.
    c. Current New York Heart Association Class II to IV congestive heart failure or uncontrolled arrhythmia.
    d. History of osteomyelitis, PJP, or bronchiectasis.
    e. Active bacterial, fungal, parasitic, or viral infection that requires antibiotic therapy. Participants with acute infections requiring treatment should delay screening/enrollment until the course of therapy has been completed and the event is considered resolved. Prophylactic antibiotics will be permitted if they have been started at least 28 days before the screening visit.
    f. History within 6 months before screening, or current presence at screening, of poorly healing wound and/or cutaneous ulcers.
    g. Prior head or neck irradiation.
    h. History of or ongoing serious illness or medical, physical, or psychiatric condition(s) that, in the investigator's opinion, would 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.
3. Positive test results for TB from the QuantiFERON-TB Gold test or T-spot.TB test at screening. If a result is indeterminate, the test should be repeated. If the repeat test result is positive, the participant is excluded. If the repeat test result is indeterminate, a purified protein derivative skin test should be done, and if there is < 5 mm of induration, the participant can be enrolled.
4. Positive serology test results for HIV antibody, hepatitis B surface antigen, hepatitis B surface antigen antibody, HBV core antibody, or HCV (HCV antibody with positive HCV-RNA) at screening.
5. Severely impaired liver function (Child-Pugh Class C).

6. Prior or ongoing therapy with:
    a. Any drug that inhibits PI3K (examples of drugs targeting this pathway include but are not limited to leniolisib, seletalisib, INCB040093, idelalisib, and duvelisib) at any time before baseline or during study.
    b. Immunologic or other immunosuppressive therapy, or B-cell targeted therapy (eg, rituximab, other anti-CD20 agents, anti-CD19 agents, anti-CD22 agents, anti-CD52 agents) or LyS-targeted therapy (eg, belimumab, CAML interactor) or other biologic investigational agent (eg, CD40L antibody) or cyclophosphamide within the prior 365 days before baseline or during study.
    c. BTK inhibitors (examples of drugs targeting this pathway include but are not limited to ibrutinib and PCI32765) within 90 days before baseline or during study.
    d. Use of anti-TNFα therapy, IL-1–receptor antagonist, monoclonal antibody to IL-1, costimulation modulator, monoclonal antibody to IL-6 or IL-6–receptor, monoclonal antibody to IL-17, monoclonal antibody to IL-23, JAK inhibitor, IV immunoglobulin, plasmapheresis, or Staph protein A column within 90 days before baseline or during study.
    e. Use of any experimental drug therapy for SS within 90 days before baseline or during study.
    f. Use of nutraceuticals, ayurvedic, herbal, and other nonprescription therapies used for SS are permitted with investigator review, provided the participant has been taking the therapy for at least 60 days as a stable regimen and agrees to continue taking the same preparation at the same dose regimen during the course of the study.
    g. Antimalarials, if ongoing, should be stable within 60 days of baseline and be anticipated to remain stable throughout the 12-week study assessment period.
    h. Glucocorticoids at doses ≥ 20 mg prednisone equivalents per day within 60 days before baseline or during study. Administration of glucocorticoids at doses of 20 mg or less must be stable within 30 days of baseline and be anticipated to remain stable throughout the 12-week study assessment period.
    i. Use of anticholinergics within 30 days before baseline or during study.
    j. Use of any potent cytochrome CYP3A4 inhibitors or inducers within 14 days or 5 half-lives (whichever is longer) before baseline or anticipated during the study.
    k. Use of cholinergic agents such as pilocarpine within 12 hours of salivary flow visits at Day 1 and Weeks 4, 8, and 12.
7. Receipt of any live vaccine in the 30 days before screening. NOTE: Participants will not be allowed to receive live or attenuated vaccines during their participation in the study or until 30 days after the last dose of study medication with the exception of influenza vaccine.
8. No major surgery within 30 days before screening. Inadequate recovery from toxicity and/or complications from a major surgery before starting therapy.

9. 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.
10. Laboratory values at screening defined in Table 6.

Table 6: Exclusionary Laboratory Values

Laboratory Parameter	Exclusion Criterion
Hematology	
Platelets	$\leq 100 \times 10^9$/L
ANC	$\leq 1.5 \times 10^9$/L
Hepatic	
ALT	>2 x ULN
AST	>2 x ULN
Renal	
eGFR	Participants with inadequate renal function defined as eGFR ≤ 50 mL/min

11. Women who are pregnant or breastfeeding.
12. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug/treatment and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.
13. Inability of the participant (or parent, guardian, or legally authorized representative) to comprehend the ICF or unwillingness to sign the ICF.

5.3. Lifestyle Considerations

No restrictions are required.

5.3.1. Meals and Dietary Restrictions

Not applicable.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study.

Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the result to be not consistent with the participant's clinical status. Additionally, a participant who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status. Participants who rescreen must reconsent and be assigned a new participant number.

5.5. Replacement of Participants

Participants will not be replaced during the study.

6. STUDY TREATMENT

6.1. Study Treatment Administered

Information regarding study drug and administration is provided in Table 7. Participants will record study drug administration daily in a diary.

Table 7: Study Treatment Information

Study treatment name:	INCB050465
Dose formulation:	Tablet
Unit dose strength/dose level:	[redacted]
Route of administration:	Oral
Administration instructions:	INCB050465 will be taken QD, orally with water and without regard to food.
Packaging and labeling:	INCB050465 will be packaged in high-density polyethylene bottles.
Storage:	Ambient (15°C-30°C/59°F-86°F)

6.2. Preparation, Handling, and Accountability

Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator (or designee) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). 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 count 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 SOP.

Further guidance and information for the final disposition of unused study treatments are provided in the study materials provided to sites.

6.3. Measures to Minimize Bias: Randomization and Blinding

Not applicable.

6.4. Study Treatment Compliance

Compliance with study drug should be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with INCB050465 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 drug 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.

6.5. Dose Modifications

6.5.1. Management of Urgent Toxicities

Investigators may employ any measures or concomitant medications necessary to optimally treat the participant after discussion with the sponsor (whenever possible).

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

Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

There are no dose modifications in this study. In some circumstances, it may be necessary to temporarily interrupt treatment with INCB050465 as a result of AEs or laboratory abnormalities that have an unclear relationship to the study drug (see Table 8). Except in cases of emergency, it is recommended that any laboratory findings be confirmed and that the investigator consult with the sponsor's medical monitor (or other representative of the sponsor) before temporarily interrupting study drug. Participants who experience a recurrence of the AEs or laboratory abnormalities upon restarting the study drug may have the study drug permanently discontinued.

Instructions for dose interruptions for INCB050465 are outlined in Table 8. Individual decisions regarding dose interruptions should be made using clinical judgment in consultation with the medical monitor (whenever possible), taking into account relatedness of the AE to the study treatment and the participant's underlying condition. Adverse events that have a clear alternative explanation, or transient (≤ 72 hours) abnormal laboratory values without associated clinically

significant signs or symptoms, may be exempt from dose interruption. Dose interruptions may occur at any time during the 12 weeks of administration.

Table 8: Criteria for Interrupting, Restarting, or Discontinuing 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 and monitor as clinically indicated.
• AST and/or ALT is > 5.0 × ULN	Discontinue study drug administration and follow-up per Protocol.
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 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.
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 and monitor as clinically indicated.
• Any recurrent Grade 3 toxicity after dose restart.	Discontinue study drug administration and follow-up per Protocol.
• Any other Grade 4 toxicity.	Discontinue study drug administration and follow-up per Protocol.

6.5.3. Criteria for Permanent Discontinuation of INCB050465

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.
- Persistent AE requiring a delay of therapy for more than 2 weeks without resolution of the AE. A greater treatment delay requires approval by the sponsor's medical monitor.

6.6. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. Any prior medication received up to 28 days before the first dose of study treatment and 30 days after the last dose of study treatment will be recorded in the eCRF. A detailed history of prior

medications use related to SS in the year before screening will be also be collected, as well as response to each treatment and reason for discontinuation.

Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant medications administered after 30 days after the last dose of study treatment should be recorded for SAEs as defined in Section 9.3. Concomitant treatments/procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1. Permitted Medications and Procedures

6.6.1.1. Prophylaxis for *Pneumocystis jirovecii* Pneumonia

Prior treatment with prednisone or equivalent may represent a risk factor for PJP in combination with other immunosuppressants. Participants who have received prednisone ≥ 20 mg per day (or equivalent) within 60 days before baseline are excluded. Participants receiving ≥ 10 to < 20 mg of prednisone (or equivalent) may be at increased risk for PJP, and prophylaxis should be considered for these participants, particularly if they have a history of PJP or have recently received any immunosuppressive therapy that may represent an increased risk. Participants receiving < 10 mg of prednisone or equivalent have some potential risk; however, PJP prophylaxis is not generally required for these participants and should be considered only in exceptional circumstances and in consultation with the medical monitor as needed.

Examples of standard PJP prophylaxis therapies include trimethoprim-sulfamethoxazole, atovaquone, dapsone with or without pyrimethamine, and pentamidine (Baden et al 2012). 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. Prophylaxis should be given while participants are receiving study drug and should continue for at least 30 days after the last dose of study drug.

6.6.1.2. Nonprescription Therapies for Sjögren's Syndrome

Use of nutraceuticals, ayurvedic, herbal, and other nonprescription therapies used for SS are permitted with investigator review provided the participant has been taking the therapy for at least 60 days as a stable regimen and agrees to continue taking the same preparation at the same dose during the course of the study.

6.6.2. Restricted Medications and Procedures

- Inducers of CYP3A4 (see Study Manual) are discouraged, and investigators should seek other options if available.
- Moderate CYP3A4 inhibitors (see Study Manual) are discouraged, and investigators should seek other options if available.
- Administration of glucocorticoids at doses of 20 mg or less must be stable within 30 days of Day 1 and be anticipated to remain stable throughout the 12-week study assessment period.

- Antimalarials, if ongoing, should be stable within 60 days of Day 1 and be anticipated to remain stable throughout the 12-week study assessment period.

6.6.3. Prohibited Medications and Procedures

The following medications and procedures are prohibited during the study from screening through the follow-up visit and before the study as indicated for individual medications:

At any time before baseline (Day 1):

- Any drug that inhibits PI3K (examples of drugs targeting this pathway include but are not limited to leniolisib, seletalisib, INCB040093, idelalisib, and duvelisib).

Within 1 year (365 days) before baseline (Day 1):

- Immunologic or other immunosuppressive therapy, or B-cell targeted therapy (eg rituximab, other anti-CD-19 agents, anti-CD-20 agents, anti-CD-22 agents, anti CD52 agents) or LyS-targeted therapy (eg, belimumab, CAML interactor) or other biologic investigational agent (eg, CD-40L antibody) or cyclophosphamide.
- Anti-TNFα therapy, IL-1–receptor antagonist, monoclonal antibody to IL-1, costimulation modulator, monoclonal antibody to IL-6 or IL-6–receptor, monoclonal antibody to IL-17, monoclonal antibody to IL-23, JAK inhibitor, IV immunoglobulin, plasmapheresis, or Staph protein A column.

Within 3 months (90 days) before baseline (Day 1):

- Any experimental drug therapy for SS.
- BTK inhibitors (examples of drugs targeting this pathway include but are not limited to ibrutinib and PCI32765).

Within 2 months (60 days) before baseline (Day 1):

- Glucocorticoids at doses > 20 mg prednisone equivalents.

Within 1 month (30 days) before baseline (Day 1):

- Anticholinergics.
- Receipt of any live vaccine. Note participants will not be allowed to receive live or attenuated vaccines during their participation in the study or until 30 days after the last dose of study medication with the exception of influenza vaccine.

Within 2 weeks (14 days) before baseline (Day 1):

- Any potent CYP3A4 inhibitors or inducers within 14 days or 5 half-lives (whichever is longer) before the first dose of INCB050465 or anticipated during the study.

Within 12 hours (< 1 day) before baseline (Day 1):

- Cholinergic agents such as pilocarpine.

6.7. Treatment After the End of the Study

There is no treatment after the end of the study.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

Participants **must** be discontinued from study treatment for the following reasons:

- The participant becomes pregnant.
- Consent is withdrawn.
  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case no further data, except data in public domain, may be solicited from or collected on the participant.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Unacceptable toxicity as noted in Section 6.5.3.
- 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 treatment 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 study treatment.
- 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 treatment, the EOT visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit. These visits are described in Table 3 and Table 4. The last date of the last dose of study drug(s)/treatment and the reason for discontinuation of study treatment will be recorded in the eCRF.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the participant's medical record and the primary reason for withdrawal must be included in the eCRF.
- The EOT visit should be performed.
- The date of the EOT visit should be recorded in the eCRF.

- Participants must be followed for safety until the time of the follow-up visit or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

If the participant discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up) then no additional data collection should occur; however, participants will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety assessments.

7.2. Participant Withdrawal From the Study

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

If the 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/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

See Table 3 and Table 4 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/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/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
  - 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.
  - The ICF must contain all required elements and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the IRB/IEC or study center.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must provide consent to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and the day the participant is enrolled in the study (Day 1). Screening may not exceed 28 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

Procedures conducted as part of the participant's routine clinical management (eg, blood count, imaging study) and obtained before signing of informed consent may be used for screening or baseline purposes provided the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study (ie, within 28 days of Day 1). For participants who are enrolled in the study, 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 once 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 assignment will be used to determine eligibility. Treatment should start as soon as possible, but within 3 days after the date of enrollment.

See Sections 5.4 and 5.5 for information regarding screen failures and replacement of participants, respectively.

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 the IRT to obtain the participant ID number during screening. Upon determining that the participant is eligible for study entry, the IRT will be contacted to obtain the study medication bottle or kit assignment. Additionally, the 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. Distribution of Reminder Cards and/or Diaries

Participants will be provided with a reminder card on Day 1 and Weeks 2, 4, and 8. The reminder card will indicate the date/time of the next visit and will also remind the participant that they should not take their morning dose of study drug on the day of each study visit as they will take it after blood draws for safety evaluation have been completed. The reminder cards for each visit will have an area on which the date and time of the last dose taken (from the previous evening) and the time of their last meal before the visit should be recorded.

Participants will also be provided with a diary on Day 1 in order to record study drug administration daily. The date and time of the last dose of study drug [redacted] will be recorded in the diary and eCRF. Daily study drug administration (see Section 6.1) will also be recorded in the diary.

8.1.5. Demography and Medical History

8.1.5.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening by the investigator or qualified designee and will include date of birth, race, ethnicity, medical and surgical history, and current illnesses. Medical history will include relevant medical or surgical treatment within the last 10 years that are considered to be clinically significant by the investigator.

8.1.5.2. Disease Characteristics and Treatment History

A disease-targeted medical and treatment history will be collected at screening. Details regarding the participant's history of SS, including date of diagnosis, relevant disease characteristics, and prior treatments (including systemic treatments, radiation, and surgical procedures), will be recorded. A medical history of other conditions related to SS will also be collected at this time.

8.2. Efficacy Assessments

8.2.1. Ultrasound of Salivary Glands

Ultrasound measurement of the parotid and submandibular glands will be performed at visits indicated in Table 3. Ultrasound of glands will be performed in the longitudinal and transverse planes with participants in a supine position. The ultrasound images will be images will be evaluated for quality then transmitted to a central vendor for reading and data summarization. The echostructure of each gland on B-mode images will be graded on a 5-point scales (0 to 4) as described by Gazeau et al 2018. Grade 0 indicates a normal homogeneous gland, Grade 1 small hypoechoic areas with hyperechoic bands, Grade 2 multiple hypoechoic areas less than 2 mm, Grade 3 multiple hypoechoic areas 2 to 6 mm, and Grade 4 multiple hypoechoic areas larger than 6 mm. For each participant at each timepoint, 4 grades will be obtained, one for each parotid and submandibular gland. The SGUS score is the numeric sum of the 4 individual grades. [redacted] Instructions for conducting and transmitting ultrasound measurements will be provided in the Study Manual.

8.2.2. EULAR Sjögren's Syndrome Disease Activity Index

Investigators will conduct overall disease assessment using the ESSDAI (Seror et al 2015) at visits indicated in Table 3. The ESSDAI assesses 12 domains: constitutional, lymphadenopathy/lymphoma, glandular, articular, cutaneous, pulmonary, renal, muscular, peripheral neuropathy, central nervous system, hematologic, and biologic. Guidance for completing the assessment will be provided in the Study Manual.

8.2.3. Salivary Flow

Stimulated and unstimulated salivary flow will be measured at visits as indicated in Table 3. Complete details for the collection and measurement of unstimulated salivary flow will be provided in the Study Manual.

8.2.4. Patient-Reported Outcomes

Patient-reported outcome instruments will be given to participants for completion at study visits indicated in Table 3. Site staff will enter completed questionnaires into the eCRF database.

8.2.4.1. Dryness Questionnaire

The dryness questionnaire will ask participants to rate the dryness of eyes, mouth, or vagina (female participants only) with 24-hour recall using an 11-point numerical rating system ranging from 0 (no dryness) to 10 (worst imaginable; see Appendix B).

8.2.4.2. EULAR Sjögren's Syndrome Patient Reported Index

The ESSPRI consists of 3 items, each with a 0 (no symptom) to 10 (maximum imaginable symptom) scale. The 3 items are dryness, fatigue, and pain. The recall period is 2 weeks.

8.2.4.3. Patient Global Impression of Change Questionnaire

The PGIC asks a single question regarding how the patient is feeling since beginning new therapy. The questionnaire uses a 7 point scale ranging from "very much worse" to "very much improved," with the midpoint as no change.

8.2.4.4. Female Sexual Function Index

The FSFI is a brief, self-report measure of female sexual function (female participants only). The questionnaire contains 19 items covering 6 domains of sexual function. The recall period is 4 weeks.

8.2.4.5. PROMIS Fatigue Short Form

The PROMIS fatigue short form includes 7 items with a rating sale of 1 to 5. The recall period is 7 days.

8.2.4.6. European Quality Of Life 5 Dimensions Questionnaire

The EQ-5D is a standardized measure of health status. It consists of 5 questions, each with a 5-item rating scale plus a visual analog scale rating from 1 to 100 for overall health status. The questionnaire probes the participants responses for the current day.

8.2.5. Health Economics

Not applicable.

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in Table 3.

See Section 6.5 for guidelines regarding the management of relevant laboratory or other safety assessment abnormalities.

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 30 days after the last dose of study drug. Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study drug. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following-up on AEs that are serious, considered related to the study treatment/procedures, or that caused the participant to discontinue the study drug. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant, such as "How are you feeling?" is the preferred method to inquire about AE occurrences. Adverse events may also be detected when they are volunteered by the participant during the screening process or between visits, or through physical examinations, laboratory tests, or other assessments. The definition, reporting, and recording requirements for AEs are described in Section 9.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

8.3.2. Physical Examinations

Physical examinations will be conducted at the timepoints listed in Table 3.

A comprehensive physical examination will include height and body weight and assessment 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. A brief neurological examination will also be performed.

A targeted physical examination should be conducted as indicated by symptoms reported by the participant, AEs, or other findings. Abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

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

8.3.3. Vital Signs

Vital sign measurements (to be taken before blood collection for laboratory tests) include blood pressure, pulse, respiratory rate, and oral body temperature. Blood pressure and pulse will be

taken with the participant in the sitting position after 5 minutes of rest. Abnormal vital sign results identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, or require concomitant therapy.

8.3.4. Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the SoA (see Table 3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. All 12-lead ECGs will be performed as indicated in Table 9 with the participant in a recumbent or semirecumbent position after 5 minutes of rest.

The 12-lead ECGs will be interpreted by the investigator at the site to be used for immediate participant management and care. Additional 12-lead ECGs may be performed as clinically indicated to manage participant safety. The decision to include or exclude a participant or withdraw a participant from the study treatment 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.

Table 9: Electrocardiogram Schedule

Study Visit	Timing of Electrocardiogram Relative to Administration of Study Drug		
	Not Applicable	Predose (Trough) ECG	Postdose ECG
Screening[a]	Single → Triple[b]		
Day 1[c]		Triple	Single → Triple[b]
Week 2[c]		Single → Triple[b]	Single → Triple[b]
Week 12[d]			Single → Triple[b]

[a] Prolonged QTcF values (> 470 milliseconds for males or > 480 milliseconds for females) at screening are to be confirmed by performing 2 additional ECGs and averaging the results to determine whether the averaged value meets the exclusion criterion.
[b] Single → Triple: Single ECG will be performed first. If prolonged QTcF intervals (defined as > 470 milliseconds for males or > 480 milliseconds for females) are observed, an additional 2 ECGs will be measured within the next 5 minutes.
[c] Day 1 and Week 2 postdose ECGs will be performed after participants complete all of the study assessments [redacted]
[d] Week12 postdose ECGs will be performed after participants complete all of the study assessments.

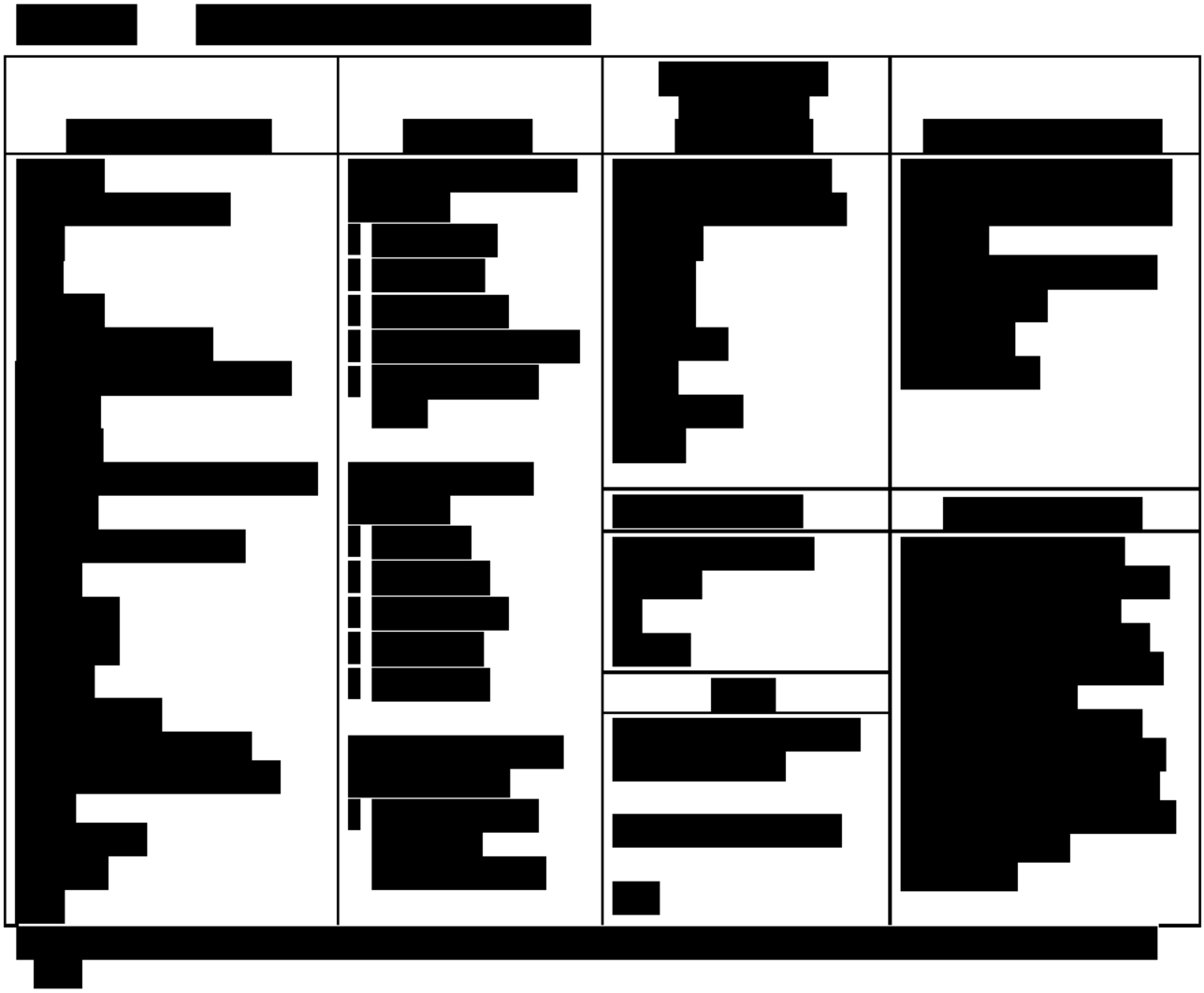
All ECG measurements should be performed before blood draws for laboratory [redacted] assessments, and all predose (trough) ECG measurements should be taken before the participant takes study drug for that day.

8.3.5. Laboratory Assessments

See Table 10 for the list of clinical laboratory tests to be performed and the Schedule of Laboratory Assessments (Table 4) for the timing and frequency. A central laboratory will perform all clinical laboratory assessments for safety (ie, blood chemistries, hematology assessments, thyroid function, and urinalysis) and will store the samples for [redacted] PD. Additional testing may be required by the sponsor based on emerging safety data. All Protocol-required laboratory assessments must be conducted in accordance with the laboratory manual and the Schedule of Laboratory Assessments (Table 4). Information regarding collection, processing, and shipping of laboratory assessments is provided in the Laboratory Manual.

Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. All laboratory tests with values considered clinically significantly abnormal during participation in the study, or within 30 days after the last dose of study treatment, should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

See Section 9.1 for information regarding laboratory abnormalities that should be recorded as an AE in the eCRF.



8.3.5.1. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during screening and at the follow-up visit. Urine pregnancy tests will be performed locally, as outlined in Table 4, as medically indicated (eg, in case of loss of menstrual cycle, when pregnancy is suspected). If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test.

If the serum pregnancy test is negative after a 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.

If a pregnancy is confirmed by a serum pregnancy test, see Section 9.6 for reporting requirements.

8.3.5.2. Serology and Virology

Hepatitis and HIV assessments will be performed at the screening visit to rule out hepatitis or HIV infection; required analytes are shown in Table 10. Serology and virology tests should be performed early in the screening process due to the length of time needed to obtain the results. Additional tests may be performed if clinically indicated.

8.3.5.3. Tuberculosis Testing

Tuberculosis B assessments will be performed at the screening visit. Test must be performed using the QuantiFERON-TB Gold test or T-SPOT.TB test. If there are 2 indeterminate tests, evaluation by a purified protein derivative test with a result of < 5 mm of induration must be conducted within 3 months of screening.

8.5. Pharmacodynamic and Translational Assessments

Peripheral blood samples (eg, serum, PBMC, RNA), tear samples, and saliva samples will be collected from participants at timepoints outlined in Table 4. All samples for PD and translational assessments will be collected before INCB050465 administration.

[redacted]

[redacted] All analyses will be conducted by Incyte Corporation (Wilmington, DE) or Incyte's designee. Information regarding handling/shipping of specimens will be provided in the Laboratory Manual.

[redacted]

[redacted]

[redacted]

8.6. End of Treatment

If a decision is made that the participant permanently discontinues study drug (early termination) or has completed the Protocol-specified duration of treatment, then an 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.

8.7. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 to 37 days after the EOT visit (or after the last dose of study drug/treatment if the EOT visit was not performed.

Adverse events and SAEs must be reported up until at least 30 days after the last dose of study drug, the date of the follow-up visit, or until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant return for the follow-up visit and report any AEs that may occur during this period.

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

9.1. Definition of Adverse Event

Adverse Event Definition
• An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.
Events <u>Meeting</u> the Adverse Event Definition
• Any safety assessments (eg ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Abnormal laboratory test results constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal lab result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though they may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the Adverse Event Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition or considered to be treatment-related by the investigator.
- Efficacy endpoints as outlined in Section 3 will not be reported as AE/SAEs, specifically, any event that is related to disease progression of the cancer under study. Unblinded aggregated efficacy endpoint events and safety data will be monitored to ensure the safety of the participants in the study. Any suspected endpoint that upon review is not progression of the cancer under study will be forwarded to Incyte Pharmacovigilance as a SAE within 24 hours of determination that the event is not progression of the cancer under study.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE if it occurred after signing informed consent. If present before entering the study, the condition should be captured as medical history.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.2. Definition of Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A Serious Adverse Event is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an adverse drug experience that places the participant, in the opinion of the initial reporter, at immediate risk of death from the adverse experience as it occurred. This does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations (Important Medical Event)

An 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 and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such events include invasive or malignant cancers (excluding the disease[s] under study in oncology protocols), intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

9.3. Recording and Follow-Up of Adverse Events and/or Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- An AE/SAE that begins or worsens after informed consent is signed should be recorded on the Adverse Event Form in the eCRF. Conditions that were present at the time informed consent was given should be recorded on the Medical History Form in the eCRF.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator (or delegate) will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completing the AE eCRF page.
- There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE/SAE.

To the extent possible, each AE/SAE should be evaluated to determine:

- The severity grade (CTCAE Grade 1 to 5). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study drug: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug as a result of the AE/SAE(s).

- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: 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 appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Non-Drug Therapy).

Assessment of Intensity

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

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
- **Grade 2:** Moderate; minimal, local, or noninvasive treatment indicated; limiting age appropriate activities of daily living.
- **Grade 3:** Severe or medical 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 treatment indicated.
- **Grade 5:** Fatal.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- The investigator will also consult the RSI in the IB and/or Product Information, for marketed products, in his/her assessment.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, the causality assessment is one of the criteria used when determining regulatory reporting requirements. **Therefore, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE.**
  - The investigator may change his/her opinion of causality in light of follow-up information and send a follow-up SAE report with the updated causality assessment.

Follow-Up of Adverse Events and Serious Adverse Events
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings, including histopathology. • New or updated information will be recorded in the originally completed eCRF. • Any updated SAE data will be submitted to the sponsor (or designee) within 24 hours of receipt of the information. • 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.

9.4. Reporting of Serious Adverse Events

All SAEs, regardless of suspected causality (eg, relationship to study drug, or study procedure[s]), occurring after the participant has signed the ICF through the last study visit or 30 + 7 days after the last dose of study drug, whichever occurs later, must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must notify the sponsor (or designee) within 24 hours of becoming aware of the event.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

If the SAE is not documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification 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.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports must be prepared for suspected unexpected adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Serious Adverse Event Reporting

- Information about all SAEs is collected and recorded on the Adverse Event Form in the eCRF.
- The investigator must also complete the Incyte Serious Adverse Event Report Form, in English. Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.
- Facsimile or email transmission of the Serious Adverse Event Report Form is the preferred method to transmit this information to Pharmacovigilance/designee (eg, C3i/Telerx). The contact information of the sponsor's study-specific representatives is listed in the Study Manual provided to each site. The original copy of the Serious Adverse Event Report Form and the confirmation sheet must be kept at the study site.
  -
- Follow-up information is recorded on an amended or new Serious Adverse Event 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 Serious Adverse Event 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.
- In rare circumstances, and in the absence of facsimile or computer equipment, notification by telephone is acceptable with a copy of the Incyte Serious Adverse Event Report Form sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Study Manual.

9.5. Adverse Events of Special Interest

Adverse events of special interest are defined as occurrences of PJP or other serious infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens; colitis; and exfoliative dermatitis.

9.6. Emergency Unblinding of Treatment Assignment

Not applicable.

9.7. 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 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 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 of a study participant must be recorded on the Serious Adverse Event Report Form and submitted to the sponsor or designee.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) are considered SAEs (if occurring in the study participant) and must be reported as described in Section 9.4. If an abnormal pregnancy outcome is reported in a study participant's partner, the event should be reported to the sponsor on the Clinical Trial Pregnancy Form.

9.8. 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 Investigator Notifications. 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.

9.9. Product Complaints

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

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

The investigator or his/her designee is responsible for reporting a complete description of the product complaint via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be recorded as described in Section 9.3.

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

9.10. Treatment of Overdose

There has been no clinical experience with overdose of INCB050465. Treatment of overdose should consist of general supportive measures.

10. STATISTICS

10.1. Sample Size Determination

The sample size is based on the demonstration of preliminary findings of efficacy, which also depends on the occurrence of safety findings. Approximately 12 participants will be enrolled, which will provide > 90% chance of detecting at least 1 AE of interest (eg, platelets, hemoglobin, ANC, liver functions, and infections) if the underlying AE rate is 20%.

[redacted]

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 the variable before or on Day 1, unless otherwise specified.

10.4.1. Efficacy Analysis

Efficacy assessments will be summarized using descriptive statistics at each visit.

For the primary endpoint, proportion of participants with 1 point or greater improvement on the SGUS for parotid and submandibular glands, as well as the secondary endpoint of PGIC, summary statistics will include sample size, frequency, and percentages.

For all other measurements in the secondary endpoints, which are continuous, summary statistics will include sample size, mean, median, standard deviation, standard error of the mean, minimum, maximum, and the 95% confidence interval where appropriate. Summary statistics will be provided for baseline, the actual measurements at each visit, and the change and percent change from baseline at each visit, if applicable. All analyses will be implemented using SAS version 9.1 or higher.

10.4.2. Safety Analyses

Safety analyses will be conducted for the FAS population. Adverse events will be coded by the MedDRA dictionary, and TEAE (ie, AEs reported for the first time or worsening of a pre-existing event after first dose of study drug) will be tabulated by preferred term and system organ class for all events, related events, and events of Grade 3 or higher. Quantitative safety variables and their changes from baseline (laboratory, vital signs, etc) will be summarized with descriptive statistics. Clinically notable abnormal values will be flagged and tabulated based on predefined criteria.

The clinical laboratory data will be analyzed using summary statistics; no formal treatment group comparisons are planned. In addition, distributions of key laboratory parameters may be plotted over time; these values will also be classified into CTCAE toxicity grades and tabulated. Descriptive statistics and mean change from baseline will be determined for vital signs at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities.

[redacted]

[redacted]

[redacted]

The secondary endpoint of change and percent change from baseline in salivary CXCL13 levels at Week 4 and 12 will be determined from saliva samples for each participant.

All analyses will be conducted by Incyte Corporation (Wilmington, DE) or Incyte's designee, and information regarding handling/shipping of specimens will be provided in the Laboratory Manual.

10.5. Interim Analysis

No formal interim analysis is planned in this study.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB/IEC requirements, institutional requirements, and applicable laws and country-specific regulations.
- 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 EDC system. The investigator will be provided with access to an EDC system so that an eCRF can be completed for each participant.

The site will be provided eCRF completion guidelines for instructions on data entry in 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.

The sponsor (or designee) will be responsible for:

- The data management of this study including quality checking of the data.
- Ensuring that study monitors perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

The investigator will be responsible for:

- Ensuring participant data relating to the study is recorded in the eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, diary data) or as otherwise specified in the Protocol. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

- Maintaining accurate documentation (source data) that supports the information entered in the eCRF.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
  - Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- 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.

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. Only the participant number 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.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 10 years after study completion unless local regulations or

institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

11.4. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies subject to Food and Drug Administration 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/her institution agree that the results of the study may be used by the sponsor, Incyte Corporation, 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.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined in line with International Committee of Medical Journal Editors authorship requirements.

11.6. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study treatment development.

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For male participants in the study:

Male participants should use a condom during treatment and through 90 days after the end of systemic exposure. If the male participant has a partner that is of child-bearing potential, the partner should also use contraception through 93 days after the end of relevant systemic exposure. In addition, male participants must refrain from donating sperm during the study through 90 days after the end of relevant systemic exposure. Males who have had a vasectomy qualify as having met the requirement for a highly effective birth control method.

For female 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:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[a]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[a]
  - oral
  - injectable
  - implantable[b]
- Intrauterine device[b]
- Intrauterine hormone-releasing system[b]
- Bilateral tubal occlusion[b]
- Vasectomized partner[b] [c]
- Sexual abstinence[d]

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[e]
- Cap, diaphragm or sponge with spermicide[e]
- Tubal ligation

[a] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.

[b] Contraception methods that in the context of this guidance are considered to have low user dependency.

[c] Vasectomized partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success.

[d] 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 study and the preferred and usual lifestyle of the participant.

[e] 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 Trials Facilitation Group 2014.

APPENDIX B. DRYNESS QUESTIONNAIRE

1. During the past 24 hours, how **severe** was the **worst** dryness of your mouth?	0-10 scale 0 = No dryness, 10 = Worst Imaginable
2. During the past 24 hours, how **severe** was the **worst** dryness of your eyes?	0-10 scale 0 = No dryness, 10 = Worst Imaginable
FOR FEMALE PARTICIPANTS ONLY 3. During the past 24 hours, how **severe** was the **worst dryness of your vagina**?	0-10 scale 0 = No dryness, 10 = Worst Imaginable

APPENDIX C. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Not applicable.