Clinical Study Protocol

INCB 54707-203

A Phase 2, Dose-Escalation, Placebo-Controlled Study of the Safety of INCB054707 in Participants With Hidradenitis Suppurativa

Product:	**INCB054707**
EudraCT Number:	**2018-000827-15**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol (Version 0):	**15 MAR 2018**
Amendment (Version) 1:	**09 AUG 2018**

INVESTIGATOR'S AGREEMENT

I have read the INCB 54707-203 Protocol Amendment 1 (Version 1 dated 09 AUG 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

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

Abbreviations and Special Terms	Definition
AE	adverse event
ALT	alanine aminotransferase
AN	abscess and inflammatory nodule
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BALT	bronchial-associated lymphoid tissue
CFR	Code of Federal Regulations
Cl/F	apparent oral dose clearance
CRF	case report form
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLQI	Dermatology Life Quality Index
DLT	Dose-Limiting Toxicity
eCRF	electronic case report form
ECG	electrocardiogram
EDC	electronic data capture
EOT	end of treatment
EOS	end of study
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FU	follow-up
GGT	Gamma-glutamyl transferase
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HiSCR	Hidradenitis Suppurativa Clinical Response is defined as at least 50% reduction in AN count with no increase in abscess count and no increase in draining fistula count relative to baseline at each visit
[redacted]	[redacted]
HIV	human immunodeficiency virus

Abbreviations and Special Terms	Definition
HS	hidradenitis suppurativa
HS Pain NRS	Hidradenitis Suppurativa Pain Numeric Rating Scale
HS-PGIC	Hidradenitis Suppurative Patient Global Impression of Change
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	identification
IEC	independent ethics committee
[redacted]	[redacted]
IL	interleukin
IPL	intense pulsed light
IRB	institutional review board
IWRS	Interactive Web Response System
ITT	Intent to treat
JAK	Janus kinase
MedDRA	Medical Dictionary for Regulatory Affairs
Nd:YAG	Neodymium-doped yttrium aluminum garnet; $Nd:Y_3Al_5O_{12}$
NRS	numeric rating scale
PGIC	Patient Global Impression of Change
P-gp	P-glycoprotein
[redacted]	[redacted]
PK	pharmacokinetic
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
RNA	ribonucleic acid
SAE	serious adverse event
SOP	standard operating procedure
SRC	Safety review committee
STAT	signal transducer and activator of transcription
TB	tuberculosis
TEAE	treatment-emergent adverse event
Th	T helper cell
TNF-α	tumor necrosis factor alpha
TYK	tyrosine kinase

Abbreviations and Special Terms	Definition
ULN	upper limit of normal
V_d/F	apparent volume of distribution after non-intravenous administration
WBC	white blood cell

1. PROTOCOL SUMMARY

Protocol Title: A Phase 2, Dose-Escalation, Placebo-Controlled Study of the Safety of INCB054707 in Participants With Hidradenitis Suppurativa

Protocol Number: INCB 54707-203

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 safety and tolerability of INCB054707.	• Frequency, duration, and severity of AEs, clinical laboratory test results, vital signs results, ECGs, and physical examination findings.
Key Secondary	
To determine the systemic exposure to INCB054707.	• Population PK parameters of INCB054707.
To determine the efficacy of INCB054707.	• Proportion of participants achieving a HiSCR at each visit. • Proportion of participants achieving an AN count of 0 to 2 at each visit. • Mean change from baseline in the HS Pain NRS scores, worst and average pain, at each visit. • Mean change from baseline to Week 8 in the modified Sartorius scale score. • Mean change from baseline in the number of draining fistulas count at each visit. • Proportion of participants at each category of Hurley Stage at baseline and Week 8. • Proportion of participants with change from baseline in Hurley Stage at Week 8. • Proportions of participants in each HS-PGIC category during the treatment period. • Actual measurements in HS-PGIC at each visit.

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	HS
Population	Men and women aged 18 to 75 years with moderate to severe HS for at least 6 months
Number of Participants	The study includes 3 cohorts and approximately 36 participants will be enrolled. In each cohort, approximately 12 participants will be randomized 3:1 (INCB054707:placebo) to 1 of 2 treatment groups.
Study Design	Randomized, dose escalation, placebo-control
Estimated Duration of Study Participation	The study will consist of a screening period of up to 28 days, an 8-week treatment period, and a 30-day safety follow-up period. The estimated total duration of study participation is approximately 16 weeks for each participant.
Data Safety Monitoring Board	No

Treatment Groups and Duration:

The study design is shown in Figure 1 below. The schedule of assessments is detailed in Table 3.

The study includes 3 cohorts and approximately 36 participants will be enrolled. In each cohort, approximately 12 participants will be randomized to receive either INCB054707 (n = 9) or placebo (n = 3). The total duration of therapy for all enrolled participants is 8 weeks with a 30-day safety follow-up period. Cohort progression will be determined by the SRC evaluation of safety data following completion of Week 4 of all participants from a cohort (see Section 6.5.2).

Table 3: Schedule of Assessments

Evaluation	Section	Screening	Treatment						Safety Follow-Up
		Day -28 to -1	Day 1[a]	Week 1 ± 1 day	Week 2[b] ± 3 days	Week 4[a] ± 3 days	Week 6[b] ± 3 days	Week 8[a] ± 3 days (EOT)	30 days + 5 days (EOS)
Administrative/screening procedures									
Informed consent	8.1.1	X							
Demography/medical history	8.1.6	X							
Inclusion/exclusion criteria	5	X	X						
Prior/concomitant medications	6.7	X	X	X	X	X	X	X	X
Serology	8.3.5.2	X							
Urinalysis	8.3.5.2	X						X	
TB screening	8.3.5.2	X							
FSH[c]	8.3.5.2	X							
Pregnancy testing[d]	8.3.5.3	X	X	X	X	X	X	X	X
Contact IWRS	8.1.3	X	X	X	X	X	X	X	
Randomization to treatment arm	8.1.3		X						
Dispense study drug	6.1		X			X			
Collect study drug and assess compliance	6.4			X	X	X	X	X	
Distribute reminder cards	8.1.4	X	X	X	X	X	X	X	
Electronic diary verification	8.1.5		X	X	X	X	X	X	X
Safety procedures/assessments									
Comprehensive physical examination[e]	8.3.2	X						X	
Targeted physical examination	8.3.2		X	X	X	X	X		X
Vital signs	8.3.3	X	X	X	X	X	X	X	X
Hematology and chemistry assessments[f]	8.3.5.1, 8.6	X	X	X	X[f]	X[f]	X[f]	X	X
Lipid panel	8.3.5.1		X					X	
CRP	8.3.5.1		X					X	
12-lead ECG (screening)[g]	8.3.4	X							
12-lead ECG (predose and postdose)[g]	8.3.4		X			X			
12-lead ECG (predose only)[g]	8.3.4							X	
Assess AEs	8.3.1, 9	X	X	X	X	X	X	X	X

Table 3: Schedule of Assessments (Continued)

Evaluation	Section	Screening	Treatment						Safety Follow-Up
		Day -28 to -1	Day 1[a]	Week 1 ± 1 day	Week 2[b] ± 3 days	Week 4[a] ± 3 days	Week 6[b] ± 3 days	Week 8[a] ± 3 days (EOT)	30 days + 5 days (EOS)
Efficacy assessments									
Hurley Stage	8.2.1	X						X	X
AN count (HiSCR)	8.2.2	X	X	X	X	X	X	X	X
Modified Sartorius score	8.2.3		X					X	X
Record rescue lesional treatment	8.2.4			X	X	X	X	X	X
HS Pain NRS[h]	8.2.5		X	X	X	X	X	X	X
Evaluate daily analgesic use	8.2.6		X	X	X	X	X	X	X
HS-PGIC	8.2.7			X	X	X	X	X	X
DLQI	8.2.8		X	X	X	X	X	X	X
Optional photography (target area)	8.2.9		X			X		X	
[redacted]									

[a] An overnight (at least 8-hour) fast will be required at these visits. Participant will take study drug at the study sites.
[b] Participants will take study drug before the study visit.
[c] For confirmation of nonchildbearing status for women who are postmenopausal, defined as amenorrhea at least 12 months before screening.
[d] For women of childbearing potential only. Serum test will be conducted at screening and urine test will be conducted at all other visits.
[e] A brief neurological examination will also be performed.
[f] If there is a potential clinically significant abnormality in chemistry or hematology assessments (particularly in platelet count) at Week 2, 4, or 6, then an unscheduled visit the following week (Weeks 3, 5, 7) to repeat the assessment is required.
[g] See Table 10.
[h] The HS Pain NRS includes worst pain and average pain in the last 24 hours.
[redacted]

2. INTRODUCTION

INCB054707 is a JAK1 inhibitor. Janus kinase signaling regulates many different proinflammatory signaling pathways and is now well-recognized as a key driver for numerous inflammatory skin diseases. [redacted]

2.1. Background

2.1.1. Hidradenitis Suppurativa

Hidradenitis suppurativa is a chronic disease characterized by recurrent, painful, deep-seated, rounded nodules and abscesses of apocrine gland-bearing skin. Abscesses typically rupture and release purulent drainage. Abscesses and nodules may heal with scarring and the formation of fistulas or sinus tracts (Revuz 2009). Thus, many patients with HS develop permanent sequelae of past inflammation that are only remediable through surgical excision of the involved skin areas. Onset is usually after puberty, although it is most common during the third decade of life and may persist in old age. The prevalence rate is about 1% (range: 0.2%-4%; Jemec et al 1996, Revuz et al 2008). Axillary and inguinal involvement is more common in females; perianal and buttocks localizations are prevalent in males. Genetic susceptibility, smoking, and obesity are important risk factors for the development of HS. An association between HS and metabolic syndrome has recently been established (Miller et al 2014).

Hidradenitis suppurativa significantly affects healthcare costs and health-related quality of life. A recent study indicates that HS imposes a greater negative impact on quality of life than does psoriasis (Hamzavi et al 2017). Rare complications of HS include fistula formation into the urethra, bladder, rectum, or peritoneum; lymphedema of the limbs or scrotal elephantiasis; and squamous cell carcinomas of the skin originating from HS lesions.

The pathogenesis of HS has not yet been fully elucidated. It has been suggested that follicular plugging followed by the release of follicular material into the dermis are primary events that activate the immune system. Defects in host defense mechanisms as well as innate and adaptive immunity may also contribute. Unravelling which cytokines are involved has been the main objective of several studies. Recently, it has been shown that the IL-23/Th17 and IL-12/Th1 pathways are expressed in HS skin (Schlapbach et al 2011). Although TNF-α presents in inflammatory HS skin, several studies indicate that it may not be the key contributor in the pathogenesis of this disease (Kelly et al 2015, van der Zee et al 2012, Moran et al 2017), suggesting opportunities for other potential therapeutic targets.

2.1.2. Current Treatment and Unmet Need in Hidradenitis Suppurativa

Treatment of HS depends on the extent and activity of disease. Current European guidelines for the treatment of HS generally recommend topical clindamycin or oral tetracycline as first-line therapy for mild disease (Gulliver et al 2016, Zouboulis et al 2015). For moderate to severe disease, oral clindamycin and rifampin combination therapy are used as first-line treatment, and adalimumab (TNF-α inhibitor) is used as a second-line treatment. Of note, the latter is the only

US FDA-approved systemic therapy for HS. In more severe cases with extensive scarring, surgical intervention is used to remove the nondynamic components of HS (eg, scarring, fistulas, and sinus tracts) that are not expected to respond to drug therapy. These comprise a number of surgical procedures (eg, incision and drainage, de-roofing, and excision) laser (Nd:YAG) and radiation therapy (Jemec 2012). Other systemic/pharmacologic therapies include drugs such as acitretin, isotretinoin, dapsone, antiandrogens (in female patients), intralesional injections of triamcinolone, and a number of TNF-α inhibitors (Rambhatla et al 2012).

Given that the current pharmacologic treatments are moderately effective at best, are not approved for HS (except for adalimumab), and are often associated with significant side effects, there is a need for new effective agents for the treatment of HS. Although several biologic agents are undergoing clinical investigation at this time (IL-17 inhibitors: bimekizumab and secukinumab), an oral treatment with a JAK1-inhibitor such as INCB054707 has the potential to address an unmet medical need for patients with HS.

2.1.3. JAK-STAT Signaling in Inflammatory Skin Disease

The JAK family of kinases includes JAK1, JAK2, JAK3, and TYK2. The JAK-STAT pathway is used by cytokines including ILs, interferons, and other molecules to transmit signals from the cell membrane to the nucleus. Upon engagement of extracellular ligands, intracellular JAK proteins, which associate with type I/II cytokine receptors, become activated and phosphorylate STAT proteins, which dimerize and then translocate into the nucleus to directly regulate gene expression. Among all JAK family members, JAK1 signaling relates primarily to cytokines involved in inflammation (Rawlings et al 2004).

Numerous inflammatory dermatoses are driven by soluble inflammatory mediators, which rely on JAK-STAT signaling. [redacted]

To date in dermatology, psoriasis has been the most studied indication for JAK inhibitors including tofacitinib, baricitinib, and ruxolitinib. The sponsor has completed 4 clinical studies with JAK1 and JAK2 inhibitors for the treatment of psoriasis. Both topical ruxolitinib (Punwani et al 2015) and oral INCB039110 (Bissonnette et al 2013) have been associated with clinical improvement and benefit in patients with chronic plaque psoriasis. [redacted]

2.2. Study Rationale

Given that TNF-α may not be the major driver for HS pathogenesis, and that there is a relatively high number of patients who do not sufficiently respond to therapy with the only approved HS medication impacting that pathway (adalimumab, a TNF-α inhibitor), there remains a significant unmet need for new treatments for HS.

2.2.1. Scientific Rationale for Study Design

Recent literature suggests that the main cytokines involved in HS pathogenesis are IL-1β, IL-17, IL-23, IL-10, and, to a lesser extent, TNF-α (Kelly and Prens 2016). The expression and/or activity of these cytokines is profoundly regulated by the intracellular level through JAK-STAT signaling, and is primarily mediated by JAK1 (see Section 2.1.3).

In this study, the safety and tolerability of 3 doses of INCB054707 will be evaluated in adult participants with moderate to severe HS and compared with placebo. A dose-escalation design has been chosen to evaluate the safety and tolerability of dose of

INCB054707 in a step-wise fashion. Placebo treatment will facilitate unbiased safety assessments and is acceptable in this patient population in the short term. Each cohort's safety data will be reviewed before advancing to the next dose level. Eight weeks study drug exposure is an adequate duration to evaluate potential adverse hematologic effects and beneficial effects in HS and to support larger subsequent studies of longer duration.

For participants experiencing bothersome symptoms related to either rapid abscess formation or secondary infection at the diseased sites, appropriate rescue treatments will be offered to immediately evacuate pus (incision and drainage), alleviate the level of inflammation (intralesional triamcinolone), or control infection (see Sections 6.7.1 and 8.2.4).

It is expected that the outcome of this study will be instrumental by informing a larger dose-ranging Phase 2b study.

2.2.2. Justification of Dose

[redacted]

This study will evaluate up to 8 weeks of daily oral doses of INCB054707 in 3 sequential ascending dose groups [redacted] with matching placebo in a blinded fashion. All doses studied are within a dose range previously shown to be safe and well-tolerated following 10 days of administration in healthy participants. Estimated exposure margins using the exposures at the no-observed-adverse-effect levels from the 6-month toxicity study in the rat and the 9-month toxicity study in the dog are approximately 4- to 6-fold in rats and approximately 0.2- to 0.3-fold in dogs. The low AUC margins in dogs are driven primarily by secondary effects caused by immunosuppression subsequent to JAK inhibition. Most notably, demodectic mange observed in longer-term dog studies, which would not be expected in humans, often progressed to the point of requiring euthanasia. There was no evidence of off-target toxicity in dogs.

[redacted]

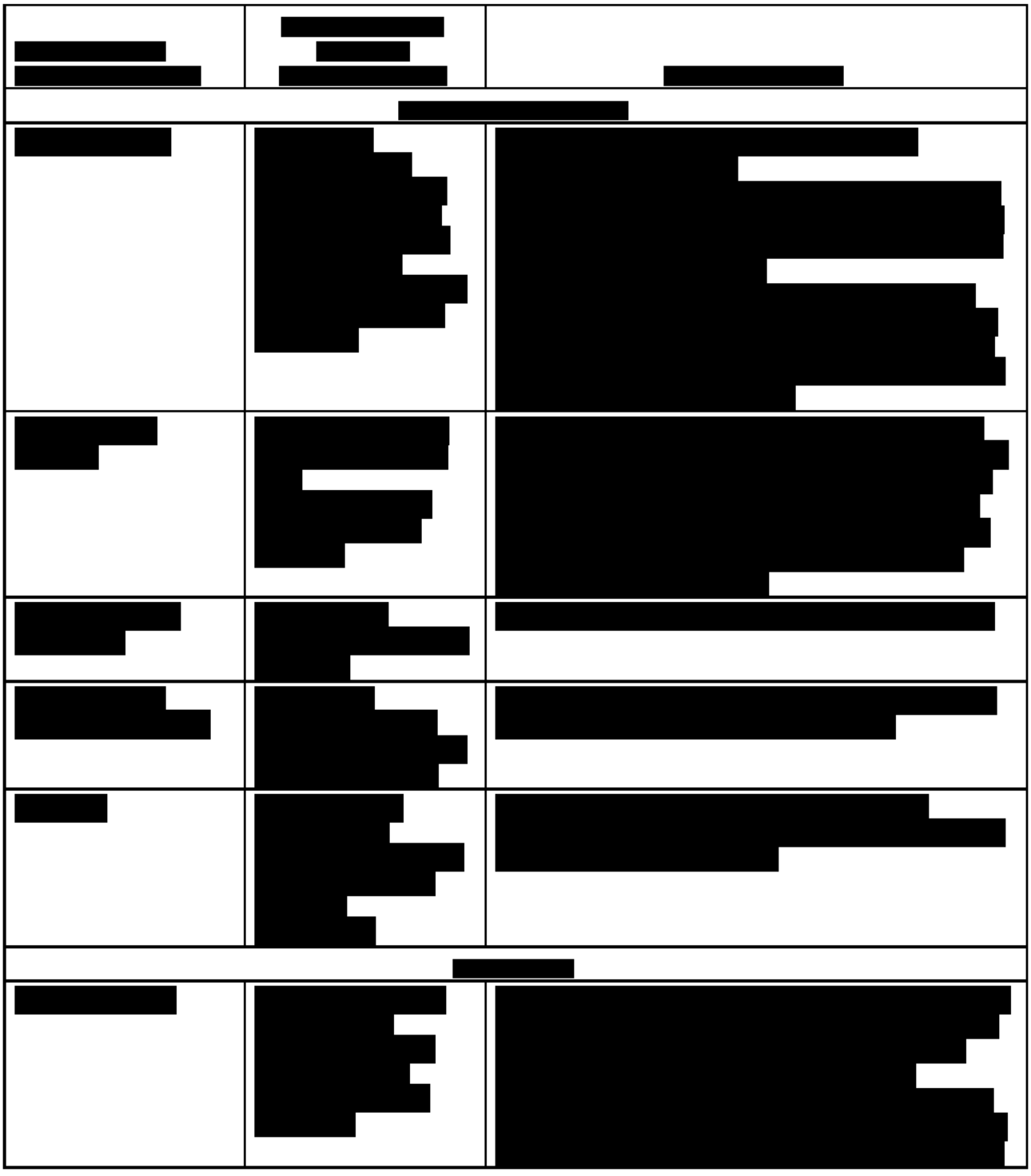
[redacted]

2.3.2. Clinical Studies

In 2 healthy volunteer studies with single doses of INCB054707 up to 405 mg, multiple doses of INCB054707 up to 120 mg, or placebo for up to 10 days, mild to moderate headaches were reported in up to 31% of participants in the multiple-dose study. The events resolved spontaneously following discontinuation of INCB054707.

[redacted]

[redacted]



2.3.3. Benefit Assessment

Participants may experience clinically meaningful improvements in their HS lesions 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).

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

2.3.4. Benefit-Risk Conclusion

Taking into account the safety measures taken to minimize risk to participants in this study, the potential risks identified in association with INCB054707 are justifiable and appropriately balanced by the anticipated efficacy benefits expected to be afforded to this specific group of participants and, more broadly, to the general population of patients with HS. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of INCB054707 may be found in the INCB054707 IB.

3. OBJECTIVES AND ENDPOINTS

Table 5 presents the objectives and endpoints.

Table 5: Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the safety and tolerability of INCB054707.	• Frequency, duration, and severity of AEs, clinical laboratory test results, vital signs results, ECGs, and physical examination findings.
Secondary	
To determine the systemic exposure to INCB054707.	• Population PK parameters of INCB054707.
To determine the efficacy of INCB054707.	• Proportion of participants achieving a HiSCR at each visit. • Proportion of participants achieving an AN count of 0 to 2 at each visit. • Mean change from baseline in the HS Pain NRS scores, worst and average pain, at each visit. • Mean change from baseline to Week 8 in the modified Sartorius scale score. • Mean change from baseline in the number of draining fistulas count at each visit. • Proportion of participants at each category of Hurley Stage at baseline and Week 8. • Proportion of participants with change from baseline in Hurley Stage at Week 8. • Proportions of participants in each HS-PGIC category during the treatment period. • Actual measurements in HS-PGIC at each visit.
To assess the need for rescue lesional treatment.	• Proportion of participants requiring rescue lesional treatment. • Number of interventions with rescue lesional treatment.
To assess patient-reported quality-of-life burden.	• Proportion of participants at each scoring category of DLQI at each visit. • Mean change from baseline in DLQI total scores at each visit.

Table 5: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, multicenter, randomized, placebo controlled, dose escalation study to evaluate the safety of INCB054707 [redacted] over an 8-week treatment period in men and women aged 18 to 75 years with moderate to severe HS with a targeted enrollment of approximately 36 participants (see Figure 1).

The study includes 3 cohorts, and approximately 36 participants will be enrolled. In each cohort, approximately 12 participants will be randomized to receive either INCB054707 (n = 9) or placebo (n = 3; randomization 3:1). The total duration of therapy for all enrolled participants is 8 weeks followed by a 30-day safety follow-up period. After all participants in each cohort have completed the Week 4 study visit and assessments, a SRC will review safety data. See Section 6.5.2 for detail procedures for cohort review and dose escalation.

4.2. Overall Study Duration

The study will consist of a screening period of up to 28 days, an 8-week treatment period, and a 30-day safety follow-up period. The estimated total duration of study participation is approximately 16 weeks for each participant.

4.3. Study Termination

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

The sponsor may terminate the study electively or if required by regulatory decision or upon advice of the SRC. If the study is terminated prematurely, the sponsor or designee will notify the investigators, the IRBs/IECs, and regulatory bodies of the decision and reason for termination of the study. The SRC will recommend termination of the study if warranted, as described in Section 6.5.2.

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. Men and women aged 18 to 75 years at the time of consent.
2. Diagnosis of HS (confirmed by a dermatologist) with a disease duration of at least 6 months before screening.
3. Stable course of HS for at least 90 days before screening, as determined by the investigator.
4. HS lesions present in at least 2 distinct anatomic areas, 1 of which must be Hurley Stage II (ie, recurrent abscessed with tract formation and cicatrization; single or multiple, widely separated lesions) or Hurley Stage III (ie, diffuse or near diffuse involvement, or multiple interconnected tracts and abscesses across the entire area) at screening.
5. Total AN count of at least 3 at screening and baseline.
6. Willingness to avoid pregnancy or fathering children based on the criteria below:
    a. Male participants must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through 90 days after the last dose of study drug. Male participants must also refrain from donating sperm during this period. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participant and his understanding confirmed.

b. Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test before the first dose on Day 1 and must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
c. Women of nonchildbearing potential (ie, surgically sterile [hysterectomy, bilateral oophorectomy, or bilateral salpingectomy] OR postmenopausal, defined as ≥ 12 months of amenorrhea before screening without an alternative medical cause, confirmed by FSH levels at screening) are eligible.

5.2. Exclusion Criteria

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

1. Women who are currently pregnant or lactating.
2. Presence of > 20 draining fistulas at screening and baseline.
3. Participants with concurrent conditions or history of other diseases, as follows:
   a. Any clinically significant medical condition other than HS, as determined by the investigator, that is not adequately controlled with appropriate treatment.
   b. Any other active skin disease or condition (eg, bacterial, fungal, or viral infection) that may interfere with the course, severity, or assessments of HS.
   c. Active systemic viral infection or any active viral infection that, based on the investigator's clinical assessment, make the participant an unsuitable candidate for the study.
   d. Current herpes zoster infection, a history of recurrent herpes zoster, a history of disseminated herpes simplex, or a history of herpes zoster.
   e. 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.
   f. Albinism.
4. Prolonged QT interval corrected for heart rate using Fridericia's formula (QTcF), defined as ≥ 450 msec.

   Note: Prolonged QTcF values of ≥ 450 msec 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.
5. Positive test result for TB from the QuantiFERON-TB Gold test, or T-SPOT.TB test at screening (or, if two indeterminate tests, then as evaluated by a purified protein derivative test with a result of < 5 mm of induration within 3 months of screening).

6. A history of active TB (treated or untreated) or a history of untreated latent TB.

   Note: If the participant has possible evidence of a latent TB infection, the participant must have documented completion of an adequate course of therapy for latent TB and provide recent (within 3 months) posteroanterior and lateral view chest X-rays without changes suggestive of active or latent TB, before baseline.

7. Positive serology test results for HIV, HBsAg, HBV core antibody, or HCV (HCV-antibody with positive HCV-RNA) at screening.

8. Decreased blood cell counts at screening, defined as follows:

   a. Leukocytes $< 3.0 \times 10^9$/L ($< 2.5 \times 10^9$/L for participants who are African-American).
   b. ANC $< 1.5 \times 10^9$/L.
   c. Lymphocytes $< 0.8 \times 10^9$/L.
   d. Hemoglobin < 10 g/dL.
   e. Platelets $< 150 \times 10^9$/L.

9. Severely impaired liver function (Child-Pugh Class C) or ALT or AST levels $\geq 1.5 \times$ ULN at screening.

10. Impaired renal function with serum creatinine > 1.5 mg/dL at screening.

11. Use of the following medications:

    a. Previous use of JAK inhibitors, systemic or topical (eg, ruxolitinib, tofacitinib, baricitinib, filgotinib, lestaurtinib, and pacritinib).
    b. Previous use of adalimumab or any other TNF-α treatment within 12 weeks or 5 half-lives (whichever is longer) before baseline.
    c. Use of any investigational or experimental treatments within 12 weeks or 5 half-lives (whichever is longer) before baseline.
    d. Systemic immunosuppressive or immunomodulating drugs (eg, oral or injectable corticosteroids, methotrexate, cyclosporine, and azathioprine) within 4 weeks or 5 half-lives (whichever is longer) before baseline.
    e. Other systemic therapies for HS (eg, retinoids and antiandrogens) with potential therapeutic impact for HS within 4 weeks or 5 half-lives (whichever is longer) before baseline.
    f. Surgical, laser, or IPL intervention in area with HS lesion within 4 weeks before baseline.
    g. Systemic anti-infectives (eg, antibiotics, antivirals, antifungals) within 4 weeks, except as described in Section 6.7.1.1 for antibiotic therapy, or topical anti-infectives on HS lesions (eg, antibiotics, antivirals, antifungals) within 2 weeks before baseline.
    h. Received live vaccine within 6 weeks before baseline or planning to receive live vaccine during the course of the study or within 6 weeks after EOT.

i. Topical antiseptic washes, creams, soaps, ointments, gels, and liquids containing antibacterial agents to treat HS, except those listed in Sections 6.7.1.3 and 6.7.1.4, within 2 weeks before baseline.
j. Potent systemic CYP3A4 inhibitors and inducers (see Study Manual) or fluconazole within 2 weeks or 5 half-lives (whichever is longer) before baseline.
Note: Topical agents with limited systemic availability are permitted.

12. Known or suspected allergy to INCB054707 or any component of the study drug.
13. Known history of clinically significant drug or alcohol abuse in the last year before baseline.
14. For participants consenting to biopsies only:
    a. Participant has a history of an allergic reaction or significant sensitivity to lidocaine or other local anesthetics.
    b. Participant has a history of hypertrophic scarring or keloid formation in scars or suture sites.
    c. Participant is taking anticoagulant medication, such as heparin, low molecular weight–heparin, warfarin, and antiplatelets (nonsteroidal anti-inflammatory drugs and low-dose aspirin will be allowed), or has a contraindication to skin biopsies.
15. Inability or unlikeliness of the participant to comply with the dose schedule and study evaluations, in the opinion of the investigator.
16. Inability of the participant (or parent, guardian, or legally authorized representative) to comprehend or unwilling to sign the ICF.

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

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

Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes that the participant would be eligible if retested. 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 are rescreened must reconsent and be assigned a new participant number.

5.5. Replacement of Participants

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

6. STUDY TREATMENT

6.1. Study Treatment Administered

Information regarding study drug and administration is provided in Table 6. Participants will record study drug administration in a daily electronic diary.

Table 6: Study Treatment Information

	Study Treatment 1	Study Treatment 2
Study treatment name:	INCB054707	Matching placebo
Dosage formulation:	Tablet	Tablet
Unit dose strength(s)/ Dosage level(s):	[redacted]	[redacted]
Route of administration:	Oral	
Administration instructions:	INCB054707 and matching placebo will be taken orally once daily with water without regard to food, preferably in the morning.	
Packaging and labeling:	INCB054707 will be provided as [redacted] tablets, packaged in blister cards, and labeled as required per country requirement.	
Storage:	Ambient (15°C-30°C/59°F-86°F)	

6.2. Preparation, Handling, and Accountability

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 tablet counts from each supply dispensed.
- Return of study drug to the investigator or designee by participants.

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

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional SOPs. 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.

Further guidance and information for the final disposition of unused study treatments are provided in the Study Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Randomization to treatment will occur centrally by IWRS (see Section 8.1.3). Full details will be provided in the IWRS Manual.

Participants, investigators, and the sponsor will be blinded to each participant's initial treatment assignment. Emergency unblinding will occur if an AE requires the investigator to be made aware of the participant's treatment assignment (see emergency unblinding procedures in Section 9.6).

6.4. Study Treatment Compliance

Compliance with all study-related treatments should be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with INCB054707 will be calculated by the sponsor based on the drug accountability documented by site personnel and monitored by the sponsor/designee using tablet counts. Participants will be instructed to bring all study drug with them to all 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-Limiting Toxicity and Determination of Maximum Tolerated Dose and/or Pharmacologically Active Dose

6.5.1. Definition of a Dose-Limiting Toxicity

Dose-limiting toxicity will be defined as the occurrence of any of the evens listed in Table 7 occurring up to Week 8 (EOT), except those with a clear alternative explanation not related to study drug. All DLTs will be assessed for severity by the investigator using CTCAE v4.03 criteria. Participants who receive at least 1 dose of study drug at the level assigned or have a DLT will be considered evaluable for determining tolerability of the dose.

Table 7: Definition of Dose-Limiting Toxicity

Toxicity	Definition
Nonhematologic	• Any liver function abnormalities that meet the definition of Hy's law.[a] • Any ≥ Grade 3 nonhematologic toxicity **EXCEPT:** – Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms. – Nausea, vomiting, and diarrhea adequately controlled with medical therapy within 48 hours. – An event clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity. – Asymptomatic changes in lipid profiles.
Hematologic	• Grade 2 neutropenia (neutrophils: 1 to < 1.5×10^9/L) with ≥ Grade 3 infection. • ≥ Grade 3 neutropenia (neutrophils: < 1×10^9/L). • ≥ Grade 2 thrombocytopenia (platelets: < 75×10^9/L). • Grade 4 anemia (hemoglobin: < 6.5 g/dL).
Events of special interest	• Serious infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens; viral reactivation; malignancy.

[a] Hy's law is defined as 1) ALT or AST elevation > 3 × ULN, 2) total bilirubin > 2 × ULN without initial findings of cholestasis (elevated serum alkaline phosphatase), AND 3) no other apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.5.2. Procedures for Cohort Review and Dose Escalation

After all participants in each cohort have completed the Week 4 visit and assessments, a SRC will review safety data on a blinded basis from that cohort. If blinded data are determined to support the safety and tolerability of the dose for that cohort, the next higher dose cohort may open to enrollment. If necessary, the SRC may request to further review unblinded safety data from that cohort at Week 4. In the case that the unblinded data at Week 4 is not enough to support dose escalation, the SRC can also choose to wait until all participants complete Week 8 assessment and then make the decision. The SRC could also make a recommendation to expand a cohort to obtain additional safety data.

A participant's randomization will be unblinded for the SRC if the participant experiences any of the DLTs listed in Table 7 and the DLT is attributed to study drug. If ≥ 3 participants in any cohort treated with INCB054707 have DLTs or the study drug is considered not tolerable, then the escalation will be terminated.

After the completion of a cohort, the sponsor may also be unblinded to safety and efficacy data from that cohort.

Telephone conferences will also be scheduled by the sponsor with active study investigators in order to review cohort-specific data and overall safety data, agree on dose escalation, adjudicate individual high-grade AEs as potentially dose-limiting, and guide other major study decisions.

6.6. Dose Modifications

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

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

6.6.2. Follow-Up of Dose-Limiting Toxicities

Any DLT should be monitored until it resolves to baseline or appears to have stabilized for a minimum of 2 weeks. During follow-up, participants should be seen as often as medically indicated to assure safety, in consultation with the medical monitor.

6.6.3. 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 INCB054707 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 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.

Table 8: Guidelines for Interrupting, Restarting, and Discontinuing Study Drug

ADVERSE EVENT	ACTION TAKEN
Chemistry	
AST and/or ALT > 3.0 × ULN	**Step 1:** Interrupt study drug administration up to 2 weeks (14 days) until the toxicity has resolved to ≤ 3.0 × ULN. **Step 2:** Restart study drug, and monitor as described specifically in Section 9.3.
AST and/or ALT > 5.0 × ULN	Discontinue study drug administration, and monitor as described specifically in Section 9.3.
Hematology	
Platelet counts 50 to < 100 × 10^9/L or ≥ 50% decrease from baseline	**Step 1:** Interrupt study drug administration up to 2 weeks (14 days) until the toxicity has resolved to ≥ 100 × 10^9/L. **Step 2:** Restart study drug, and monitor as described in Section 9.3.
ANC 0.5 to < 1.0 × 10^9/L	**Step 1:** Interrupt study drug administration up to 2 weeks (14 days) until the toxicity has resolved to ≥ 1 × 10^9/L or the baseline value. **Step 2:** Restart study drug, and monitor as described specifically in Section 9.3.
Hemoglobin 8 to < 10 g/dL or > 2 g/dL decrease from baseline	**Step 1:** Interrupt study drug administration up to 2 weeks (14 days) until the toxicity has resolved ≥ 10 g/dL or ≤ 2 g/dL decrease from baseline. **Step 2:** Restart study drug, and monitor as described specifically in Section 9.3.
• Platelet count < 50 × 10^9/L • ANC < 0.5 × 10^9/L • ANC < 1.0 × 10^9/L with an oral temperature of at least 38.5°C OR with ≥ Grade 3 infection • Hemoglobin < 8 g/dL	Discontinue study drug administration, and monitor as described specifically in Section 9.3.
Other toxicities	
Any Grade 1 or Grade 2 toxicity	Continue study drug and treat the toxicity; monitor as described specifically in Section 9.3.
Any Grade 3 toxicity except those defined in Table 7 (exception for any ≥ Grade 3 nonhematologic toxicity)	**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 described specifically in Section 9.3.
Any other Grade 4 toxicity	Discontinue study drug administration and follow-up as described in specifically Section 8.8.

6.7. 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 HS 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 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.

6.7.1. Permitted Medications and Procedures

6.7.1.1. Antibiotic Therapy

After Week 4, if a participant experiences signs or symptoms indicative of an infection at an HS site (eg, fever and local/regional lymphadenopathy), the following antibiotic therapy may be initiated without interruption of study drug administration:

- Amoxicillin 500 mg/clavulanic acid 125 mg, 2 tablets, 3 times daily for 3 days

In participants for whom amoxicillin is contraindicated, the investigators should consult with the sponsor or designee to discuss alternative treatment options.

6.7.1.2. Analgesic Therapy

If a participant experiences significant pain after baseline, one of the following analgesic regimens may be initiated at any time:

- Ibuprofen (at a dose of up to 800 mg orally every 6 hours) not to exceed 3200 mg/24 hours.
- Acetaminophen not to exceed 4 g/24 hours.

If pain is not sufficiently controlled with one of the above regiments, a revised analgesic regiment can be considered in consultation with the sponsor or designee.

Dose modifications in these analgesics on an as needed basis up to the maximum permitted dose and frequency are allowed during the study.

Analgesic usage (yes/no) will be recorded daily (see Study Manual).

6.7.1.3. Antiseptic Therapy

Permitted antiseptic washes are limited to one of the following: chlorhexidine gluconate, triclosan, benzoyl peroxide, or diluted bleach in bathwater.

6.7.1.4. Wound Care

Concomitant use of wound care dressings on HS wounds is allowed. Options are limited to alginates, hydrocolloids, and hydrogels.

6.7.2. Prohibited Medications and Procedures

The following medications are prohibited for all participants **in the study**:

- JAK inhibitors, systemic or topical (eg, ruxolitinib, tofacitinib, baricitinib, filgotinib, lestaurtinib, and pacritinib).
- Adalimumab or any other TNF-α treatment or any investigational or experimental treatments.
- Systemic immunosuppressive or immunomodulating drugs (eg, oral or injectable corticosteroids, methotrexate, cyclosporine, and azathioprine) except as described in Sections 6.7.3 and 8.2.4.
- Systemic therapies for HS (eg, retinoids and antiandrogens) with potential therapeutic impact for HS.
- Surgical, laser, or IPL intervention in area with HS lesion, except as specified in Section 8.2.4 for rescue lesional treatment.
- Systemic anti-infectives (eg, antibiotics, antivirals, and antifungals), except as described in Section 6.7.1.1 for antibiotic therapy, or topical anti-infectives on HS lesions.
- Conventional therapies with potential therapeutic impact for HS.
- Topical antiseptic washes, creams, soaps, ointments, gels, and liquids containing antibacterial agents to treat HS, except those listed in Sections 6.7.1.3 and 6.7.1.4.
- Potent systemic CYP3A4 inhibitors or inducers (see Study Manual) or fluconazole.

  Note: Topical agents with limited systemic availability are permitted.
- Concomitant uses of P-gp inhibitors and inducers (refer to the Study Manual) need to be consulted with the medical monitor.
- Live vaccines (during the study and within 6 weeks after EOT).

6.7.3. Rescue Lesional Treatments

Rescue lesional treatments are described in Section 8.2.4, as the need for rescue lesional treatment is considered an efficacy assessment.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

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

- The participant becomes pregnant.
- Consent is withdrawn.

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

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

- If, during 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 discontinued from the 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 discussion regarding the participant's continued participation.

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 an EOT visit. These visits are described in Table 3 and Section 8.7. The last date of the last dose of study drug 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 (discontinue date + 30 days) 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 or disease assessment), 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/efficacy 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 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The participant will be counseled regarding 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 with a primary reason of lost to follow-up.

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 country in which the study is being conducted as well as 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

Each participant will be identified in the study by a participant ID number, which is a combination of the site ID and participant number.

Screening is the interval between signing the informed consent and the day that the participant is randomly assigned to the study drug (Day 1). Screening assessments for determination of eligibility may be performed over a period lasting up to 28 days.

Procedures conducted as part of the participant's routine clinical management (eg, clinical laboratory tests) and collected before informed consent is obtained may be used for screening or baseline purposes, provided the procedure meets the Protocol-defined criteria and has been performed within 28 days before Day 1. All information associated with eligibility requirements, including demography and medical history, must be entered into the appropriate eCRF pages.

Results from the screening assessments will be reviewed by the investigators to confirm eligibility before randomization and administration of study drug. Tests results that do not meet eligibility requirements may be repeated once during screening if the investigator believes there is a reasonable possibility that the participant would be eligible if retested. For screening assessments that are repeated, the most recent available result before administration of study drug will be used to determine eligibility. See Section 5.4 regarding screen failures.

8.1.3. Interactive Web Response System 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 personnel should use the IWRS to obtain the participant ID number during screening. Upon determining that the participant is eligible for randomization, the IWRS will be contacted to obtain the treatment assignment. Additionally, the IWRS will be contacted to update the study drug supply (see Table 3). Additional details are provided in the IWRS manual.

8.1.4. Distribution of Reminder Cards

Participants will be provided with a reminder card at the visits indicated at Table 3. The reminder card will indicate the date/time of the next visit and will also remind the participant that they should not take study drug on Day 1, Week 4, and Week 8 as they will take it after blood draws for safety evaluation have been completed.

8.1.5. Electronic Diary

The date and time of the last dose of study drug and the time of their last meal preceding each PK sample collection visit (see Table 12) will be recorded in the eCRF. Daily study drug administration HS pain NRS (see Section 8.2.5) and daily analgesic use (see Section 8.2.6) will be recorded in the electronic diary, which will be completed through the web or by phone.

8.1.6. Demography and Medical History

8.1.6.1. 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 year that are considered to be clinically significant by the investigator.

8.1.6.2. Disease Characteristics and Treatment History

A disease-targeted medical and treatment history will be collected at screening. A detailed history of prior medications use related to HS in the year before screening will be also be collected, as well as response to each treatment and reason for discontinuation.

8.2. Efficacy Assessments

An example of the lesion count worksheet is provided in the Study Manual and will be used for assessment of Hurley Stage, HiSCR, modified Sartorius scale, [redacted] It includes assessment of 12 anatomic regions: left/right axilla, left/right sub/inframammary area, intermammary area, left/right buttock, left/right inguino-crural fold, perianal area, perineal area, and other areas. Additionally, the need for rescue lesional treatment, including number of interventions, will be documented in this worksheet.

8.2.1. Hurley Stages of Hidradenitis Suppurativa

Hurley Stages of HS are defined in Table 9. The investigator will determine the Hurley Stage in each affected anatomical region at the designated study visits listed in Table 3. If more than 1 stage is present in a region, the **worst** stage in each region should be documented. The participant is assigned Hurley Stage corresponding to the Hurley Stage of his or her **worst** involved anatomic region. The Hurley Stages of HS in screening visit is considered as baseline value.

Table 9: Hurley Stages of Hidradenitis Suppurativa

Stage	Description
I	Abscess formation (single or multiple) without sinus tracts and cicatrization.
II	Recurrent abscesses with tract formation and cicatrization; single or multiple, widely separated lesions.
III	Diffuse or near-diffuse involvement or multiple interconnected tracts and abscesses across the entire area.

8.2.2. Hidradenitis Suppurativa Clinical Response (Abscess and Inflammatory Nodule Count)

An HiSCR is defined as at least 50% reduction in AN count with no increase in abscess count and no increase in draining fistula (see definition below) count relative to baseline at each visit (refer to the Study Manual; Kimball et al 2016).

A fistula is a pathologic passageway connecting to the skin surface from dermis or subcutaneous tissue. Draining fistulas are fistulas that drain serous or purulent fluid, either spontaneously or by gentle palpation.

8.2.3. Modified Sartorius Scale

The modified Sartorius scale is a measure of the severity of HS (refer to the Study Manual; Sartorius et al 2003).

Points are given as follows for each body area: 2 points for each nodule (both inflammatory and noninflammatory); 4 points for each abscess; 4 points for each fistula (both draining and nondraining); 1 point for each scar; 2 to 6 points for the longest distance between 2 lesions or 0 points if no lesions; and 6 points if lesions are not separated by normal skin or 0 points if lesions are separated by normal skin. The "other area" only with the highest modified Sartorius scale at baseline will be calculated, and the same area should be evaluated throughout the study. The total modified Sartorius scale score is the sum of the 12 anatomic region scores.

8.2.4. Need for Rescue Lesional Treatment

The need for lesional rescue treatment will be recorded as a measure of efficacy.

In the event of an acutely painful lesion that requires immediate intervention, investigators will have the option to perform Protocol-allowed interventions. Two types of interventions are permitted: injection with intralesional triamcinolone acetonide suspension (up to 30 mg in total at the same visit) and/or incision and drainage. If incision and drainage is performed, participants should continue using the same over-the-counter antiseptic as previously. New systemic and topical therapies following incision and drainage, including antibiotics, are prohibited. Concomitant use of wound care dressings is allowed as described in Section 6.7.1.4. Participants should continue using any oral and topical therapies during the study, consistent with the allowances and restrictions described in Section 6.7.1.

From Day 1 through Week 8 (EOT), an intervention can occur on a maximum of 2 different lesions at the same visit or on the same lesion at 2 different study visits. The same lesion cannot be treated 2 times during the same visit. If participants require more than 2 interventions before Week 8 (EOT), then the study drug will be discontinued for those participants.

Study procedures must be performed before any interventions. Any lesion undergoing an intervention will be documented in the lesion count worksheet (refer to the Study Manual). The site will be required to count any lesion that undergoes an intervention as permanently present from the date of the intervention, and must account for it in the source and on the appropriate eCRF.

8.2.5. Hidradenitis Suppurativa Pain Numeric Rating Scale

The HS Pain NRS (refer to the Study Manual) will be completed in a daily diary by participants from Day1 through the follow-up visit (EOS). An 11-point scale will be used to assess the worst skin pain and the average skin pain due to HS. Ratings for the 2 items range from 0 ("no skin pain") to 10 ("skin pain as bad as you can imagine"). Assessments will be recorded before bedtime (participants who go to bed after midnight should complete the assessment before midnight) and will be based on a recall period of the last 24 hours.

8.2.6. Analgesic Use

From Day1 through the follow-up visit (EOS), participants will complete a daily electronic diary of their analgesic use (yes/no; refer to the Study Manual). All analgesics and dose modifications will be captured in the source and on the appropriate eCRF.

8.2.7. Hidradenitis Suppurativa Patient Global Impression of Change

Participants will complete the HS-PGIC questionnaire at the designated study visits listed in Table 3. The HS-PGIC consists of 1 self-administered item that assesses change in the severity of skin in the HS area. Participants are asked to indicate their impression of change compared with their previous visit. The participant will answer the following: "Since your last visit, your HS is: (1) very much improved, (2) much improved, (3) minimally improved, (4) no change, (5) minimally worse, (6) much worse, or (7) very much worse." The participant should complete the questionnaire before site personnel perform any efficacy assessments.

8.2.8. Dermatology Life Quality Index

Participants will complete a DLQI questionnaire (refer to the Study Manual) from Day1 through the follow-up visit (EOS). The DLQI will be used to assess the symptoms and the impact of skin problems on quality of life (Hongbo et al 2005). The DLQI can be used to evaluate the impact of HS on daily activities, based on 6 areas: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Participants will be asked to respond to the 10 items of the DLQI based on a recall period of "the last week." Decreased scores indicate improved health-related quality of life. The participant should complete the questionnaire before site personnel perform any efficacy assessments.

8.2.9. Photography of Target Lesions

For participants who consent to photography, a target area for each participant will be identified at screening and the same area should be photographed at visits specified in Table 3 for purposes of documentation. The lesion should be located in an area with inflammatory nodules and/or abscesses that are a good representation of the disease severity.

8.3. Safety Assessments

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF up until the end of the safety follow-up period. Adverse events that begin or worsen after informed consent should be recorded on the Adverse Event 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, or that caused the participant to discontinue the study treatment. 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 time points 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 include blood pressure, pulse, respiratory rate, and body temperature. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after 5 minutes of rest. Any abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

8.3.4. Electrocardiograms

All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after at least 5 minutes of rest. Electrocardiograms should be performed as indicated in Table 3 and Table 10. Additional 12-lead ECGs may be performed at other visits as deemed clinically necessary.

Electrocardiograms will be interpreted by the investigator at the site or designee, and the results will be used for immediate management of the participant's care. The decision to include or exclude a participant or withdraw a participant from the study based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate. Any abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

Table 10: Electrocardiogram Schedule

Study Visit	Timing of Electrocardiogram Relative to Administration of Study Drug		
	Not Applicable	Predose (Trough) ECG[a]	Postdose (Postdose 2) ECG[b]
Screening[c]	Single → Triple[d]		
Day 1		Triple[e]	Single → Triple[d]
Week 4		Single → Triple[d]	Single → Triple[d]
Week 8		Single → Triple[d]	

[a] Predose ECG should be performed 5 to 10 minutes before the predose [redacted].

[b] Postdose ECGs will be performed after participants complete all of the study assessments but before the collection of the second postdose (postdose 2) [redacted] (see Table 12). Postdose ECG will be measured [redacted]

[c] Prolonged QTcF values of ≥ 450 msec 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.

[d] Single → Triple: Single ECG will be performed first. If prolonged QT interval (corrected for heart rate using Fridericia's formula [QTcF], defined as ≥ 450 msec) are observed, an additional 2 ECGs will be measured within the next 5 minutes.

[e] Day 1 predose ECG will be performed in triplicate, and values will be averaged to calculate the baseline values.

8.3.5. Laboratory Assessments

8.3.5.1. Safety Assessments

Required laboratory tests are listed in Table 11. Safety laboratory tests include hematology, chemistry, CRP, and lipid panel (see Table 3). Participants may have a light snack before these visits but should allow for an overnight fast (at least 8 hours) before sample collection for the lipid panel.

If there is a potential clinically significant abnormality in hematology or chemistry assessments (particularly in platelet count) at Weeks 2, 4 or 6, then an unscheduled visit the following week (Weeks 3, 5, 7; see Section 8.6) to repeat laboratory assessments is required.

Clinical laboratory tests will be performed at a central laboratory (refer to the Laboratory Manual for sample handling and shipping instructions).

8.3.5.2. Screening Assessments

Screening laboratory tests (see Table 11) include urinalysis, serology, TB screening, pregnancy test (for women of childbearing potential) and an FSH test for confirmation of nonchildbearing status in women who are postmenopausal, defined as amenorrhea at least 12 months before screening. Refer to the Laboratory Manual for screening assessment instructions.

8.3.5.3. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during screening. Urine pregnancy tests will be conducted as outlined in Table 3, as medically indicated, or per country-specific requirement. Urine pregnancy tests will be performed locally. If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test, which may be performed locally.

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

If a pregnancy is confirmed by a serum pregnancy test, see Section 9.7 for reporting requirements.

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted] [redacted]

	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]
[redacted]		[redacted]	[redacted]
[redacted]	[redacted]		[redacted]
[redacted]		[redacted]	[redacted]
[redacted]	[redacted]		[redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

8.6. Unscheduled Visits

Unscheduled visits may occur at any time at the investigator's discretion, and appropriate clinical and laboratory tests may be performed, as clinically indicated.

If there is a potential clinically significant abnormality in hematology or chemistry assessments (particularly in platelet count) at Weeks 2, 4 or 6, an unscheduled visit the following week (Weeks 3, 5, 7) to repeat hematology assessments is required (see Section 8.3.5.1). See Section 6.5 for the instruction of dose interruption and restart. The investigator must inform and consult sponsor with any hematological abnormality.

8.7. End of Treatment and/or Early Termination

If a participant permanently discontinues study drug or has completed the Protocol-specified duration of treatment, 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 follow-up visit (EOS).

8.8. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled safety follow-up visit, which should occur 30 to 35 days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed). Adverse events and SAEs must be reported up until the end of the safety follow-up period, 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.

For purposes of analysis, participants who complete through Week 8 will be considered to have completed the study.

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 Meeting 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 it 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.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

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.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE if it occurred after signing the ICF. 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 the 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 an Adverse Event and/or Serious Adverse Event

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 to sponsor or designee 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 the 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; intervention not indicated.
- **Grade 2:** Moderate; minimal, local, or noninvasive intervention 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 intervention 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 INCB054707 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 to the sponsor or designee. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data** to sponsor or designee.
  - The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up 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 or designee to elucidate the nature and/or causality of the AE/SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee 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 up until the end of the safety follow-up period, 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 INCB054707 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 SUSARs 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 the PhV/designee. 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

AEs of special interest are defined as decreases in platelets, ANC below the LLN, or the occurrence of serious infections.

9.6. Emergency Unblinding of Treatment Assignment

In a medical emergency, if knowledge of the treatment assignment is necessary to determine optimal medical management of the participant, the procedure for emergency unblinding is provided in the Study Manual. This option may be used *only* if the participant's well-being requires the investigator to be aware of the participant's treatment assignment. If a participant's treatment assignment is unblinded, the sponsor or its designee must be notified immediately by telephone and follow up by email.

If an investigator, site personnel performing assessments, or participant is unblinded, the participant must be withdrawn from the study treatment, unless there are ethical reasons to have the participant remain on the study treatment. In these cases, the investigator must obtain specific approval from the sponsor's (or its designee's) medical monitor for the participant to continue in the study.

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 (female participants only).
- 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.

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 INCB054707 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 INCB054707. Treatment of overdose should consist of general supportive measures.

For this study, any dose of INCB054707 greater than [redacted] (depending on which cohort the participant is assigned to) within a 24-hour time period will be considered an overdose. Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until INCB054707 can no longer be detected systemically (at least 3 days).
- Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study treatment if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

10. STATISTICS

10.1. Sample Size Determination

The study is a standard dose-escalation design, and the sample size depends on the occurrence of safety findings. Approximately 9 participants will be randomized in each dose level, which will provide > 85% chance of detecting at least 1 AE of interest (eg, platelets, hemoglobin, ANC, liver functions and infections) if the underlying rate is 20%.

[redacted]

10.3. Level of Significance

This is a safety study. No formal efficacy hypotheses will be tested.

10.4. Statistical Analyses

10.4.1. Safety Analyses

Safety endpoints are listed in Section 3. Safety analyses will be conducted using the FAS population and are summarized in Table 14.

Table 14: Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	**Adverse Events** A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study drug administration. Adverse events will be coded using MedDRA and tabulated by preferred term and system organ class. Severity of AEs will be based on the CTCAE v4.03 using Grades 1 through 5. The subset of AEs considered by the investigator to have a relationship to study drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, then the AE will be considered treatment-related. The incidence of AEs and treatment-related AEs will be tabulated. **Clinical Laboratory Tests** Actual values and changes from baseline in clinical laboratory test results will be summarized using descriptive statistics. Laboratory test values outside the normal range will be assessed for severity based on the normal ranges for the clinical reference laboratory. The incidence of abnormal laboratory values will be tabulated. Laboratory data will be classified into Grades 1 through 4 using CTCAE v4.03. The following summaries will be produced for the laboratory data: Number and percentage of participants with worst postbaseline CTCAE grade (regardless of baseline value) will be summarized. Each participant will be counted only for the worst grade observed postbaseline. Shift tables from baseline to the worst postbaseline value using CTCAE grade. For laboratory parameters where CTCAE grades are not defined, shift tables to the worst postbaseline value using the low/normal/high classifications based on laboratory reference ranges will be provided. **Vital Signs** Descriptive statistics and mean change from baseline will be summarized for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time. **Electrocardiograms** Twelve-lead ECGs will be obtained for each participant during the study. Electrocardiogram abnormalities, both at baseline and postbaseline visits, will be tabulated by treatment group. Incidences of abnormalities will be listed with study visit, assigned treatment group, and a description of the abnormality. Participants exhibiting clinically notable ECG abnormalities will be listed.

10.4.2. Efficacy Analyses

Efficacy analyses will be conducted using the FAS. Efficacy assessments will be summarized using descriptive statistics at each visit. The baseline value for a variable will be defined as the last nonmissing value for this variable before or on Day 1, unless otherwise specified.

Categorical variables, including proportions of participants achieving HiSCR, achieving an AN count of 0 to 2, requiring rescue lesional treatment, at each category of Hurley Stage, with a change in Hurley Stage, in each HS-PGIC category, and at each scoring category of DLQI, will be summarized using descriptive statistics, including sample size, frequency, and percentages. Actual measurements of HS-PGIC, mean, change from baseline, and percentage change from baseline in DLQI, HS pain NRS, modified Sartorius scale, and in the number of draining fistulas will be summarized using descriptive statistics, including sample size, mean, median, standard deviation, standard error of the mean, minimum, and maximum. A logistic regression model will be fit for assessment of the dose-response relationship on HiSCR at Week 8.

10.4.3. Other Analyses

Pharmacokinetic endpoints are listed in Section 3. Pharmacokinetic analyses will be performed using the PK population. The INCB054707 plasma concentration data will be analyzed by a population PK modeling approach. Such data may be combined with data from other studies in the clinical development program to develop or refine population PK models. This model may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of INCB054707 and to determine measures of individual exposure (such as steady-state peak, trough, and/or time averaged concentrations). A data analysis plan and results of population PK will be reported separately.

Translational endpoints are listed in Section 3. Details of translational analyses will be provided in the Statistical Analysis Plan.

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) 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 reported on the CRF or 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 and the participant's initials (participant's initials will only be recorded if allowable by local regulations) will be recorded in the eCRF, where permitted; if the participant's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with local data protection laws.

11.4. Financial Disclosure

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

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

11.5. Publication Policy

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

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 from screening 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 90 days after the end of relevant systemic exposure. In addition, male participants must refrain from donating sperm from screening 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 and female partners of male 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 Trial Facilitation Group 2014.

APPENDIX B. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	09 AUG 2018

Amendment 1 (09 AUG 2018)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to remove the exclusion of women of childbearing potential.

1. **Section 1, Protocol Summary (Table 3: Schedule of Assessments); Section 2.3.2, Clinical Studies (Table 4: Potential Risks Associated With INCB054707); Section 5.1, Inclusion Criteria; Section 5.2, Exclusion Criteria; Section 8.3.5, Laboratory Assessments (Table 10: Required Laboratory Analytes); Section 8.3.5.2, Screening Assessments; Section 8.3.5.3, Pregnancy Testing; Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

   Description of change: Removed exclusion of women of childbearing potential. Added pregnancy tests at every study visit.

   Rationale for change: Results of reproductive toxicology studies allow for enrollment of women of childbearing potential in this study.

2. **Section 1, Protocol Summary (Table 3: Schedule of Assessments); Section 8.1.4, Distribution of Reminder Cards**

   Description of change: Removed the fasting requirement at Week 1.

   Rationale for change: No fast is needed at Week 1, because neither lipid panel sampling nor serum sampling for biomarkers occurs at this visit.

3. **Section 1, Protocol Summary (Table 3: Schedule of Assessments); Section 8.2.9, Photography of Target Lesions**

   Description of change: Added "Optional" photography and removed "for each participant."

   Rationale for change: The photography of target lesions will be optional.

4. **Section 6.1, Study Treatment Administered (Table 6: Study Treatment Information); Section 8.1.5, Electronic Diary; Section 8.4, Pharmacokinetic Assessments**

   Description of change: Table 6 was updated to indicate that study drug and matching placebo are to be taken orally, once daily, and preferably in the morning. Daily study drug administration will be recorded in an electronic diary, which will be completed through the web or by phone. References to a separate device were removed. The date and time of the last dose of study drug and the time of the last meal preceding each PK sample collection visit will be recorded in the electronic case report form only.

   Rationale for change: To clarify study drug administration and documentation.

5. **Section 6.7, Concomitant Medications and Procedures**

   Description of change: Removed the sentence "Concomitant medications administered after 30 days after the last dose of study treatment should be recorded for SAEs as defined in Section 9.3."

   Rationale for change: Concomitant medication administration 30 days after the last dose of treatment should not be recorded for SAEs.

6. **Section 8.2, Efficacy Assessments**

   Description of change: Removed "the number and size of ulcerated HS lesions."

   Rationale for change: Ulcerated HS lesion count and size are not evaluated in this study.

7. **Section 8.2.2, Hidradenitis Suppurativa Clinical Response (Abscess and Inflammatory Nodule Count)**

   Description of change: Removed sinus tract description.

   Rationale for change: Sinus is considered as a draining fistula.

8. **Section 8.2.7, Hidradenitis Suppurativa Patient Global Impression of Change; Section 8.2.8, Dermatology Life Quality Index;** [redacted]

   Description of change: Revised text such that the HS-PGIC, DLQI, and [redacted] should be assessed before all efficacy assessments.

   Rationale for change: To clarify the timing of patient-reported outcome assessments.

9. **Section 8.3.4, Electrocardiograms (Table 10: Electrocardiogram Schedule)**

   Description of changes: Added that predose and postdose ECGs should be performed 5 to 10 minutes before the predose and postdose [redacted], respectively.

   Rationale for change: To clarify the timing for ECG and PK sample collections.

10. **Section 8.3.5, Laboratory Assessments (Table 10: Required Laboratory Analytes)**

    Description of change: Added mean platelet volume under hematology assessment and clarified that microscopic evaluation for urinalysis results are in case of abnormal urinalysis results.

    Rationale for change: Mean platelet volume should be included in routine hematology laboratory tests. No extra blood draw is required. Microscopic evaluation is only required if abnormal urinalysis is observed.

11. **Section 8.3.1, Adverse Events; Section 8.8, Safety Follow-Up**

    Description of change: Updated the AE and SAE reporting timeframe from up until at least 30 days after the last dose of study drug to up until the end of the safety follow-up period.

    Rationale for change: To be consistent with the safety follow-up timeframe (30-35 days).

[redacted]

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