Official Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of the Efficacy and Safety of INCB054707 in Participants With Hidradenitis Suppurativa

NCT Number: NCT04476043

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Clinical Study Protocol

INCB 54707-204

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of the Efficacy and Safety of INCB054707 in Participants With Hidradenitis Suppurativa

Product:	**INCB054707**
IND Number:	[redacted]
EudraCT Number:	**2020-001981-13**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol:	**29 APR 2020**
Amendment 1:	**10 SEP 2021**

INVESTIGATOR'S AGREEMENT

I have read the INCB 54707-204 Protocol Amendment 1 (dated 10 SEP 2021) 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)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AE	adverse event
ALT	alanine aminotransferase
AN	abscess and inflammatory nodule
ANC	absolute neutrophil count
ANF	abscess, inflammatory nodule, and draining fistula
AST	aspartate aminotransferase
[redacted]	[redacted]te
CFR	Code of Federal Regulations
[redacted]	[redacted]
CSR	Clinical Study Report
[redacted]	[redacted]
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP3A4	cytochrome P450 3A4 enzyme
d	days
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
EOT1	end of treatment during the placebo-controlled period
EOT2	end of treatment during the open-label extension period
[redacted]	[redacted]
[redacted]	[redacted]
E-R	exposure-response
ET1	early termination during the placebo-controlled period
ET2	early termination during the open-label extension period
[redacted]	[redacted]
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation

Abbreviations and Special Terms	Definition
Group	participants who are receiving the same dose or treatment (eg, INCB054707 treated group, 15 mg group, placebo group)
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act of 1996
HiSCR	hidradenitis suppurativa clinical response
[redacted]	[redacted]
HIV	human immunodeficiency virus
HS	hidradenitis suppurativa
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IHS4	International Hidradenitis Suppurativa Severity Score System
IL	interleukin
IPL	intense pulsed light
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
JAK	Janus kinase
LDL	low-density lipoprotein
LTE	long-term extension
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
NCI	National Cancer Institute
[redacted]	[redacted]
OLE	open-label extension
PD	pharmacodynamic(s)
Period	time intervals within a study (eg, screening period, placebo-controlled treatment period, open-label period, and follow-up period)
PK	pharmacokinetic(s)
PO	orally
PP	per protocol
PPD	purified protein derivative
[redacted]	[redacted]
QALYs	quality-adjusted life years

Abbreviations and Special Terms	Definition
QD	once daily
QFT-GIT	QuantiFERON®-TB Gold In-Tube test
QTcF	measurement made on an electrocardiogram used to assess some of the electrical properties of the heart corrected by Fridericia's formula
RNA	ribonucleic acid
SAE	serious adverse event
SoA	schedule of activities
SOP	standard operating procedure
STAT	signal transducer and activator of transcription
Study drug	This term refers to Incyte medicinal investigational product or matching placebo used for this study.
Study treatment	This term refers to all medications that the participant is required to receive as part of this study.
[redacted]	[redacted]
TB	tuberculosis
TEAE	treatment-emergent adverse event, defined as adverse events reported for the first time or worsening of a pre-existing event after first dose of study treatment
[redacted]	[redacted]
TNF-α	tumor necrosis factor alpha
TYK2	tyrosine kinase 2
ULN	upper limit of normal
W	week
WOCBP	women of childbearing potential
WONCBP	women of nonchildbearing potential
[redacted]	[redacted]

1. PROTOCOL SUMMARY

Protocol Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of the Efficacy and Safety of INCB054707 in Participants With Hidradenitis Suppurativa

Protocol Number: INCB 54707-204

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 efficacy of INCB054707	• Mean change of AN count at Week 16 relative to baseline.
Key Secondary	
To further evaluate the efficacy of INCB054707	• Proportion of participants who achieve HiSCR at Week 16. Hidradenitis suppurativa clinical response is defined as at least a 50% decrease from baseline in AN count with no increase in the number of abscesses or draining fistulas.

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	Treatment of patients 18 years and older with hidradenitis suppurativa.
Population	Men or women aged 18 to 75 years who have been diagnosed with HS (Hurley Stage I, II, or III) for at least 3 months with a total AN count of at least 5 and inflammatory lesions that affect at least 2 distinct anatomical areas.
Number of Participants	Approximately 200 participants will be randomized 1:1:1:1 to 1 of 3 INCB054707 treatment groups or the placebo group (approximately 50 participants per group). Participants will be enrolled globally from approximately 50 study sites. The 36-week OLE period will include all participants who successfully complete the initial 16-week treatment period (placebo-controlled). All eligible participants will be invited to continue treatment for an additional 48-week LTE period (also open label).

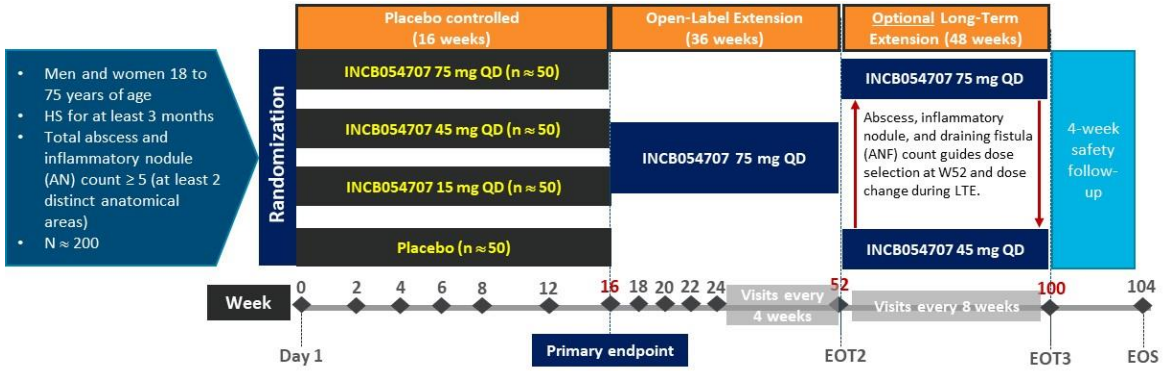
Table 2: Key Study Design Elements (Continued)

Study Design	This is a Phase 2, multicenter, parallel group, placebo-controlled, double-blind, randomized study to evaluate the efficacy and safety of INCB054707 (15, 45, and 75 mg QD) over a 16-week treatment period. Upon completion of the 16-week treatment period, participants will continue for 36 weeks of open-label INCB054707 treatment (75 mg QD). At the end of the OLE, all eligible participants will have the option to continue treatment for additional 48 weeks in an LTE period, to collect long-term safety and efficacy data for a total of 104 weeks. A safety follow-up visit will be conducted approximately 4 weeks after the last dose of study drug.
Estimated Duration of Study Participation	Up to 30 days for screening, followed by continuous treatment in the placebo-controlled period for 16 weeks, followed by a 36-week OLE period, an optional 48-week LTE period, and then a 28-day safety follow-up visit. It is estimated that an individual will participate for approximately 14 months (without the LTE period), or approximately 25 months if participating in the LTE period.
DMC	Yes (internal)
Coordinating Principal Investigator	Joslyn Sciacca Kirby, MD, MS, MEd

Treatment Groups and Duration:

The study design is shown in Figure 1. The SoA is detailed in Table 3.

Figure 1: Study Design Schema



After providing informed consent, participants will be assessed for study eligibility at the screening visit. Participants will undergo screening within 30 days prior to randomization. Participants who continue to meet eligibility criteria at baseline will undergo Day 1 (Week 0) assessments and be randomized to 1 of 4 treatment groups. Participants will be stratified based on geographical region (North America and outside of North America) and disease severity (Hurley Stages I, II, and III) with no more than 25% of the total number of participants as Hurley Stage III.

Approximately 200 participants will be randomized 1:1:1:1 to receive double-blinded study treatment of placebo or 1 of 3 doses of INCB054707 (15, 45, or 75 mg) PO QD for 16 weeks. At Week 16, participants will enter the 36-week OLE period (INCB054707 75 mg QD). At the

completion of the OLE period, Week 52 visit, eligible participants may enter the 48-week LTE period. A safety follow-up visit will be scheduled approximately 4 weeks after the end of the OLE period (Week 56 visit) or the LTE period (Week 104 visit).

Study visits will occur at screening, baseline (Day 1/Week 0), Weeks 2, 4, 6, 8, 12, 16 (EOT1), 18, 20, 22, 24, 28, 32, 36, 40, 44, 48, 52 (EOT2), 56 (EOS, for participants not continuing into the LTE) and early termination if the participant discontinues before Week 16 (ET1) or during the OLE period and before Week 52 (ET2). After Week 52, the study visits during the optional LTE period will occur at Weeks 60, 68, 76, 84, 92, 100 (EOT3), 104 (EOS), and early termination if the participant discontinues during the LTE period and before Week 100 (ET3). Each visit denoted by Week 2, Week 4, Week 6, etc represents a target visit date corresponding to the end of the specified week; therefore, Weeks 2, 4, and 6 respectively represent Days 14, 28, and 42 of the study. Additionally, all participants will be contacted by phone 1 week before the baseline visit (Day 1/Week 0) to ensure that daily assessments [redacted] are being recorded.

Visits in the LTE are named to reflect continuation from the OLE study, with the first visit of the LTE occurring at Week 52. The eligibility assessment for the LTE occurs at Week 52. Participants who enter the safety-follow period immediately after the Week 52 visit are not allowed to start the LTE period. Participants who are currently tolerating INCB054707 in the OLE, as assessed by the investigator, and who demonstrate willingness and ability to comply with the scheduled visits, will be considered eligible for the LTE period. Furthermore, details on the LTE dose assignment and dose change are described in Section 2.1.5 and Section 6.5.1.

Efficacy [redacted] will be assessed throughout the study at selected visits (see Table 3). Safety and tolerability will be evaluated throughout the study. Adherence to the study design requirements, including those specified in the SoA (see Table 3), is essential and required for study conduct.

Table 3: Schedule of Activities

Visit Day/Range	Section	Screening Days -30 to -1	Baseline (W0/Day 1)	Treatment (Placebo-Controlled Period) W2 ± 3d	W4 ± 3d	W6 ± 3d	W8 ± 3d	W12 ± 3d	W16 ± 3d; EOT1 (or ET1)	Treatment (Open-Label Extension) W18, W20, W22 and W24; ± 3d	W28-W48, visits every 4 weeks; ± 3d	W52 ± 3d; EOT2 (or ET2)	Treatment (Long-Term Extension) W60-W92, visits every 8 weeks; ± 7d	W100 ± 7d; EOT3 (or ET3)	Follow-Up W56 + 7d or W104 + 7d; or 28 (+ 7) days after last dose of study drug (EOS)
Administrative Procedures															
Informed consent	8.1.1	X													
Inclusion/exclusion criteria	5.1/5.2	X	X												
Demographic, HS disease history, alcohol use, and medical history	8.1.5	X													
Nicotine use	8.1.5	X							X			X		X	
Prior/concomitant medications	8.1.5	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT	8.1.3	X	X		X		X	X	X	X (W20, W24)	X	X	X	X	
Randomization to treatment group	8.1.3		X												
Dispense study drug	8.1.3		X		X		X	X	X	X (W20, W24)	X	X (LTE only)	X		
Collect study drug and assess compliance	6.4			X	X	X	X	X	X	X	X	X	X	X	
Distribute reminder card	8.1.4	X	X	X	X	X	X	X	X	X	X	X	X	X	
Distribute diary	8.1.4	X													
Diary review and/or collection	8.1.4		X	X	X	X	X	X	X	X	X	X	X	X	
Follow-up phone call	8.1.6	X													

Table 3: Schedule of Activities (Continued)

Visit Day/Range	Section	Screening Days -30 to -1	Baseline (W0/Day 1)	Treatment (Placebo-Controlled Period) W2 ± 3d	W4 ± 3d	W6 ± 3d	W8 ± 3d	W12 ± 3d	W16 ± 3d; EOT1 (or ET1)	Treatment (Open-Label Extension) W18, W20, W22 and W24; ± 3d	W28-W48, visits every 4 weeks; ± 3d	W52 ± 3d; EOT2 (or ET2)	Treatment (Long-Term Extension) W60-W92, visits every 8 weeks; ± 7d	W100 ± 7d; EOT3 (or ET3)	Follow-Up W56 + 7d or W104 + 7d; or 28 (+ 7) days after last dose of study drug (EOS)
Safety Assessments															
AE assessments	8.3.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive physical examination	8.3.2	X	X						X			X		X	
Targeted physical examination	8.3.2			X	X		X	X		X (W18, W20, W24)	X		X		X
Vital signs	8.3.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	8.3.4	X										X		X	
Chest x-ray	8.3.5	X													
Efficacy Assessments															
Lesion counts	8.2.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hurley stage	8.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]															

Table 3: Schedule of Activities (Continued)

Visit Day/Range	Section	Screening Days -30 to -1	Baseline (W0/Day 1)	Treatment (Placebo-Controlled Period) W2 ± 3d	W4 ± 3d	W6 ± 3d	W8 ± 3d	W12 ± 3d	W16 ± 3d; EOT1 (or ET1)	Treatment (Open-Label Extension) W18, W20, W22 and W24; ± 3d	W28-W48, visits every 4 weeks; ± 3d	W52 ± 3d; EOT2 (or ET2)	Treatment (Long-Term Extension) W60-W92, visits every 8 weeks; ± 7d	W100 ± 7d; EOT3 (or ET3)	Follow-Up W56 + 7d or W104 + 7d; or 28 (+ 7) days after last dose of study drug (EOS)
[redacted]															
Laboratory Assessments															
Serum FSH (WONCBP only)	8.3.7.2	X													
Serum pregnancy test (WOCBP)	8.3.7.2	X							X			X		X	
Urine pregnancy test (WOCBP)	8.3.7.2		X		X		X	X		X (W20, W24)	X		X		X
TB screening	8.3.6	X													
HIV testing	8.3.7.1	X													
Hepatitis testing	8.3.7.1	X													

Table 3: Schedule of Activities (Continued)

Visit Day/Range	Section	Screening: Days -30 to -1	Baseline (W0/Day 1)	Treatment (Placebo-Controlled Period): W2 ± 3d	W4 ± 3d	W6 ± 3d	W8 ± 3d	W12 ± 3d	W16 ± 3d; EOT1 (or ET1)	Treatment (Open-Label Extension): W18, W20, W22 and W24; ± 3d	W28-W48, visits every 4 weeks; ± 3d	W52 ± 3d; EOT2 (or ET2)	Treatment (Long-Term Extension): W60-W92, visits every 8 weeks; ± 7d	W100 ± 7d; EOT3 (or ET3)	Follow-Up: W56 + 7d or W104 + 7d; or 28 (+ 7) days after last dose of study drug (EOS)
Laboratory Assessments (Continued)															
Urinalysis	8.3.7.1	X					X		X	X (W24)	X (W32)	X	X (W76)	X	
Urine nicotine metabolite	8.3.7		X						X			X		X	
Hematology and chemistry assessments	8.3.7	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipid panel	8.3.7		X				X		X	X (W24)	X (W32, W40)	X	X	X	X
Inflammation markers	8.3.7	X	X		X		X		X	X (W24)	X (W32, W40)	X	X	X	X
[redacted]															

2. INTRODUCTION

INCB054707 is a JAK inhibitor, with selectivity for JAK1. Janus kinase signaling regulates many different proinflammatory signaling pathways and is now well-recognized as a key driver for numerous inflammatory skin diseases. [redacted] results from a recent Phase 2a study with INCB054707 demonstrated proof of concept in HS. [redacted] and supports further investigation of oral INCB054707 in a Phase 2 dose-ranging study in participants with HS.

2.1. Background

2.1.1. Study Rationale

Hidradenitis suppurativa is a chronic inflammatory disease characterized by painful nodules and abscesses, distributed to apocrine-bearing skin (sweat glands) that appears to result from a pathologic change in the pilosebaceous-apocrine unit (Hoffman et al 2017). [redacted]

In 2 clinical studies of participants with HS, INCB 54707-202 (15 mg only) and INCB 54707-203 (placebo and 30, 60, and 90 mg), INCB054707 QD was administered for up to 8 weeks and proof-of-concept was established by demonstrating a decrease in AN count, a percentage of participants achieving HiSCR, and an improvement in quality of life, in addition to an adequate safety profile. With the goal of informing dose selection for future Phase 3 clinical trials, the proposed study aims to further explore the efficacy and safety of INCB054707 in addition to its dose-response curve in participants with HS.

2.1.2. Scientific Rationale for Study Design

Recent literature suggests that the cytokines IL-1β, IL-17, IL-23, IL-10, and, to a lesser extent, [redacted] Adalimumab (Humira®), a TNF-α fully human monoclonal antibody administered via subcutaneous injection, was approved in 2015 by the FDA for the treatment of moderate to severe HS in patients 12 years of age and older and currently remains the only approved therapy. Given the modest response rates observed with adalimumab treatment (42% and 59% vs placebo 26% and 28%, respectively in each of the Phase 3 trials) and the significant dropout rates in existing studies due to lack of efficacy (27% to 50%; Frew et al 2020), additional treatments for HS patients are needed.

In the proposed study, the clinical efficacy and safety of 3 doses (15, 45, and 75 mg) of INCB054707, a small molecule JAK1 inhibitor, will be evaluated in adult participants with HS

and compared with placebo for 16 weeks. Since HS is a chronic inflammatory disorder, all participants will enter the 36-week OLE period to evaluate the long-term safety and efficacy of INCB054707 in HS (up to 52 weeks in total). Participants will receive INCB054707 75 mg QD in the OLE period. To further evaluate long-term safety and efficacy of INCB054707 in HS, all eligible participants will have the option to continue treatment for an additional 48 weeks (LTE period). Participants who are currently tolerating INCB054707 in the OLE, as assessed by the investigator, and who demonstrate willingness and ability to comply with the scheduled visits, will be considered eligible for the LTE period.

The primary efficacy endpoint is based on the count of AN, as this appears to be a relevant measure of INCB054707 anti-inflammatory activity. The AN count also serves as the basis of the key secondary endpoint, HiSCR, which is defined as at least a 50% decrease in AN count with no increase in the number of abscesses or draining fistulas, relative to baseline. Participants who experience rapid abscess formation at diseased sites will receive appropriate rescue treatments.

It is expected that the outcome of this study will be instrumental in the selection of a single treatment regimen to be evaluated in a Phase 3 study.

2.2. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks, and reasonably expected AEs of INCB054707, may be found in the IB.

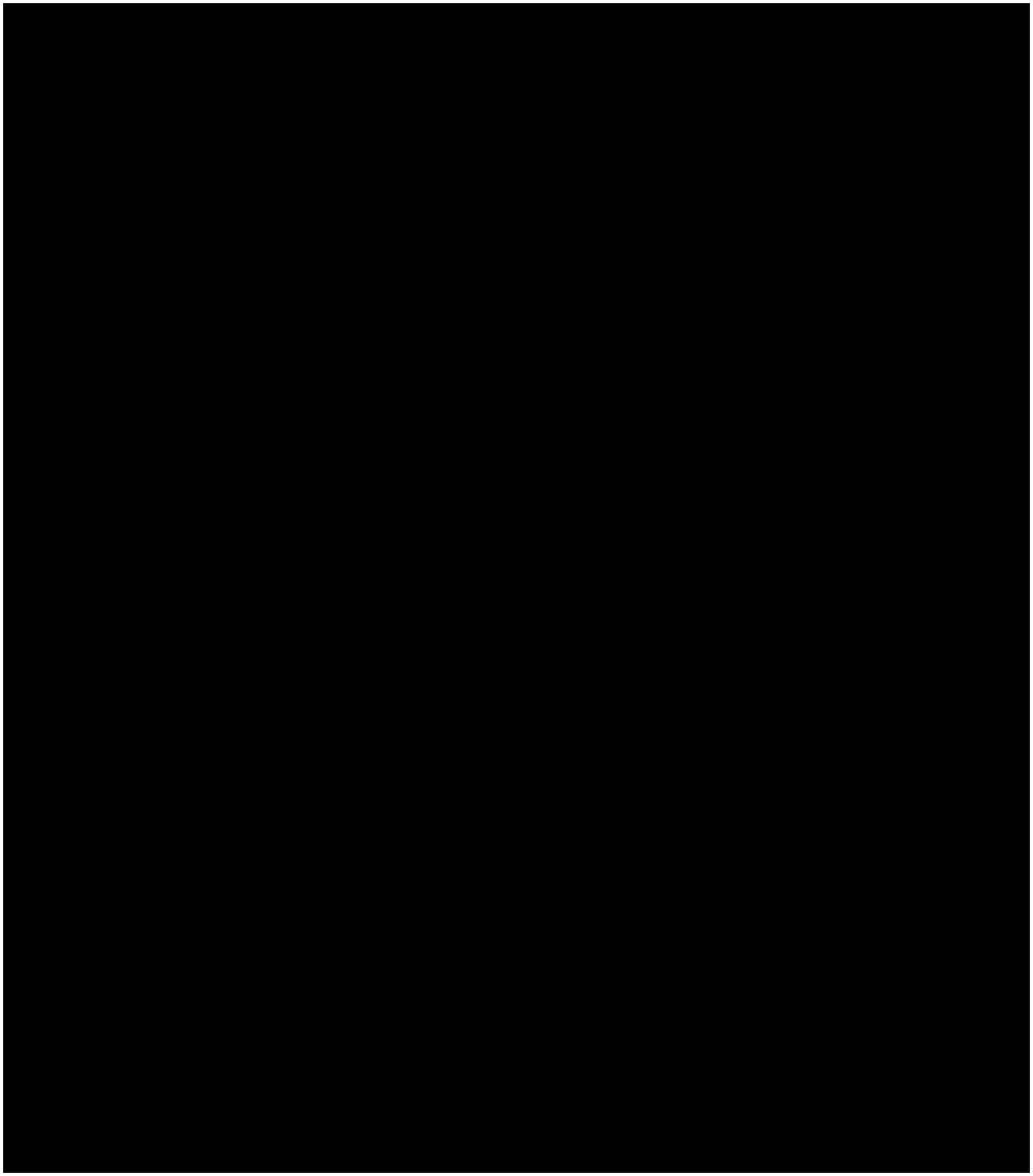
2.2.1. Clinical Studies

Single doses of INCB054707 up to 405 mg and multiple doses of INCB054707 up to 120 mg QD for up to 10 days have been evaluated in 2 placebo-controlled studies in healthy participants. The most common TEAEs were mild-to-moderate headaches in 31% of participants who received INCB054707 in the multiple-dose study; the events resolved spontaneously following discontinuation of INCB054707. Furthermore, decreases in platelet counts were observed among participants treated with INCB054707 at doses ≥ 60 mg QD. The magnitude of the decrease was larger for participants treated at 120 mg QD compared with those who received 60 mg QD suggesting a dose-related trend. Of note, for the participants with a treatment-emergent decrease in platelets, platelet counts remained within the normal range.

In 2 clinical studies in participants with HS, INCB 54707-202 (15 mg only) and INCB 54707-203 (placebo and 30, 60, and 90 mg), QD doses of study treatment were administered for up to 8 weeks. Thrombocytopenia was observed in 4 of 8 participants who received INCB054707 90 mg QD after 4 weeks of exposure, which lead to dose interruption for a maximum of 2 weeks, and resolved without medical intervention. All participants returned to their normal dosing schedule after dose interruption and completed the study without clinical sequelae or reemergence of thrombocytopenia. Platelet count decreases have been transient and stabilize over time, as observed in studies with other JAK1 inhibitors for treatment of other dermatological indications, such as abrocitinib in atopic dermatitis (Gooderham et al 2019) and itacitinib in plaque psoriasis (Bissonnette et al 2016). Thrombocytopenia TEAEs were judged as treatment-related. Hemoglobin levels remained within the normal limits and mostly unchanged during the study, while neutrophil counts showed a mild dose-dependent decrease within the normal limits. Mild-to-moderate headaches were observed in 11% (4 of 36) of the participants exposed to INCB054707, and in 22% (2 of 9) of participants exposed to placebo. Across the 2 studies, the most common TEAE was fatigue, observed in 7 out of the 45 participants; clinically significant fatigue, identified via FACIT-Fatigue scores, has been reported as affecting

40% of patients with HS (Dufour et al 2014). No serious or fatal TEAEs were reported in the studies; more details are provided in the IB.

Based on the available nonclinical and clinical data, the potential risks to participants and the risk mitigations are summarized in Table 4.



[redacted]

2.2.2. Benefit Assessment

Based on the expected mode of action of INCB054707, participants randomly assigned to 1 of the 3 active treatment groups may experience clinically meaningful improvements in their HS lesions during the placebo-controlled (16-week) period, and may continue to receive benefit from treatment during the OLE (36 weeks) and LTE (48 weeks) periods.

Participants 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 patients' well-being and daily functioning.

2.2.3. Benefit-Risk Conclusion

Considering the safety measures initiated 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 participants.

3. OBJECTIVES AND ENDPOINTS

Table 5 presents the objectives and endpoints.

Table 5: Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the efficacy of INCB054707	• Mean change of AN count at Week 16 relative to baseline.
Secondary	
To further evaluate the efficacy of INCB054707	• **Key secondary endpoint:** Proportion of participants who achieve HiSCR at Week 16. Hidradenitis suppurativa clinical response is defined as at least a 50% decrease from baseline in AN count with no increase in the number of abscesses or draining fistulas. • Proportion of participants who achieve HiSCR at each visit from Weeks 2 to 12. • Proportion of participants who achieve at least a 75% decrease from baseline in AN count with no increase in the number of abscesses or draining fistulas from Weeks 2 to 16. • Mean change from baseline in the severity of the disease, as assessed by the IHS4 score, from Weeks 2 to 16. • Proportion of participants achieving AN50, AN75, AN90, and AN100 (at least 50%, 75%, 90%, and 100% reduction in AN count relative to baseline, respectively) from Weeks 2 to 16. • Mean change in AN count at Weeks 2 to 12, relative to baseline. • Proportion of participants with a total AN count of 0 to 2 from Weeks 2 to 16. • Mean change in draining fistula count from Weeks 2 to 16, relative to baseline. • Mean change in ANF count from Weeks 2 to 16, relative to baseline.
To evaluate the safety and tolerability of INCB054707	• Frequency and severity of AEs, including the evaluation of clinical laboratory results, vital signs, ECGs, and the results of physical examinations.

Table 5: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	[redacted]

Table 5: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

Table 5: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

Table 5: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

Table 5: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

Table 5: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, multicenter, randomized, parallel group, placebo-controlled, dose-ranging study to evaluate the efficacy and safety of INCB054707 (15, 45, and 75 mg QD) over a 16-week treatment period followed by a 36-week OLE period (INCB054707 75 mg QD) and an additional optional 48-week long-term extension period (LTE). The study will enroll men and women aged 18 to 75 years with HS. Approximately 200 participants will be enrolled globally. Figure 1 presents the study design schema, and Table 3 presents the SoA.

Participants will be screened for up to 4 weeks before the first dose of study drug. Key entry criteria for participants are diagnosis of HS (Hurley Stage I, II, or III) for at least 3 months and a total AN count of at least 5 at screening and baseline affecting at least 2 distinct anatomical areas. Participants will also agree to NOT use topical antiseptics on the areas affected by HS lesions as well as systemic antibiotics (for HS treatment) during the placebo-controlled (16-week) period. Individual lesion rescue treatment (incision and drainage or intralesional corticosteroid injection) will be allowed during the 16-week placebo-controlled, OLE and LTE periods, and is further discussed in Section 6.6.4. Screening will include medical and medication history, physical examination including clinical assessments, vital sign measurements, routine laboratory assessments, pregnancy testing, and ECGs.

Participants who meet all the study inclusion criteria and none of the exclusion criteria will return to the study site on Day 1/Week 0 of dosing and be randomized to treatment in a 1:1:1:1 ratio to 1 of 4 treatment groups (placebo or INCB054707 15, 45, or 75 mg). Participant randomization will be stratified based on geographical region (North America and outside of North America) and disease severity (Hurley Stages I, II, and III) with no more than 25% of the total number of participants as Hurley Stage III.

Approximately 200 participants will receive blinded study treatment of placebo or 1 of 3 doses of INCB054707 PO QD for 16 weeks. At Week 16, participants will enter the 36-week OLE period (INCB054707 75 mg QD). At the completion of the OLE period, all eligible participants will have the option to continue treatment for an additional 48 weeks (LTE period). A safety follow-up visit will be scheduled 4 weeks after the last dose of study drug.

The eligibility assessment for the LTE period will occur at Week 52. Participants who enter the safety-follow period immediately after the Week 52 visit are not allowed to start the LTE period. Participants who are currently tolerating INCB054707 in the OLE as assessed by the investigator, and who demonstrate willingness and ability to comply with the scheduled visits, will be considered eligible for the LTE period.

Efficacy will be assessed via mean change in AN count, mean change in ANF count, proportion of participants achieving HiSCR, mean change in IHS4, mean change in draining fistula count, [redacted]

Participants will be assessed for safety and tolerability by monitoring the frequency and severity of AEs, performing physical examinations, ECGs, vital sign measurements, and clinical laboratory assessments at various timepoints during the study.

[redacted]

4.2. Overall Study Duration

Participants will be on-study for a duration of up to 60 weeks (if not participating in the LTE), or 108 weeks (if participating in the LTE), as follows: screening, up to 30 days; placebo-controlled period, 16 weeks; OLE period, 36 weeks; LTE period, 48 weeks; and a 28-day (+ 7 days) safety follow-up.

The study begins when the first participant (or guardian or legally authorized representative) signs the ICF. The end of the study is defined as the date of the last visit of the last participant in the study or the last scheduled procedure shown in the SoA for the last participant in the study.

A participant who does not continue into the LTE period is considered to have completed the study if he/she has completed both the placebo-controlled period and the OLE period of the study, including the last visit or the last scheduled procedure shown in the SoA. A participant who continues into the LTE period is considered to have completed the study if he/she has completed the placebo-controlled; OLE and LTE periods of the study, including the last visit or the last scheduled procedure shown in the SoA (see Table 3).

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 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 if, for example, required by regulatory decision. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and the regulatory bodies of the decision and reason for termination of the study.

5. STUDY POPULATION

The study population will include men and women aged 18 to 75 years who have had a diagnosis of HS (Hurley Stage I, II, or III) for at least 3 months and who have at least a 5 AN count at screening and baseline with inflammatory lesions that affect at least 2 distinct anatomical areas.

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 age 18 to 75 years inclusive at the time of signing the ICF.
2. HS disease duration of at least 3 months before screening.
3. Diagnosis of HS defined as:
    a. A total of at least 5 inflammatory lesions (AN) at screening AND baseline
    AND
    b. Inflammatory lesions present in at least 2 distinct anatomical areas
4. Willingness to avoid pregnancy or fathering children based on the criteria below.
    a. Male participants with childbearing potential must agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 90 days after the last dose of study drug and must 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 participants and their understanding confirmed.
    b. Female participants with childbearing potential must have a negative serum pregnancy test at screening 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. Female participants without childbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR postmenopausal, defined as amenorrhea ≥ 12 months prior to screening), confirmed by FSH levels at screening, are eligible.
5. Participants agree NOT to use topical antiseptics (see Section 6.6.2) on the areas affected by HS lesions during the placebo-controlled 16-week treatment period.
6. For Germany only, participants must have a history of inadequate response or intolerance to an adequate course of oral antibiotics for treatment of HS, as assessed by the investigator through study participant interview and review of medical history.

5.2. Exclusion Criteria

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

1. Inability of the participant (or guardian or legally authorized representative) to comprehend the ICF or unwillingness to sign the ICF.
2. Presence of > 20 draining fistulas at screening or baseline.
3. Women who are pregnant (or who are considering pregnancy) or lactating.
4. Participants with concurrent conditions or history of other diseases, as follows:
    a. Thrombocytopenia, coagulopathy, or platelet dysfunction.
    b. Any clinically significant medical condition other than HS, as determined by the investigator, that is not adequately controlled with appropriate treatment OR may interfere with the course, severity, or assessments of HS.
    c. Any other active skin disease or condition (eg, bacterial, fungal, or viral infection) that may interfere with the course, severity, or assessments of HS.
    d. Active systemic viral infection or any active viral infection that, based on the investigator's clinical assessment, makes the participant an unsuitable candidate for the study.
    e. Current herpes zoster infection, a history of disseminated herpes simplex, or a history of herpes zoster.
    f. History of malignancy, including lymphoma and leukemia within 5 years before baseline, other than a successfully treated nonmetastatic cutaneous squamous cell carcinoma, basal cell carcinoma, or localized carcinoma in situ of the cervix.
    g. Albinism.

6. Prolonged QTcF, defined as ≥ 450 milliseconds.

   Note: Prolonged QTcF values of ≥ 450 milliseconds at screening are to be confirmed by performing 2 additional ECGs and averaging the results to determine if the averaged value meets the exclusion criterion.

7. Have evidence of active or latent or inadequately treated infection with *Mycobacterium tuberculosis* (ie, TB) as defined by the following:

   - A positive QuantiFERON®-TB Gold In-Tube test (QFT-GIT) or positive Mantoux/PPD tuberculin skin test (if appropriate, per Section 8.3.6) performed at or within the 12 weeks prior to Day 1 is exclusionary; a negative test is required for eligibility. It is recommended that participants with a history of Bacille Calmette Guérin vaccination be tested with the QFT-GIT, since the Mantoux/PPD tuberculin skin test may be positive due to vaccination. See Section 8.3.6 for requirements for Mantoux/PPD tuberculin skin testing. A QFT-GIT or Mantoux/PPD tuberculin skin test is not required if the participant has previously received a documented adequate course of therapy for either latent or active TB infection.
   - A history of either untreated or inadequately treated latent or active TB infection.

- If a participant has previously received an adequate course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multidrug TB resistance are < 5% or an acceptable alternative regimen) or active (acceptable multidrug regimen) TB infection, neither a QFT-GIT nor a Mantoux/PPD tuberculin skin test is needed, but a chest radiograph(s), performed within 3 months of Day 1, is required. To be considered eligible for the study, the radiograph(s) must be negative for active tuberculosis infection as determined by a qualified radiologist. Documentation of adequate treatment for TB and negative chest radiograph(s) results must be obtained prior to Day 1.
- A participant who is currently being treated for active TB infection is to be excluded.

8. Participants known to be infected with HIV, hepatitis B, or hepatitis C (see Table 10).
9. Decreased blood cell counts at screening, defined as follows:
   a. Leukocytes < 3.0×10^9/L (< 2.5×10^9/L for African-American participants).
   b. ANC < 1.5×10^9/L.
   c. Lymphocytes < 0.8×10^9/L.
   d. Hemoglobin < 9 g/dL.
   e. Platelet count < 150×10^9/L.
10. Severely impaired liver function (Child-Pugh Class C) or ALT or AST levels ≥ 2 × ULN or total bilirubin ≥ 2 × ULN, unless due to Gilbert's syndrome.
11. Impaired renal function with serum creatinine > 1.5 mg/dL.
12. Known hypersensitivity or severe reaction to INCB054707 or excipients of INCB054707 (refer to the IB).
13. Known history of clinically significant drug or alcohol abuse in the last year prior to baseline.
14. Inability or unlikeliness of the participant to comply with the dose schedule and study evaluations, in the opinion of the investigator.
15. Any other condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.
16. The following patients are excluded in France: vulnerable populations according to article L.1121-6 of the French Public Health Code and adults under legal protection or who are unable to express their consent per article L.1121-8 of the French Public Health Code.

5.3. Lifestyle Considerations

No lifestyle restrictions are required for this study; however, nicotine and alcohol use will be evaluated as indicated in the SoA (see Table 3). Additional information regarding nicotine and alcohol use data collection is provided in the Study Manual.

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 (or designee) 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 (or designee) 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

Participants may be replaced at any time during this study, at the discretion of the medical monitor or designee.

5.6. Data Monitoring Committee

An internal DMC will be established to provide independent oversight of the study. The primary responsibility of the DMC will be to ensure the safety of study participants. The specific responsibilities of the DMC will be detailed in a separate DMC charter.

6. STUDY TREATMENT

6.1. Study Treatments Administered

Information regarding study drug and administration is provided in Table 6. Participants will record study drug administration in a daily diary. Further information regarding treatment administration is provided in Appendix B.

6.2. Preparation, Handling, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatments received and any discrepancies are reported and resolved before use of the study treatment.

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

The investigator (or designee) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. The investigator or designee must maintain records that document:

- Delivery of study drugs to the study site.
- Inventory of study drugs at the site.
- Participant use of the study drugs, including pill counts from each supply dispensed.
- Return of study drugs 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 the investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

Randomization to treatment in the double-blind period of the study will occur centrally via the IRT system (see Section 8.1.3). Participant randomization will be stratified based on geographical region (North America and outside of North America) and disease severity (Hurley

Stages I, II, and III) with no more than 25% of the total number of participants as Hurley Stage III. Full details for randomization will be provided in the Study Manual.

Participants, investigators, and the sponsor will be blinded to each participant's initial treatment assignment for the double-blind treatment period. 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 9.5).

During the 36-week open-label treatment period, participants will receive INCB054707 75 mg QD. During the LTE period (also open label), participants will receive INCB054707 up to 75 mg QD, with the possibility of dose change and dose decrease, as described in Section 6.5.1.

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 study drug will be calculated by the sponsor based on the drug accountability (eg, tablet counts) documented by the site staff and monitored by the sponsor/designee. Participants will be instructed to bring all unused study drugs with them to the study visits in order for site personnel to conduct tablet counts to assess study drug accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

6.5. Dose Modifications

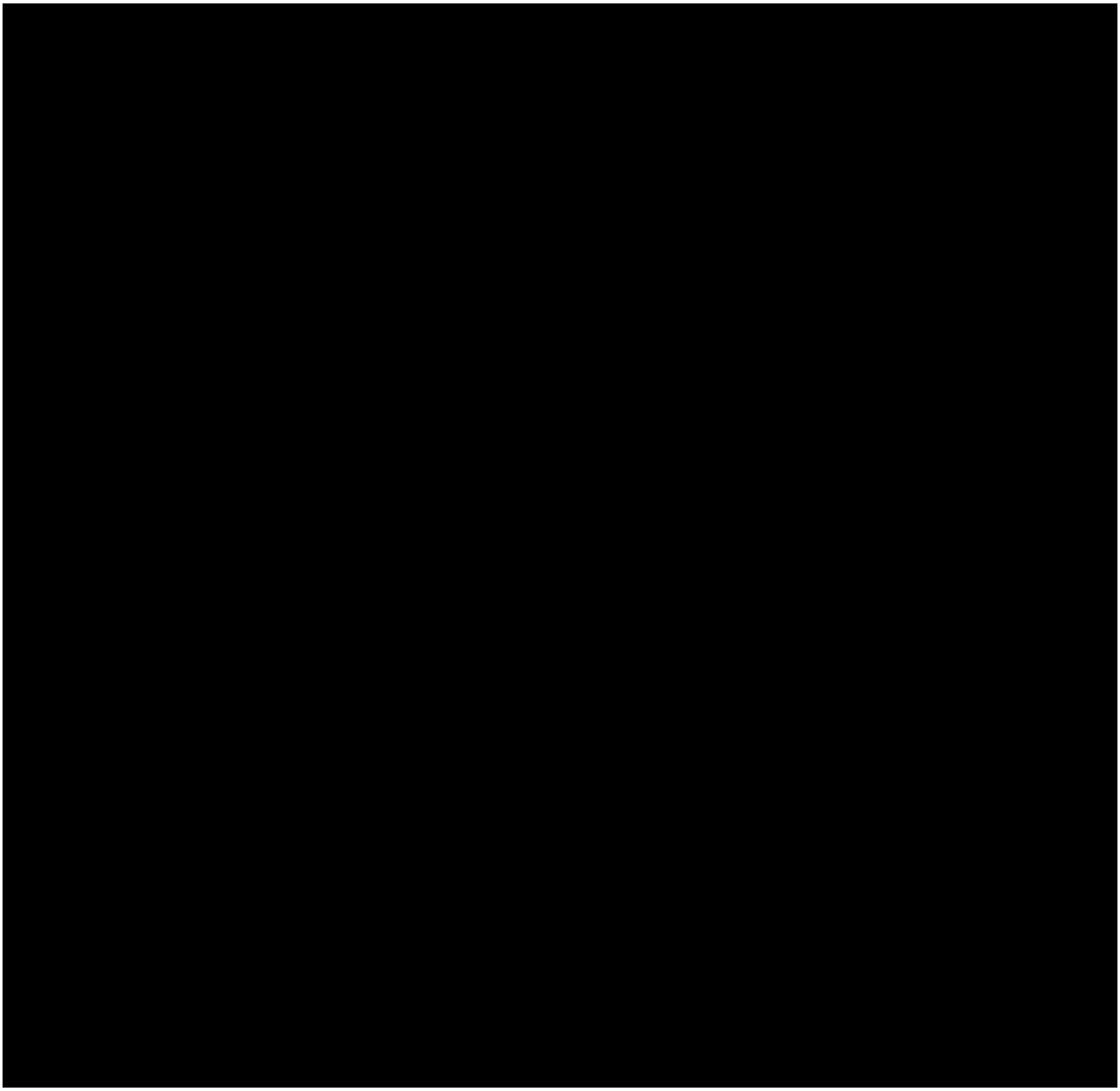
6.5.1. Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug

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

No dose modifications will be allowed during the placebo-controlled period. In some circumstances, it may be necessary to temporarily interrupt study treatment as a result of AEs or laboratory abnormalities that have an unclear relationship to the study drug (see Table 7).

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 designee) before temporarily interrupting study drug. Participants who experience a recurrence of the AEs or laboratory abnormalities upon restarting the study drug at the previously administered dose may have the study drug permanently discontinued.

[redacted]



6.5.2. Criteria for Permanent Discontinuation of Study Drug

The occurrence of unacceptable severity of an AE not caused by the underlying disease will be presumed to be related to study drug treatment and will require that the study drug be permanently discontinued. Unacceptable severity is defined as follows:

- The occurrence of an AE that is related to study drug that, in the judgment of the investigator or the sponsor's medical monitor (or designee), compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.
- Participant presents with a worsening of HS that requires treatment with a prohibited concomitant medication.

Additionally, study drug will be discontinued as outlined in Section 6.5.1 and Section 6.6.4.

See Section 7 for discontinuation procedures.

6.6. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. Any prior medication received up to 30 days before the first dose of study treatment and within 35 days after the last dose of study treatment will be recorded in the eCRF. A detailed history of prior medications related to HS used 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 (or designee) should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1. Permitted Medications and Procedures

6.6.1.1. Analgesic Therapy

Analgesic (nonopioid and opioid) use is allowed during the entire study [redacted] Further information will be provided in the Study Manual. The following analgesics may be used:

- Nonsteroidal anti-inflammatory drugs, as needed, without exceeding the recommended dose on the label.
  - Low dose acetyl salicylic acid (aspirin, ≤ 100 mg QD) is permitted for the purpose of cardiovascular prophylaxis at the discretion of the investigator.
- Acetaminophen/paracetamol, intermittently (not to exceed 1 g/day).
- Prescribed analgesics, at the discretion of the medical monitor or designee.

6.6.1.2. Wound Care

Concomitant use of wound care dressings on HS wounds is allowed.

6.6.2. Restricted Medications and Procedures

The following are permitted during the study under specified conditions:

- Use of antihyperglycemic agents (eg, metformin, liraglutide, sitagliptin, saxagliptin, linagliptin, pioglitazone, rosiglitazone) is allowed unless if prescription is intended for HS treatment.
- Use of hormonal therapies (eg, finasteride, spironolactone) is allowed unless if prescription is intended for HS treatment.
- Use of systemic and topical anti-infectives (eg, antibiotics, antivirals, and antifungals):
  - [redacted]
  - [redacted]
- Use of topical antiseptics such as washes, creams, soaps, ointments, gels, and liquids containing chlorhexidine, zinc gluconate, triclosan, benzoyl peroxide, or diluted bleach:
  - [redacted]
  - [redacted]
- Use of corticosteroid inhalers and intranasal sprays are allowed for stable asthma participants.

6.6.3. Prohibited Medications and Procedures

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

- Conventional therapies with potential therapeutic impact on HS, per discretion of investigator or designee.
- JAK or TYK2 inhibitors (systemic or topical) other than INCB054707 (eg, ruxolitinib, tofacitinib, baricitinib, filgotinib, lestaurtinib, pacritinib, abrocitinib, brepocitinib).
- Anticoagulants or medications known to cause thrombocytopenia (unless considered safe to stop and washout for the duration of the study).
- Acetyl salicylic acid (aspirin).

  Note: Low dose acetyl salicylic acid (≤ 100 mg QD) is permitted for the purpose of cardiovascular prophylaxis at the discretion of the investigator.
- Use of biologics (eg, anti–TNF-α, anti–IL-12/23, anti–IL-17, anti–IL-23, anti–CD-40, anti–IL-1, anti–C5a, anti–T-cell inhibitors).
- Adalimumab or any other investigational or experimental treatments for HS.
- Apremilast, crisaborole, or any other systemic or topical PDE-4 inhibitor.

[redacted]

- Systemic immunosuppressive or immunomodulating drugs (eg, oral or injectable corticosteroids, methotrexate, cyclosporine, dapsone, azathioprine) except as described in Section 6.6.4 and Section 8.2.3.
- Systemic and topical retinoids if prescribed for HS treatment (eg, acitretin, isotretinoin, adapalene, tazarotene, trifarotene).

[redacted]

- Strong and moderate systemic CYP3A4 inhibitors and strong systemic CYP3A4 inducers. Examples include but are not limited to the following medications (refer to Study Manual for details): erythromycin, rifampicin/rifampin, ciprofloxacin, some azole antifungals (eg, ketoconazole, fluconazole), nefazodone, St. John's Wort, diltiazem, mibefradil, verapamil, and grapefruit/grapefruit juice.
- Live vaccines (during the study and within 6 weeks after the last dose of study drug).

6.6.4. Rescue Interventions

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

(ie, nonresponder lesion) from the date of the intervention and must account for it in the source file and on the appropriate eCRF.

Concomitant use of wound care dressings is allowed as described in Section 6.6.1.2. Participants should continue using any oral and topical therapies during the study, consistent with the allowances and restrictions described in Section 6.6.

6.6.4.1. Types of Rescue Intervention

The following types of rescue interventions are permitted (further information to be included in the Study Manual):

- Injection with intralesional corticosteroids.
- Incision and drainage.

6.6.4.2. Number of Rescue Interventions

The number of rescue interventions during each study period are provided below.

During the placebo-controlled period:

- **Total of 2 Protocol-allowed interventions.**
- An intervention can occur on maximally 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 at the same visit.
- If a participant requires more than 2 interventions within the first 16 weeks, then they must be withdrawn from the study.

During the OLE or LTE periods:

- **Maximum of 2 interventions every 4 weeks.**
- An intervention can occur on 2 different lesions at the same visit or on the same lesion at 2 different study visits.
- Within each 4-week period, the same type of intervention cannot be used 2 times on the same lesion.
- If a participant requires more than 2 interventions within a 4-week period or has 2 of the same interventions on the same lesion within that period, then they must be withdrawn from the study.

6.7. Treatment After the End of the Study

After completion of the double-blind, placebo-controlled, 16-week treatment period, participants will receive INCB054707 75 mg for 36 weeks during an OLE period. At the completion of the 36-week OLE period, all eligible participants will have the option to continue treatment with INCB054707 for an additional 48 weeks (LTE period). Upon completion of the study, additional treatment will not be available.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

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

- The participant becomes pregnant.
- Consent is withdrawn.
  Note: Consent withdrawn means that the participant has explicitly indicated that he/she does not want to be followed any longer; in this case no further data, except data in public domain, may be solicited from or collected on the participant. Participants may choose to discontinue study treatment and remain in the study to be followed for safety monitoring.
- Further participation would be injurious to the participant's health or well-being, in the investigator's (or designee) medical judgment.
- Any adverse event of unacceptable severity as noted in Section 6.5.
- Participant meets discontinuation criteria as described in Section 6.6.4.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

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

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

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment, the ET1/EOT1 (during the placebo-controlled period), ET2/EOT2 (during the OLE period), or ET3/EOT3 (during the LTE period) visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit. These visits are described in Table 3. The last date of the last dose of study drug and the reason for discontinuation of study drug will be recorded in the eCRF.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for discontinuation must be documented in the participant's medical record and the primary reason for discontinuation must be included in the eCRF.

- The ET1/EOT1, ET2/EOT2, or ET3/EOT3 visit should be performed and date recorded.
- The status of the participant should be updated to EOT1, EOT2, or EOT3 as applicable, in the IRT.
- Participants must be followed for safety until the time of the follow-up visit or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

If the participant discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up 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. When a participant is withdrawn from the study, the ET visit procedures should be performed; if possible, the safety follow-up visit should also be conducted within 35 days of the last dose of study treatment. This study has an ET1, applicable for the placebo-controlled period; an ET2, applicable for the OLE period; and an ET3, applicable for the LTE period. See Table 3 for data to be collected at the ET1, ET2, or ET3 visit.

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.

7.3. Lost to Follow-Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the participant. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF must contain all required elements and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the countries 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 during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and the day the participant is randomly assigned to study drug (Day 1). Screening assessments for determination of eligibility may be performed over a period lasting up to 30 days. For participants who are randomized in the study, information associated with eligibility requirements must be entered into the appropriate eCRF pages.

Results from the screening visit evaluations will be reviewed to confirm eligibility before randomization or the administration of study drug. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before randomization will be used to determine eligibility.

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

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of the site ID and participant number. Site staff should contact the IRT to obtain the participant ID number during screening. Upon determining that the participant is eligible for randomization, the IRT will be contacted to obtain the treatment assignment. Additionally, the IRT will be contacted at predetermined visits (see Table 3) to update the study drug supply. Additional details are provided in the IRT Manual.

8.1.4. Distribution of Study Reminder Cards and Diaries

Participants will be provided a diary and study reminder cards as outlined in Table 3. Reminder cards will indicate the schedule of the next visit [redacted], they should withhold self-administration of the study treatment on the visits at Week 4, Week 8, Week 16, and Week 24, when dose will be administered at the study site (see Table 6 for further information). The Day 1 dose will also be administered at the study site.

Study participants will be instructed on the use of the diary. [redacted]

8.1.5. Demography and Medical History

8.1.5.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening by the investigator or qualified designee and will include year of birth/age, race, ethnicity, medical and surgical history, and current illnesses as well as nicotine and alcohol use information. Nicotine use information will also be collected at EOT1, EOT2, and EOT3 visits. Medical history will

include relevant medical treatment within the last year or surgical procedures that are considered clinically significant by the investigator.

8.1.5.2. Disease Characteristics and Treatment History

A disease-targeted medical, surgical, and treatment history will be collected at screening for the past year. A detailed history of prior medication use related to HS in the year before screening will also be collected, as well as response to each treatment and reason for discontinuation. Surgical history beyond the past year will also be recorded if considered relevant by the investigator or designee.

8.1.6. Follow-Up Phone Call

All participants will be contacted by phone 1 week prior to the baseline visit (Day 1/Week 0) to ensure that daily assessments [redacted] are being recorded; study sites are also encouraged to contact participants 1 week after the baseline visit to ensure compliance with the daily assessments. If daily assessments are not completed for at least the 7 consecutive days before the baseline visit, the participant may not be randomized (at the discretion of investigator or designee). [redacted]

8.2. Efficacy Assessments

Efficacy assessments, [redacted] are provided in this section. Unless an exception is required, the same investigator/designee should perform the efficacy assessments for a participant at each of the participant's efficacy evaluation visits.

The lesion count worksheet (provided in the Study Manual) will be used for recording the abscess, nodule (inflammatory and noninflammatory), fistula (draining and nondraining), and hypertrophic scar counts, and the assessment of Hurley stage. The lesion counts will be used for calculation (by Incyte or designee) of efficacy parameters, including HiSCR and IHS4. Additionally, the number and type of lesional interventions will be documented on this worksheet.

8.2.1. Lesion Counts

The definition of each HS lesion to be recorded in the lesion count worksheet is outlined in Table 8. The worksheet includes assessment of anatomical regions such as left/right axilla, left/right sub/inframammary area, intermammary area, left/right buttock, left/right inguino-crural fold, perianal area, and perineal area. The lesion counts will be used for calculation of efficacy parameters (see Table 5 for objectives and endpoints), as follows: AN and ANF counts (see Section 8.2.1.1), HiSCR (see Section 8.2.1.2), IHS4 (see Section 8.2.1.3), [redacted]

Table 8: Definition of Hidradenitis Suppurativa Lesions

HS Lesion	Definition
Abscess	A circumscribed collection of purulent exudate frequently associated with swelling and other signs of inflammation, such as fluctuance, tenderness, and pain
Inflammatory nodules	A tender, erythematous, well-defined nodule. The lesion has no evidence of fluctuance. A pyogenic granuloma-like lesion is considered an inflammatory nodule; a papule or pustule is not considered an inflammatory nodule.
Noninflammatory nodules	Nontender or minimally tender, nonerythematous nodules.
Draining fistula (or draining tunnel)	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.
Sinus tracts (nondraining fistula/tunnel)	Sinus tracts are a subtype of (nondraining) fistula in which the passageway links 2 or more areas underneath the skin surface but does not communicate with the skin surface.
Hypertrophic scar	Enlargement or overgrowth of a scar so that it extends above the surrounding skin surface

8.2.1.1. AN and ANF Counts

The AN and ANF counts will be recorded at all visits. The AN results will be used to calculate change in AN count relative to baseline, as well as AN50, AN75, AN90, and AN100, defined respectively as at least a 50%, 75%, 90%, and 100% decrease in AN count relative to baseline. The ANF results will be used to calculate the change in ANF count relative to baseline. Further information will be provided in the Study Manual.

8.2.1.2. Hidradenitis Suppurativa Clinical Response

The HiSCR was originally developed based on the underlying Phase 2 trial of adalimumab and validated against meaningful changes in pain score and DLQI (Kimball et al 2016c, Sabat et al 2020). The achievement of HiSCR is defined as at least 50% reduction in AN count with no increase in either abscess or draining fistula counts, relative to baseline. Further information will be provided in the Study Manual.

8.2.1.3. International Hidradenitis Suppurativa Severity Score System

The IHS4 (Zouboulis et al 2017) is a composite, dynamic score and validated tool used to determine HS severity. It employs a weighted scale using the number of inflammatory nodules, the number of abscesses, and the number of draining tunnels (fistulas or sinuses), with respective weight factors of 1, 2, and 4. Further information will be provided in the Study Manual.

[redacted]

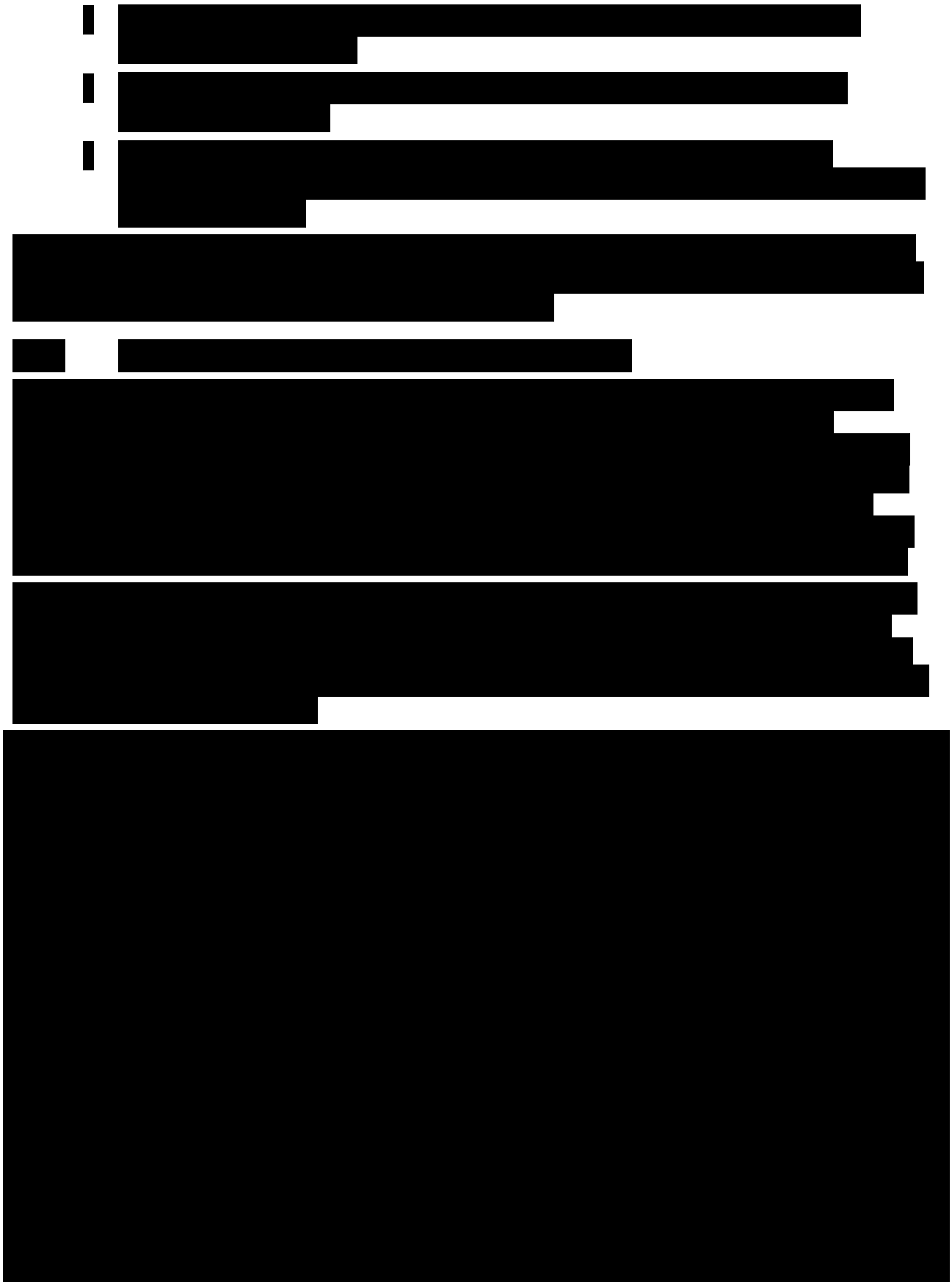
8.2.2. Hurley Stages of Hidradenitis Suppurativa

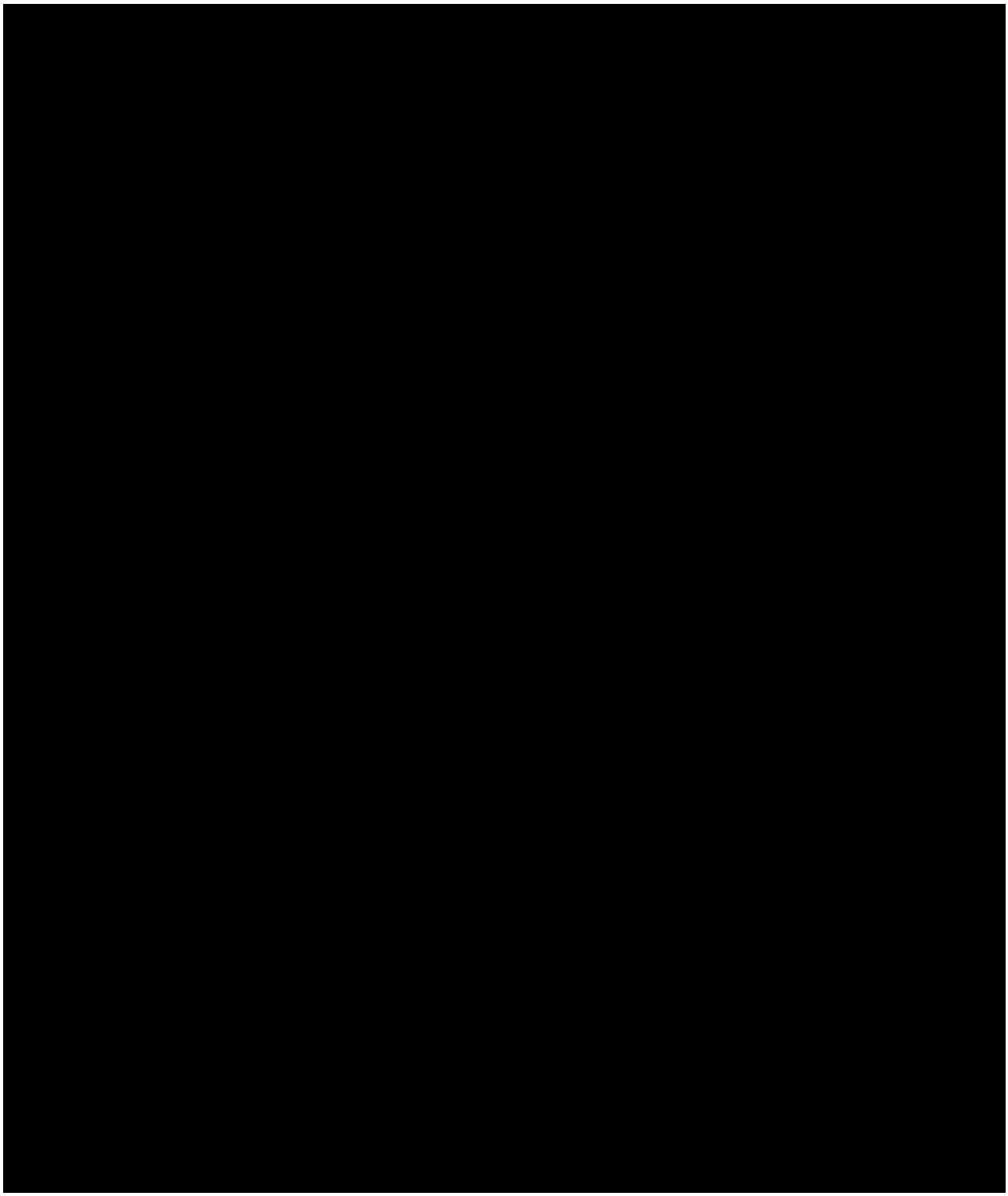
The Hurley classification is a static score and was originally designed for selection of the appropriate treatment modality in a certain body location (Zouboulis et al 2017): medical therapy for Stage I, local surgery for Stage II, and wide surgical excision for Stage III (see description in Table 9). The investigator (or designee) 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 the same region, the **worst** stage in that region should be documented. The participant will be assigned an overall Hurley stage classification corresponding to the stage of the **worst** involved anatomical region.

Table 9: Hurley Stages of Hidradenitis Suppurativa

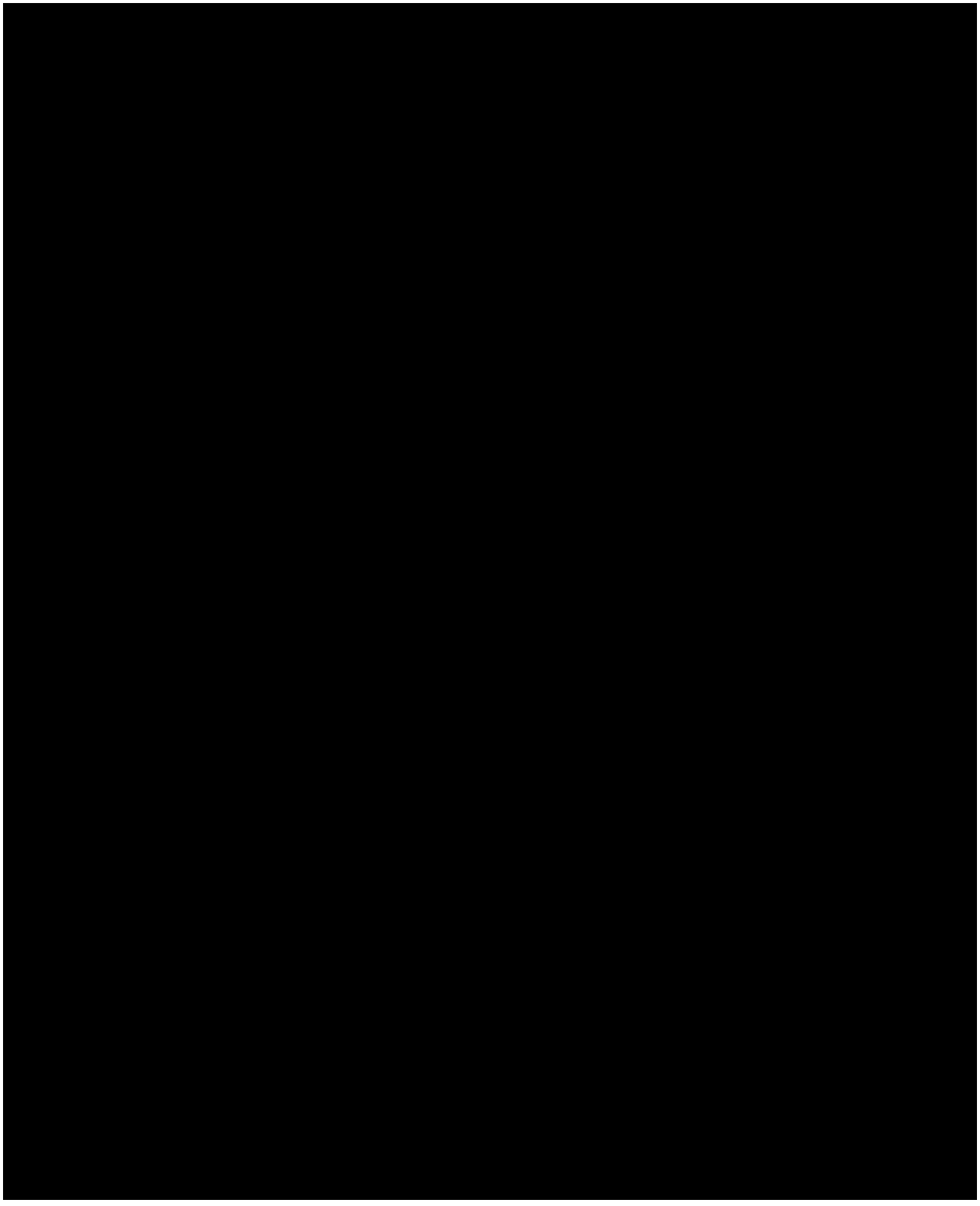
Hurley Stage	Description
I	Abscess formation, single or multiple, without sinus tracts and cicatrization (scarring).
II	One or more widely separated recurrent abscesses with tract formation and cicatrization (scarring).
III	Multiple interconnected tracts and abscesses across the entire area, with diffuse or near diffuse involvement.

[redacted]





[redacted]



8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (see Table 3). See Section 6.5 for guidelines regarding the management of relevant laboratory or other safety assessment abnormalities.

8.3.1. Adverse Events

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

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

All SAEs will be recorded and reported to the sponsor or designee immediately, without undue delay and not later than within 24 hours. The investigator will submit any updated SAE data to the sponsor immediately, without undue delay and not later than within 24 hours of it being available.

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

8.3.2. Physical Examinations

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

A comprehensive physical examination will include height (at screening only) 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 (or designee) are to be reported as AEs.

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

8.3.3. Vital Signs

Vital sign measurements (to be taken before blood collection for laboratory tests), include blood pressure, pulse, respiratory rate, and body temperature. If vital signs cannot be taken before blood collection for laboratory tests, there must be a minimum of 30 minutes from the completion of the blood collection procedures to the beginning of the vital signs collection. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after 5 minutes of rest. Vital sign results identified after the first dose of study treatment constitute an AE if they are considered clinically significant in the judgement of the investigator.

8.3.4. Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the SoA (see Table 3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after 5 minutes of rest. Prolonged QTcF values of ≥ 450 milliseconds are to be confirmed by performing 2 additional ECGs (within the next 5 minutes) and averaging the results to determine the averaged value.

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. Refer to the Study Manual for additional details on ECGs.

8.3.5. Chest X-Ray

As per Section 8.3.6, at the discretion of the medical monitor (or designee), participants may be required to have a chest radiograph (posterior-anterior and lateral views) or other appropriate diagnostic image (ie, computed tomography or magnetic resonance imaging) taken at screening or within 12 weeks prior to Study Day 1 and read by a qualified radiologist.

8.3.6. Tuberculosis Screening

At the time of screening, all participants will undergo TB testing unless performed within 12 weeks before Day 1. The QFT-GIT is the preferred testing method. If the QFT-GIT cannot be performed, or if the results cannot be determined by the reference laboratory to be either positive or negative, then participants may be screened using the PPD tuberculin skin test (Mantoux method) with approval of the medical monitor (or designee).

In addition to TB testing as specified in this clinical Protocol, a chest x-ray (see Section 8.3.5) may be requested to aid in TB status determination.

The QFT-GIT is an indirect test for *Mycobacterium tuberculosis* infection (including disease) and is intended for use in conjunction with risk assessment, radiography, and other medical and diagnostic evaluations.

A negative PPD test can be substituted for the QFT-GIT only if the central laboratory is unable to perform the QFT-GIT or cannot determine the results to be positive or negative and the medical monitor (or designee) approves it, on a case-by-case basis.

Purified Protein Derivative Test

If the QFT-GIT cannot be performed, or if the results cannot be determined to be positive or negative, then participants may be screened using the PPD tuberculin test (Mantoux method), with the approval of the medical monitor (or designee).

Participants must have the PPD test administered and evaluated by a health care professional 48 to 72 hours later in order to be eligible for the study, unless performed and documented within the last 3 months. The test should be performed according to local standards with induration of < 5 mm required for inclusion.

8.3.7. Laboratory Assessments

See Table 10 for the list of clinical laboratory analytes to be performed and Table 3 for the laboratory assessment visit schedule. A central laboratory will perform all clinical laboratory assessments for safety (ie, blood chemistries, hematology assessments, urinalysis, inflammation markers, and lipid panel). [redacted] Additional testing may be required by the sponsor based on emerging safety data. All Protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual and Table 3. Information regarding collection, processing, and shipping of samples for laboratory assessment is provided in the Laboratory Manual.

Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 4 weeks after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If screening laboratory assessments are performed more than 30 days before Day 1, then the tests must be repeated and eligibility confirmed before study drug administration on Day 1. Laboratory sample collection on Day 1 must be performed before study drug administration.

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

Table 10: Required Laboratory Analytes

Chemistry	Hematology	Urinalysis	Serology/Infection	Pregnancy testing
• Albumin • Alkaline phosphatase • ALT • AST • Bicarbonate or CO_2 • Blood urea nitrogen or urea • Calcium • Chloride • Creatine kinase • Creatinine • Glucose • Gamma-glutamyl transferase (GGT) • Lactate dehydrogenase • Phosphate • Potassium • Sodium • Total bilirubin • Direct bilirubin (if total bilirubin is elevated above ULN) • Total protein	**Complete blood count, including:** • Hemoglobin • Mean corpuscular volume • Hematocrit • Platelet count • Mean platelet volume • In samples with abnormalities in platelet count or size distribution (as indicated by an automated analyzer), a blood film should be examined. • Red blood cell count • Red blood cell distribution width • White blood cell count • Hemoglobin A1c **Differential count (% and absolute values), including:** • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils **Biomarkers:** • Hepcidin • Ferritin	• Color and appearance • pH and specific gravity • Bilirubin • Glucose • Ketones • Leukocyte esterase • Nitrite • Occult blood • Protein • Microscopic evaluation (in case of abnormal urinalysis results) • Nicotine metabolite screen (at specified visits in Table 3) **Lipid Panel** • Total cholesterol • Triglycerides • LDL • HDL **Observation:** Fasting not required	• Hepatitis B surface antigen and Hepatitis B core antibody* • Hepatitis C antibody* • HIV • QFT-GIT (see Section 8.3.6) (*DNA & RNA only if serology is positive) **Inflammation Markers** • High sensitivity C-reactive protein (hsCRP)	**Pregnancy testing will only be performed for female participants.** **Further instructions are provided in Section** 8.3.7.2. • **Serum FSH test:** For confirmation of nonchildbearing status; to be performed at screening only. • **Serum pregnancy test:** For WOCBP only; to be performed at screening and at visits indicated in Table 3. • **Urine pregnancy test:** For WOCBP only; to be performed at visits indicated in Table 3. Pregnancy tests (serum or urine) should be repeated if required by local regulations.

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

8.3.7.1. Serology Testing

Screening laboratory tests (see Table 3 and Table 10) include serology, TB screening, pregnancy test (for WOCBP), serum FSH test (for confirmation of nonchildbearing status), urinalysis, hematology, chemistry assessments, and inflammation markers. Refer to the Laboratory Manual for further screening assessment instructions.

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

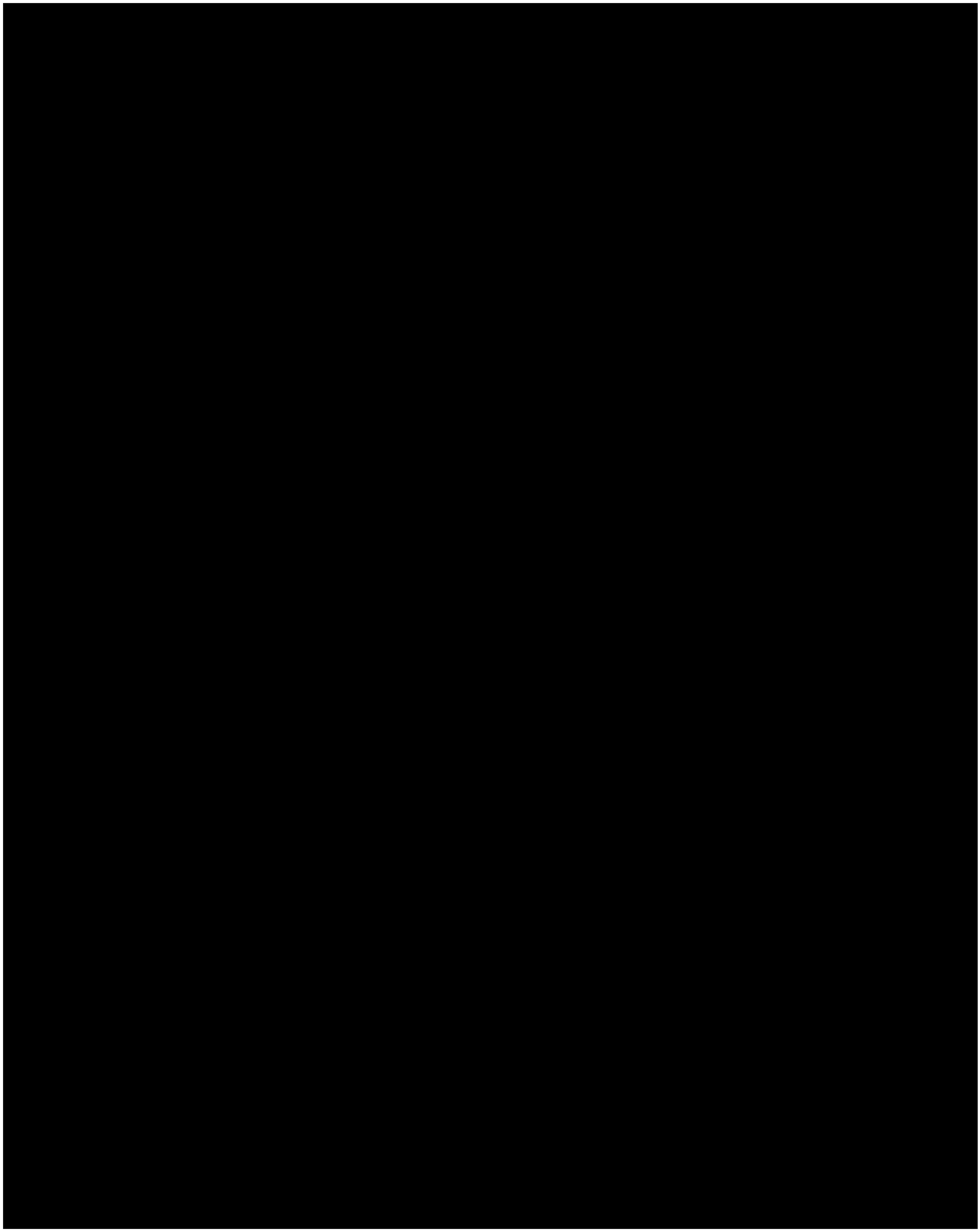
8.3.7.2. Pregnancy Testing

A serum pregnancy test will be required for all WOCBP during screening (before the first dose of study drug) and at the EOT visits, as applicable. Urine pregnancy tests will be performed locally as outlined in Table 3, as medically indicated (eg, in case of loss of menstrual cycle, when pregnancy is suspected), or per country-specific requirement (note that country-required urine pregnancy testing will be outlined and communicated to investigational sites under separate cover). If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test.

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

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

A serum FSH test will be required for all WONCBP during screening (before the first dose of study drug) for confirmation of nonchildbearing status. Women of nonchildbearing potential are defined as surgically sterile with a hysterectomy and/or bilateral oophorectomy OR postmenopausal defined as amenorrhea ≥ 12 months prior to screening.



8.6. Unscheduled Visits

Unscheduled visits may occur at any time at the investigator's (or designee'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) during the study, an unscheduled visit within the following week should occur to repeat laboratory assessments (further details are provided in Table 7 and Section 8.3.7). See Section 6.5.1 for instructions on dose interruption and restart. The investigator must inform and consult the sponsor (or designee) with any hematological abnormality.

8.7. End of Treatment and/or Early Termination

When the participant permanently discontinues study drug, whether the participant is terminating the study early (ET) or the participant has completed the study, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. This study has an EOT1, applicable for the placebo-controlled period; an EOT2, applicable for the OLE period; and an EOT3, applicable for the LTE period. The ET1, ET2, and ET3 procedures to be followed (see Table 3) are respectively the same as EOT1, EOT2, and EOT3. The participant should be encouraged to return for the follow-up visit (EOS).

8.8. Follow-Up

8.8.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit (EOT1, EOT2, or EOT3) and the scheduled safety follow-up visit, which should occur 28 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 1) at least 28 days after the last dose of study drug or 2) 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. In exceptional cases when the participant cannot return to the site for the safety follow-up visit, the participant should be contacted by telephone for assessment of AEs and SAEs and the site should properly document the contact.

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 laboratory test result (eg, low hemoglobin, platelet count decreased).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though they may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "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 an 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.
- Efficacy endpoints as outlined in Section 3 will not be reported as AE/SAEs, specifically, any event that is related to disease progression of the disease under study. Unblinded aggregated efficacy endpoint events and safety data will be monitored to ensure the safety of the participants in the study. Any suspected endpoint that upon review is not progression of the disease under study will be forwarded to Incyte Pharmacovigilance as an SAE within 24 hours of determination that the event is not progression of the disease under study.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE if it occurred after signing informed consent. If present before entering the study, the condition should be captured as medical history.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.2. Definition of Serious Adverse Event

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations (Important Medical Event)

An event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent 1 of the outcomes listed in the above definition. Examples of such events include new invasive or malignant cancers, intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

Adverse Event and Serious Adverse Event Recording

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

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

- The severity grade (CTCAE v5 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 treatment (including study drug): suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on Adverse Event Form and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Non-Drug Therapy).

Assessment of Intensity

The severity of AEs will be assessed using CTCAE v5 Grades 1 through 5. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity.

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

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

- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- **Grade 4:** Life-threatening consequences; urgent treatment indicated.
- **Grade 5:** Fatal.

Assessment of Causality

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

Follow-Up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- Any updated SAE data will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.
- Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome.
- When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves.

See Appendix C for the management of potential Hy's Law cases.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study drug or study procedures), all SAEs 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) immediately, without undue delay and not later than 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) immediately, without undue delay and not later than within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information after conclusion of 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) immediately, without undue delay and not later than 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 an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

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

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

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

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB 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. 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.

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.

9.6. Pregnancy

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

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

9.7. Warnings and Precautions

Special warnings or precautions for the study drug, derived from safety information collected by the sponsor or its designee, are presented in the 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.

9.8. Product Complaints

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

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

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

9.9. Treatment of Overdose

For this study, any dose of study treatment greater than the assigned daily dose (depending on the participant's treatment assignment) within the same day will be considered an overdose. The 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.

There has been no clinical experience with overdose of INCB054707. Treatment of overdose should consist of general supportive measures.

10. STATISTICS

10.1. Sample Size Determination

[redacted]

10.2. Populations for Analysis

The populations for analysis are provided in Table 13.

Table 13: Populations for Analysis

Population	Description
ITT	The ITT population includes all randomized participants. Treatment groups for this population will be defined according to the treatment assignment at randomization.
PP	The PP population includes randomized participants who are considered to be sufficiently compliant with the Protocol.
Safety	The safety population includes all participants who received at least 1 dose of study drug. Treatment groups for this population will be determined according to the actual treatment the participant received on Day 1.
[redacted]	[redacted]

10.3. Level of Significance

[redacted]

[redacted]

10.4. Statistical Analyses

[redacted]

10.4.1. Primary Analysis

[redacted]

10.4.2. Secondary Analysis

[redacted]

All other secondary [redacted] variables will be summarized using descriptive statistics. For categorical measurements, summary statistics will include sample size, frequency, and percentages. For continuous measurements, summary statistics will include sample size, mean, median, standard deviation, minimum, and maximum. Summary statistics for continuous measures will be provided for baseline, the actual measurements at each visit, and the change and percentage change from baseline at each visit, if applicable.

10.4.3. Safety Analyses

Safety analyses will be conducted for the safety population. A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug until the end of the safety follow-up period. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study drug administration. Adverse events will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the NCI CTCAE v5.0 using Grades 1 through 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.

The clinical laboratory data will be analyzed using summary statistics; no formal treatment group comparisons are planned. Laboratory test values outside the normal range will be assessed for

severity based on the normal ranges for the clinical reference laboratory. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated. Descriptive statistics and mean change from baseline will be determined for vital signs (ie, blood pressure, pulse, respiratory rate, and body temperature) at each assessment time. Descriptive statistics and mean change from baseline will be determined for each ECG parameters at each assessment time.

10.5. Interim Analysis

An interim analysis will not be performed for 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 approval from both Health Authorities and IRB/IEC 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.

11.1.1. Identification of the Coordinating Principal Investigator

A coordinating principal investigator has been appointed by the Sponsor. As part of her responsibilities, the coordinating principal investigator will review the final CSR. Agreement with the final CSR will be documented by the dated signature of the coordinating principal investigator.

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 with 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. Other data outside the EDC system required in the study conduct of the Protocol such as documents or results transmitted to the sponsor via a central laboratory or specialized technical vendors and, as designated by the sponsor, will have their own data flow management plans, study charters, [redacted] as applicable.

The sponsor (or designee) will be responsible for:

- Managing the integrity of the data and the quality of the conduct of the study, such as 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.
- Managing and reconciling the data generated, and/or collected including documents and results such as laboratory or imaging data analyzed centrally by a designated vendor of the sponsor.

The investigator will be responsible for:

- Recording, or ensuring the recording of, all relevant data relating to the study in the eCRF.
- Delivering, or ensuring the delivery of, all other results, documents, data, know-how, or formulas relating to the study to the sponsor or designee electronically and/or centrally (eg, laboratory data, imaging data, [redacted] [redacted] diary data), or as otherwise specified in the Protocol.
- 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, or sent to a central vendor designated by the sponsor, or as described in other study and data flow manuals.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
  - Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current applicable medical records must be available.
- May have responsibility for sending participants' data, either as unique samples, or copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
- 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 protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that sensitive personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable. Appropriate consent for collection, use and disclosure and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws.

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

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 30 years after study completion unless local regulations require otherwise. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

11.4. Financial Disclosure

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

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

11.5. Publication Policy

By signing the study Protocol, the investigator and his/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 or 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 (assessed for surgical success) qualify as having met the requirement for a highly effective birth control method.

For female participants in the study:

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

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

Unacceptable 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 unacceptable.

Source: Clinical Trials Facilitation and Coordination Group 2014.

[redacted]

[redacted]

[redacted]

APPENDIX D. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1	10 SEP 2021

Amendment 1 (10 SEP 2021)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to obtain additional long-term safety and efficacy data through 104 weeks; and to incorporate changes from country-specific amendments for Germany (dated 04 DEC 2020) and Canada (dated 08 MAR 2021). Additional changes are summarized below.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Table 3: Schedule of Activities); Section 2.1.2, Scientific Rationale for Study Design; Section 2.1.3, Justification of Dose; Section 2.2.2, Benefit Assessment; Section 3, Objectives and Endpoints (Table 5: Objectives and Endpoints); Section 4.1, Overall Design; Section 4.2, Overall Study Duration; Section 6.1, Study Treatments Administered (Table 6: Study Treatment Information); Section 6.3, Measures to Minimize Bias: Randomization and Blinding; Section 6.5.1, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug; Section 6.6.2, Restricted Medication and Procedures; Section 6.6.4.2, Number of Rescue Interventions; Section 6.7, Treatment After the End of the Study; Section 7.1.2, Discontinuation Procedures; Section 7.2, Participant Withdrawal From the Study; Section 8.7, End of Treatment and/or Early Termination**

   Description of change: At the completion of the 36-week OLE period (preceded by the 16-week placebo-controlled period), all eligible participants will have the option to continue treatment for an additional 48 weeks (LTE period), followed by a 4-week safety follow-up period.

   Rationale for change: To obtain additional long-term safety and efficacy data through 104 weeks.

4. **Section 2.1.4, Justification for Placebo**

   Description of change: Added Section 2.1.4, Justification for Placebo.

   Rationale for change: Per request made by the Germany's Health Authority to provide a rationale for a placebo arm in this HS study.

5. **Section 2.1.5, Justification for Doses in the Long-term Extension**

   Description of change: Added Section 2.1.5, Justification for Doses in the Long-term Extension.

   Rationale for change: To provide a rationale for the long-term extension and the doses available in that period.

6. **Section 5.1, Inclusion Criteria**

   Description of change: Added Inclusion Criterion 6.

   Rationale for change: Per request made by the Germany's Health Authority to determine that participants must have been previously exposed to at least 1 line of HS treatment (systemic antibiotics) before starting this study.

7. **Section 6.5.1, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 7: Guidelines for Interruption, Restart, and Discontinuation of Study Drug)**

   Description of change: Added clarification on the guidance for study drug interruption/restart when AST and/or ALT > 3.0 × ULN.

   Rationale for change: To clarify that Appendix C should be consulted and to specify that the study drug can only be interrupted/restarted up to 2 times.

8. **Section 6.5.1, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug (Table 7: Guidelines for Interrupting, Restarting, and Discontinuing Study Drug)**

   Description of change: Revised sentences that explained study treatment reinitiation after study treatment is interrupted when a platelet count between 50×10^9/L to $< 75 \times 10^9$/L is observed.

   Rationale for chance: Per request made by Health Canada to provide a clarification that study treatment in the open-label extension will be reinitiated when platelet count is $\geq 100 \times 10^9$/L.

9. **Section 8.3.7, Laboratory Assessments (Table 10: Required Laboratory Analytes)**

   Description of change: Creatine kinase was added to the list of analytes in the chemistry column.

   Rationale for change: To align with emerging literature suggesting that JAK inhibitors may lead to increases in creatine kinase.

10. **Section 8.3.7, Laboratory Assessments (Table 10: Required Laboratory Analytes)**

    Description of change: Erythrocyte sedimentation rate (ESR) was removed from the Inflammation Markers subheading.

    Rationale for change: The inflammation markers assessment will focus on the high sensitivity C-reactive protein results, thus not requiring ESR evaluation.

11. **Section 9.4, Reporting of Serious Adverse Events**

    Description of change: Added clarification for timing of SAE reporting.

    Rationale for change: Per request made by the Germany's Health Authority to clarify that SAE reporting must happen immediately and not later than within 24 hours.

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

    Description of change: The following updates (deletions indicated by strikethroughs; insertions indicated by underlines) were made:

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

    [e] A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered unacceptable~~, but not highly effective birth control methods~~.

    Rationale for change: To clarify the contraceptive methods that are not allowed in the study, and to ensure consistency between the information on contraceptive methods presented in Appendix A and the requirements described in Inclusion Criterion 4b.

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

Signature Page for VV-CLIN-010474 v2.0

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