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Clinical Study Protocol

INCB 18424-221

A Phase 2, Double-Blind, Randomized, Vehicle-Controlled, Efficacy, and Safety Study of Ruxolitinib Cream in Participants With Hidradenitis Suppurativa

Product:	**Ruxolitinib Cream**
IND Number:	**77,101**
EudraCT Number:	**2022-002662-33**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803 USA**
Original Protocol:	**19 AUG 2022**

INVESTIGATOR'S AGREEMENT

I have read the INCB 18424-221 Protocol (dated 19 AUG 2022) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
AN	abscess and inflammatory nodule
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BID	twice daily
BSA	body surface area
CFR	Code of Federal Regulations
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DBVC	double-blind, vehicle-controlled
[redacted]	[redacted]
DNA	deoxyribonucleic acid
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
[redacted]	[redacted]
EQ VAS	EuroQol visual analogue scale
ET	early termination
FDA	Food and Drug Administration (US)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GFR	glomerular filtration rate
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HiSCR	hidradenitis suppurativa clinical response
[redacted]	[redacted]

Abbreviations and Special Terms	Definition
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
HS	hidradenitis suppurativa
hsCRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	independent ethics committee
IGA	Investigator's Global Assessment
IGA-TS	Investigator's Global Assessment-Treatment Success (IGA score of 0 or 1 with ≥ 2-grade improvement from baseline)
IL	interleukin
INF	interferon
IRB	institutional review board
IRT	interactive response technology
IHS4	International Hidradenitis Suppurativa Severity Score System
ITT	intent-to-treat
JAK	Janus kinase
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
NRS	numeric rating scale
OLE	open-label extension
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PRO	patient-reported outcome
QD	once daily
QTL	quality tolerance limits
RNA	ribonucleic acid
RSI	Reference Safety Information
SAE	serious adverse event
SoA	schedule of activities
SOP	standard operating procedure

Abbreviations and Special Terms	Definition
STAT	signal transducer and activator of transcription
TEAE	treatment-emergent adverse event
Th1	T-helper 1
TNF	tumor necrosis factor
TYK	tyrosine kinase
ULN	upper limit of normal
WOCBP	woman of childbearing potential
[redacted]	[redacted]

1. PROTOCOL SUMMARY

A Phase 2, Double-Blind, Randomized, Vehicle-Controlled, Efficacy, and Safety Study of Ruxolitinib Cream in Participants With Hidradenitis Suppurativa

Protocol Number: INCB 18424-221

Objectives and Endpoints:

Table 1 presents the primary objective and endpoint.

Table 1: Primary Objective and Endpoint

Objectives	Endpoints
Primary	
To establish the efficacy of ruxolitinib 1.5% cream BID in participants with HS.	Change from baseline in abscess and inflammatory nodules (AN) count at Week 16.

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 with hidradenitis suppurativa
Population	Men or women ≥ 18 years of age, who have been diagnosed with HS (Hurley Stage I and II) for at least 3 months; with total AN count of 3 to ≤ 10. The AN count of 3 may affect at least 1 distinct anatomical area; however, an AN count of > 3 to ≤ 10 must be affecting at least 2 distinct anatomical areas.
Number of Participants	Approximately 60 participants will be randomized 1:1 to 1 of 2 treatment groups (ruxolitinib 1.5% cream BID or vehicle cream BID).
Study Design	This is a randomized, 16-week DBVC study followed by a 16 week OLE with an active treatment for participants who complete 16 weeks of DBVC period, followed by a 30-day post-treatment, safety follow-up visit.
Estimated Duration of Study Participation	Estimated total duration of participants is up to approximately 40 weeks, including up to 4 weeks for screening, up to 32 weeks for treatment, and 30 days for safety follow-up.
Data Safety Monitoring Board/Data Monitoring Committee	No
Coordinating Principal Investigator	To be determined

Treatment Groups and Duration:

This is a Phase 2, randomized, DBVC study with DBVC period of 16 weeks followed by an OLE period of 16 weeks.

Participants will be screened for up to 28 days prior to the first application of ruxolitinib 1.5% cream or vehicle cream. Key entry criteria for participants are diagnosis of HS (Hurley Stage I or II) for at least 3 months before screening visit and a **total AN count of 3 to ≤ 10 with no draining tunnels** at screening and baseline. The AN count of 3 may affect at least 1 distinct anatomical area; however, an AN count of > 3 to ≤ 10 must be affecting at least 2 distinct anatomical areas.

Approximately 60 eligible participants ≥ 18 of age will be randomized 1:1 to either ruxolitinib 1.5% cream or vehicle cream (see Figure 1). Participants will be stratified by baseline AN count (≥ 3 to 4 or ≥ 5 to 10). Participants will apply either ruxolitinib 1.5% cream or vehicle cream (both BID) through Week 16 to the all affected areas identified at baseline.

At Week 16, participants who meet the criteria (compliant with the Protocol and without safety concerns) will enter the 16-week OLE period. Participants randomized to vehicle BID in the DBVC period will be crossed over to ruxolitinib 1.5% cream BID and participants randomized to ruxolitinib 1.5% cream BID at baseline will remain on ruxolitinib 1.5% cream BID through Week 32 in an open-label fashion. At Week 16, the HS treatment area will be evaluated by the investigator to assess the disease and confirm whether treatment continuation is required (AN count ≥ 1 and/or Skin Pain NRS ≥ 1) during the OLE period or can otherwise (re)enter an observation/no treatment cycle (AN count = 0 and Skin Pain NRS = 0). During the OLE, participants will only treat symptomatic lesions (eg, presence of lesion, pain, and/or itch) including new lesions, not exceeding a total of 20% BSA.

Treatment assignment during the DBVC period will remain blinded to investigators and participants until after all participants have completed study or discontinued and completed the safety follow-up period.

During the DBVC and OLE periods, participants who are treated with HS lesional rescue medications and/or procedures (see Section 6.6.3), are considered nonresponsive to therapy, and will be discontinued from the study.

The COVID-19 global pandemic may present challenges to the normal conduct of this study (including AE and laboratory assessments), requiring the implementation of potential mitigation strategies described in Appendix B.

Figure 1 presents the study schema, Table 3 present the SoA.

Figure 1: Study Design Schema

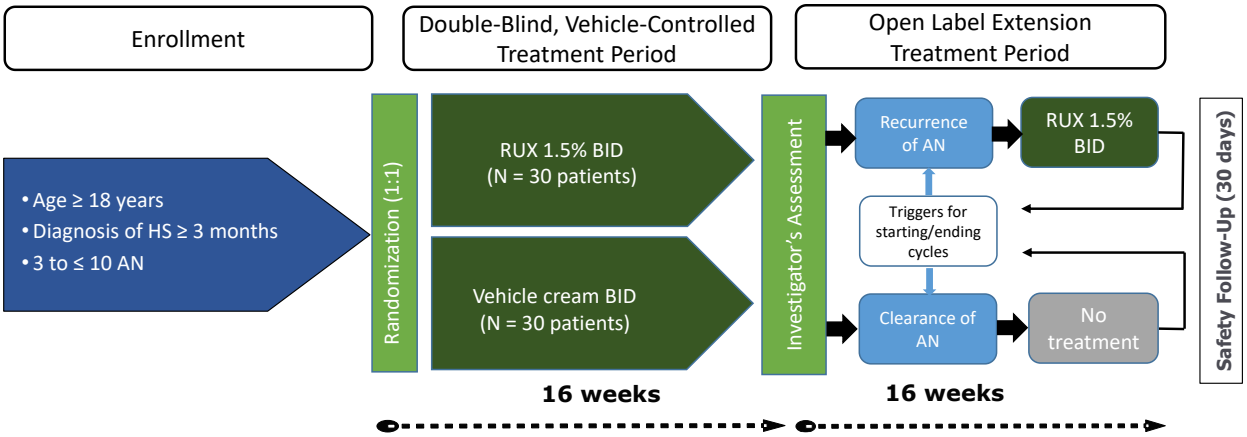


Table 3: Schedule of Activities

Visit Day (Range)	Screening	Baseline	Treatment (vehicle-controlled period)					Treatment (open-label extension)[a]				Unscheduled Visit	Follow-up
	Days −28 to −1	(Day 1)	Wk 2 (± 3 d)	Wk 4 (± 3 d)	Wk 8 (± 3 d)	Wk 12 (± 3 d)	Wk 16[a] ± 3 d/ ET1	Wk 20 (± 3 d)	Wk 24 (± 3 d)	Wk 28 (± 3 d)	Wk 32 (± 3 d/ ET2)		30 days (+ 7) days after last application)
Administrative procedures													
Informed consent	X												
Inclusion/exclusion criteria	X	X											
Demographic, medical history	X												
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT	X	X	X	X	X	X	X	X	X	X	X		
Randomization		X											
Distribute ediary	X												
Distribute reminder cards		X	X	X	X	X	X	X	X	X	X		
eDiary verification		X	X	X	X	X	X	X	X	X	X		
Apply study drug in clinic		X											
Weigh/dispense study drug		X	X	X	X	X	X	X	X	X			
Collect/weigh study drug and review study drug diary			X	X	X	X	X	X	X	X	X		
Assess study drug compliance			X	X	X	X	X	X	X	X	X	X	
Safety assessments													
AE assessments	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X[b]						X[c]				X[b]	X[c]	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and body weight	X												
Efficacy assessments													
%BSA	X[d]	X	X	X	X	X	X	X	X	X	X		X
Lesion count and assessment	X	X	X	X	X	X	X	X	X	X	X	X	X
Overall Hurley Stage	X	X			X		X				X		X
Patient-reported outcome													
Skin Pain NRS	Completed each evening through the last application of study drug.												
Itch NRS	Completed each evening through the last application of study drug.												
[redacted]													

Table 3: Schedule of Activities (Continued)

Visit Day (Range)	Screening Days −28 to −1	Baseline (Day 1)	Treatment (vehicle-controlled period) Wk 2 (± 3 d)	Wk 4 (± 3 d)	Wk 8 (± 3 d)	Wk 12 (± 3 d)	Wk 16[a] ± 3 d/ ET1	Treatment (open-label extension)[a] Wk 20 (± 3 d)	Wk 24 (± 3 d)	Wk 28 (± 3 d)	Wk 32 (± 3 d/ ET2)	Unscheduled Visit	Follow-up 30 days (+ 7) days after last application)
Patient-reported outcome (continued)													
[redacted]													
Laboratory assessments													
Chemistry assessments	X	X[e]					X				X	X[f]	X
Hematology assessments	X	X[e]					X				X	X[f]	X
hsCRP		X			X		X				X		
FSH[g]	X												
Serum Pregnancy test[h]	X												X
Urine Pregnancy test[h]		X		X	X	X	X	X	X	X	X		
HIV/Hepatitis Serology	X												
Translational assessments													
[redacted]													
Photography (at selected sites)		X			X		X				X		
[redacted]													

[a] All Week 16 assessments must be completed before the participant can continue in the OLE.
[b] Comprehensive physical examination at screening and Week 32/ET2 visit. The comprehensive physical examination will include assessment(s) of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes; as well as a brief neurological examination.
[c] A targeted physical examination may be conducted at Week 16. Targeted physical examination can be done for assessment of AE and during other visits including unscheduled visit as per discretion of the investigator. A targeted physical examination should only be conducted as indicated by symptoms reported by the participant, AEs, or other findings.
[d] Total HS BSA (excluding the scalp) should be ≤ 20% to be eligible for study entry and continued participation.
[e] Not necessary if screening assessment performed within 14 days of Day 1.
[f] Laboratory assessment is optional during unscheduled visits based on investigator's discretion and clinical judgement.
[g] Women of nonchildbearing potential only. Follicle-stimulating hormone is not needed in women with a documented hysterectomy, documented bilateral salpingectomy, or documented bilateral oophorectomy.
[h] Female participants of childbearing potential will have a serum test at screening and follow-up and a urine test at other visits noted. A positive urine test must be confirmed by a serum test.

2. INTRODUCTION

2.1. Background

Ruxolitinib cream is a topical formulation of ruxolitinib phosphate under development for a variety of dermatological conditions. Ruxolitinib 1.5% cream is approved by the FDA for the treatment of mild to moderate AD in nonimmunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable (Opzelura™ 2021). Ruxolitinib phosphate is an inhibitor of the JAK family of protein TYKs. Inflammatory cytokines are strongly implicated in the pathogenesis of a number of inflammatory dermatoses. Because JAKs serve to translate extracellular signals from a number of relevant cytokines and growth factors upregulated in these inflammatory diseases, JAK inhibitors represent potential therapeutic agents for these disease states (Chapman et al 2022).

Hidradenitis suppurativa is a debilitating, chronic inflammatory skin condition that affects the hair follicle leading to a perifollicular lympho-histiocytic inflammation (Zouboulis et al 2015). It is characterized by persistent or recurrent painful inflamed nodules and abscesses, and purulent-discharging tunnels referred to as sinus tracts and fistulas often localized in skin folds of axillary, inguinal, gluteal, and perianal areas of the body (Saunte et al 2017). In more severe disease, irreversible scarring is identified (Sabat et al 2020). Hidradenitis suppurativa diagnosis is made on clinical assessment and disease severity may be measured based on clinical manifestations including nodule phenotype in intertriginous body areas. The course of the disease may vary from mild disease (recurrent appearance of solitary or multiple isolated abscess formation without sinus tracts or scarring) to severe disease (deep fluctuant abscesses, draining sinuses, and severe, interconnected sinus tracts or scars; Frew et al 2021). The quality of life of HS patients is significantly impacted leading to psychological impairment (eg, anxiety, depression, etc) and poor-body image (Kurek et al 2013, Schneider-Burrus et al 2018).

The estimated prevalence of HS varies depending on the different populations and methods of reporting. The highest prevalence (approximately 4%) has been reported in those between 20 to 40 years of age with onset of disease usually at 20 years of age, and declining after the fifth decade of life (Jemec and Kimball 2015). The incidence of HS in females has been reported to be as high as 3 times that of men (Canoui-Poitrine et al 2013).

The etiology of HS is multifactorial, comprised of genetic and environmental factors, lifestyle (eg, smoking), hormonal status, and other comorbidities (metabolic syndrome, cardiovascular disorders, inflammatory bowel disease, etc; Zouboulis et al 2017).

Current treatment guidelines recommend tailoring HS treatment based on its individual subjective impact and objective severity of disease (Zouboulis et al 2015). The aim of initial management of patients with HS is to reduce lesion development and minimizing disease progression. Treatments may include topical antiseptics, antibiotics (clindamycin, rifampin, tetracyclines) as the first line of therapy, followed by intralesional steroid injections (triamcinolone), retinoids (acitretin), hormonal therapy (Estrace, Prefest), biologics (adalimumab, infliximab) and in more advanced cases, surgery. Currently, adalimumab

(Humira®), a TNF-α fully human monoclonal antibody administered via subcutaneous injection, is the only FDA-approved therapy for patients 12 years of age and older with moderate-to-severe HS. Adalimumab has shown modest HiSCR response rates (42% and 59% vs placebo 26% and 28%, respectively) in each of the Phase 3 trials (Frew et al 2020). Currently, there are no FDA-approved therapies for patients with mild HS. Therapies to treat patients with mild HS remain an unmet medical need to manage disease progression into a moderate-to-severe condition.

Increased expression of JAK-mediated inflammatory cytokines in HS skin suggests a potential therapeutic strategy for JAK-inhibitor treatment of this debilitating disease (Rumberger et al 2020; Zouboulis et al 2021). Data suggests that the cytokines IL-1β, IL-17, IL-23, IL-10, and, to a lesser extent, TNF-α are involved in the pathogenesis of HS (Kelly and Prens 2016). The expression and/or activity of these cytokines is mediated at the intracellular level through JAK-STAT signaling, and primarily JAK1. Therefore, it can be reasonably expected that interference with the transduction of intracellular signals generated by those cytokines will modify/decrease the level of inflammation seen in HS and thus moderate or control disease activity and related signs and symptoms. JAK1 inhibitors have the potential to treat the signs and symptoms of HS. Studies investigating the effects of oral JAK1 inhibition (INCB054707) in HS showed AN count decrease, improvement in disease-specific patient-reported outcomes, and changes in disease-associated serum biomarkers after 8 weeks of treatment (Alavi et al 2022). Data taken collectively suggest that JAK inhibition may be expected to be efficacious in HS.

Ruxolitinib is a small molecule inhibitor of the JAKs with specificity for JAK1 and JAK2, which play an important role in signal transduction following cytokine and growth factor binding to their receptors. Increased production of inflammatory cytokines and growth factors are strongly implicated in the pathogenesis of a number of inflammatory conditions, including, AD, vitiligo, and other autoimmune diseases of the skin. Because JAKs serve to translate extracellular signals from a number of relevant cytokines and growth factors upregulated in these inflammatory diseases, JAK inhibitors represent potential therapeutic agents for these diseases (Chapman et al 2022) and worth assessing for the treatment of HS.

The efficacy of ruxolitinib cream, a JAK 1/2 inhibitor, is well established in AD and vitiligo. Ruxolitinib cream has shown statistically significant and clinically meaningful efficacy in 2 pivotal Phase 3 studies (INCB 18424-303 and -304) in participants with mild to moderate AD and 3% to 20% BSA (excluding the scalp; Papp et al 2021). In both AD Phase 3 studies, over 50% (53.8% and 51.3%) of participants (≥ 12 years of age) who applied ruxolitinib 1.5% cream BID for 8 weeks achieved an IGA-TS (ie, IGA of 0 or 1 with ≥ 2-point improvement from baseline) compared with 15.1% and 7.9% of participants who applied vehicle cream. Participants who applied ruxolitinib cream also saw a substantial improvement in itch compared with participants who applied vehicle cream in both studies (50.7% and 52.2% for ruxolitinib cream versus 16.3% and 15.4% for vehicle, respectively). Similarly, decreases in worst skin pain scores were observed in the ruxolitinib 1.5% cream treatment group by Week 2 and continued to decrease through Week 8, with the largest decreases at each visit occurring for participants who applied ruxolitinib 1.5% cream. In addition, ruxolitinib 1.5% cream administered BID was safe and well-tolerated in adolescent and adult participants with AD. Ruxolitinib 1.5% cream is approved by the FDA for the treatment of mild to moderate AD in nonimmunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies, or when those therapies are not advisable (Opzelura™ 2021).

Ruxolitinib 1.5% cream has demonstrated efficacy in vitiligo. Two Phase 3 studies (INCB 18424-306 and -307), were identically-designed, randomized, vehicle-controlled in adolescent and adult participants (≥ 12 years old, ≈10% of whom were adolescents) with vitiligo. Participants received blinded study treatment for 24 weeks and were then offered the opportunity to receive an additional 28 weeks of treatment with ruxolitinib 1.5% cream BID. Both met the primary endpoint ($p < 0.0001$ for both studies), demonstrating that significantly more participants treated with ruxolitinib 1.5% cream BID achieved a ≥ 75% improvement from baseline in the facial vitiligo area scoring index compared to participants treated with a vehicle control at Week 24.

Based on all collective evidence, a topical JAK-inhibitor such as ruxolitinib may be an appropriate treatment for HS. Therefore, this study is designed to evaluate the efficacy and safety of ruxolitinib 1.5% cream in participants with HS and a total AN count of 3 to ≤ 10 with no draining tunnels.

2.2. Study Rationale

Since the pathophysiology of HS appears to involve JAK1 associated cytokines, the primary purpose of this study is to assess the efficacy and safety of ruxolitinib 1.5% cream BID (topical JAK1 and JAK2 inhibitor) in participants with HS and a total AN count of 3 to ≤ 10 with no draining tunnels.

2.2.1. Scientific Rationale for Study Design

JAK1 associated cytokines (IL-1β, IL-17, IL-23, IL-10, IFN-γ, and TNF-α) have been shown to be involved in the pathogenesis of HS (Zouboulis et al 2020). Since the expression and/or activity of these cytokines is mediated at the intracellular level through JAK-STAT signaling, ruxolitinib, a selective JAK 1/2 inhibitor, may be an appropriate treatment of HS. Moreover, ruxolitinib is a selective inhibitor of JAK1 and JAK2 based on its demonstrated efficacy in both AD and vitiligo pivotal Phase 3 trials (INCB 18424-303/-304 and INCB 18424-306/-307, respectively).

This study will evaluate the efficacy and safety of ruxolitinib 1.5% cream BID in adult participants with 3 and ≤ 10 AN count compared to vehicle cream for 16 weeks. All participants completing the 16-week DBVC period and who have no safety concerns will then enter the OLE period to receive active treatment for an additional 16 weeks. This design will provide a well-controlled assessment of the efficacy and safety of ruxolitinib 1.5% cream in mild HS compared to vehicle.

2.2.2. Justification for Dose

The ruxolitinib cream strength and application frequency (ruxolitinib 1.5% cream BID) for this study was selected primarily based on data from the Phase 3 pivotal studies (INCB 18424-303 and -304) in participants ≥ 12 years of age with AD, which evaluated the safety and efficacy of ruxolitinib 1.5% cream BID and ruxolitinib 0.75% cream BID. Overall, ruxolitinib 1.5% cream was found to be more efficacious than its ruxolitinib 0.75% cream, while the safety and tolerability profiles of both treatment arms were comparable and nondifferentiating. Phase 3 AD studies also demonstrated; 1) rapid (as early as 12 hours) and substantial decrease in itch following application of ruxolitinib 1.5% cream with better efficacy against itch when compared

to ruxolitinib 0.75% cream; and 2) Skin Pain NRS scores decreased over time, with the largest decreases at each visit occurring for participants who applied ruxolitinib 1.5% cream. Similarly, Phase 3 pivotal studies in vitiligo (INCB 18424-306 and -307) provide further support for the superior efficacy of ruxolitinib cream 1.5% versus vehicle cream.

In this study, the comparison to vehicle cream is relevant to better understand the effect of ruxolitinib cream in the treatment of HS. The use of vehicle cream is justified considering that there are no available HS-specific therapies to be used as a comparator for this milder population (AN count 3 to ≤ 10). After the 16-week vehicle-controlled period, all participants will receive ruxolitinib 1.5% cream for up to 16 weeks in the OLE period.

Given the known data and the pathogenic and clinical manifestations of HS, ruxolitinib 1.5% cream BID, the highest formulated strength was selected as the treatment regimen for this study.

2.3. Benefit/Risk Assessment

Ruxolitinib 1.5% cream showed statistically significant and clinically meaningful improvement in the signs and symptoms of AD in participants with mild to moderate AD, including IGA (Papp et al 2021) and symptoms such as pain. Decreases in worst skin pain scores for participants in the ruxolitinib cream treatment groups (0.75% and 1.5%) in both Phase 3 studies (INCB 18424-303 and -304) were observed by Week 2 and continued to decrease through Week 8 of treatment. Given that pain along with other clinical manifestations, is a very bothersome symptom of HS, it is anticipated that participants with HS will benefit from application of ruxolitinib cream.

Safety data from the Phase 3 AD studies demonstrated that ruxolitinib 1.5% cream BID applied continuously for 8 weeks followed by prolonged (44 weeks) intermittent use was safe and well-tolerated. The TEAEs were generally Grade 1 or 2 in severity and were most often events of nasopharyngitis and upper respiratory tract infection. Frequencies of these events were within the expected range for the general AD population.

Safety and tolerability in the Phase 2 and Phase 3 studies in vitiligo (INCB 18424-211, -306, and -307) showed that the rate of Grade 3 TEAEs, SAEs, and TEAEs leading to discontinuation was low. There were no significant TEAEs or application site events and no clinically relevant hematological changes suggestive of systemic toxicity. The majority of participants with vitiligo had good local tolerability with ruxolitinib cream use and reported application site reactions were all Grades 1 or 2 in severity. The most commonly reported application site reactions were application site pruritus in 15 participants (2.0%) and application site acne in 7 participants (1.0%). All other application site reactions in participants with vitiligo were reported in < 1% of participants overall.

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

In summary, the cumulative efficacy and safety data of ruxolitinib 1.5% cream BID in the treatment of AD (≤ 20% BSA with long-term intermittent dosing) and vitiligo (≤ 10% BSA with long-term continuous dosing), demonstrated that it is safe and well-tolerated with no evidence of systemic JAK inhibition, as expected given the low systemic exposures for the topical formulation.

Based on cumulative efficacy and safety data from AD and vitiligo studies, pathogenesis of HS, and role of Th1 cytokines in HS, it is expected that benefit-risk ratio of ruxolitinib cream in HS will be positive.

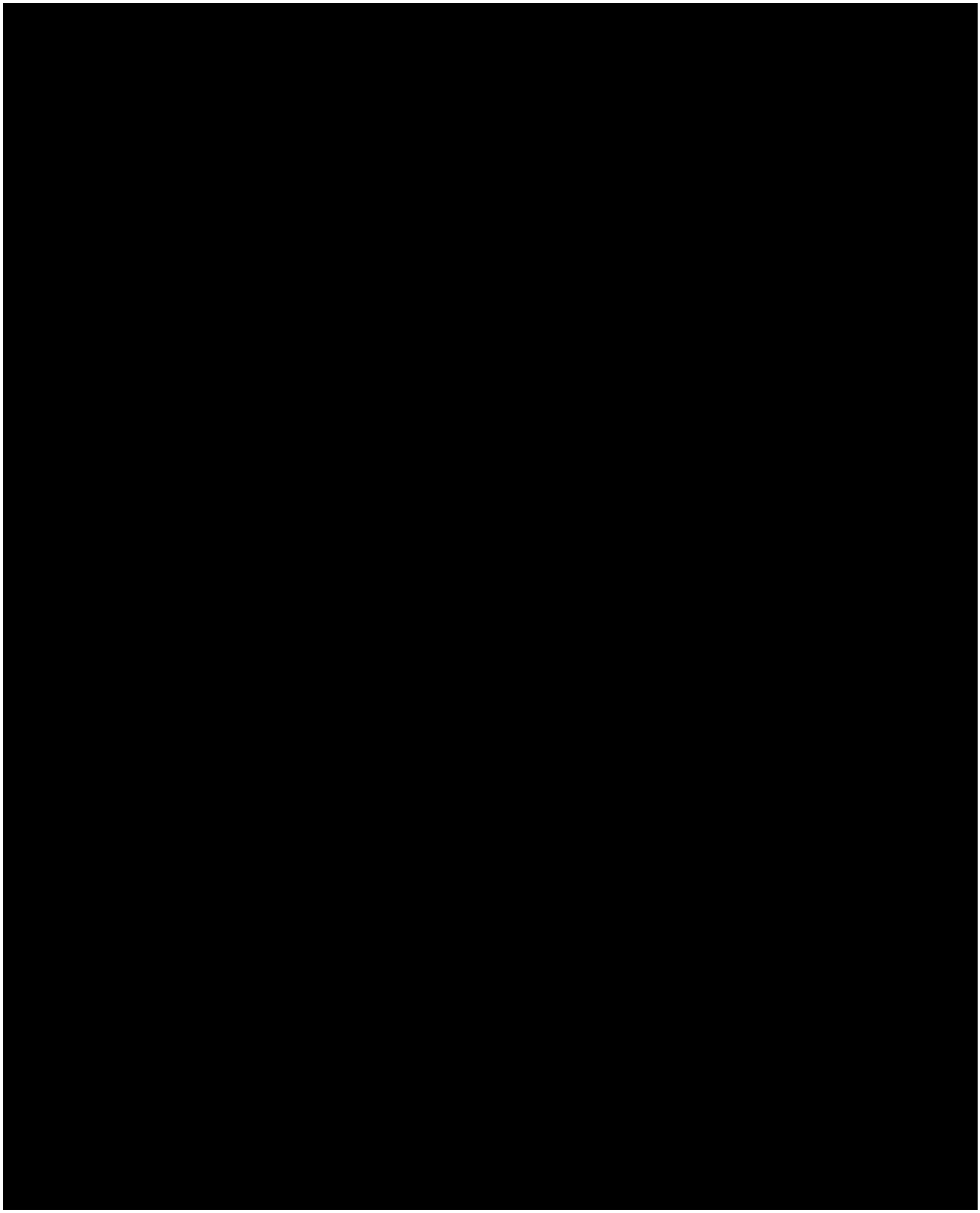
3. OBJECTIVES AND ENDPOINTS

Table 4 presents the objectives and endpoints.

Table 4: Objectives and Endpoints

Objectives	Endpoints
Primary	
To establish the efficacy of ruxolitinib 1.5% cream BID in participants with HS.	Change from baseline in AN count at Week 16.
Secondary	
To further evaluate the treatment effect of ruxolitinib 1.5% cream BID in participants with HS.	• Proportion of participants achieving AN50, AN75, AN90, and AN100 (at least 50%, 75%, 90%, and 100% reduction respectively in AN count relative to baseline) at Week 16. • Change from baseline in the Skin Pain NRS score at Week 16. • Change from baseline in the Itch NRS score at Week 16. • Proportion of participants who achieve HiSCR at Week 16. Note: HiSCR is defined as at least 50% reduction in AN count with no increase in either abscess or draining fistula counts, relative to baseline. • Change from baseline in the International Hidradenitis Suppurativa Severity Score System (IHS4) score at Week 16. Note: IHS4 score is calculated by the number of inflammatory nodules (multiplied by 1) plus the number of abscesses (multiplied by 2) plus the number of draining tunnels (multiplied by 4).
To evaluate the safety and tolerability of ruxolitinib 1.5% cream BID in participants with HS.	The type, frequency, and severity of AEs, and changes in vital signs and hematology and serum chemistry parameters.

Table 4: Objectives and Endpoints (Continued)



4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, randomized, DBVC study in participants ≥ 18 years of age with confirmed diagnosis of HS. The study will consist of a 16- week DBVC period followed by a 16-week OLE period.

Participants will be screened for up to 28 days prior to the first application of ruxolitinib 1.5% cream or vehicle cream. Key entry criteria for participants are diagnosis of HS (Hurley Stage I or II) for at least 3 months before screening visit and a **total AN count of 3 to ≤ 10 with no draining tunnels** at screening and baseline. The AN count of 3 may affect at least 1 distinct anatomical area; however, an AN count of > 3 to ≤ 10 must be affecting at least 2 distinct anatomical areas.

Approximately 60 eligible participants ≥ 18 of age will be randomized 1:1 to either ruxolitinib 1.5% cream or vehicle cream (see Figure 1). Participants will be stratified by baseline AN count (≥ 3 to 4 or ≥ 5 to 10). Participants will apply either ruxolitinib 1.5% cream or vehicle cream (both BID) through Week 16 to the all affected areas identified at baseline.

At Week 16, participants who meet the criteria (compliant with the Protocol and without safety concerns) will enter the 16-week OLE period. Participants randomized to vehicle BID in the DBVC period will be crossed over to ruxolitinib 1.5% cream BID and participants randomized to ruxolitinib 1.5% cream BID at baseline will remain on ruxolitinib 1.5% cream BID through Week 32 in an open-label fashion. At Week 16, the HS treatment area will be evaluated by the investigator to assess the disease and confirm whether treatment continuation is required (AN count ≥ 1 and/or Skin Pain NRS ≥ 1) during the OLE period or can otherwise (re)enter an observation/no treatment cycle (AN count = 0 and Skin Pain NRS = 0). During the OLE, participants will only treat symptomatic lesions (eg, presence of AN lesion(s) and/or pain) including new lesions not exceeding 20% BSA. Treatment assignment during the DBVC period will remain blinded to investigators and participants until after all participants have completed the study or discontinued and completed the safety follow-up period.

During the DBVC and OLE periods, participants who require and are treated with lesional rescue interventions (eg, incision and drainage or intralesional corticosteroid injection), are considered nonresponsive to therapy, and will be discontinued from the study.

Figure 1 presents the study design schema, and Table 3 presents the SoA. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

The COVID-19 global pandemic may present challenges to the normal conduct of this study (including AE and laboratory assessments), requiring the implementation of potential mitigation strategies described in Appendix B.

4.2. Overall Study Duration

The study begins when the first participant signs the study ICF. It is estimated that an individual will participate for approximately 40 weeks, including up to 28 days for screening, 16 weeks for treatment during the DBVC period, 16 weeks for treatment during the OLE period, and up to 30 days for follow-up after the last application of study treatment.

The end of the study is defined as the date of the last visit of the last participant in the study. A participant is considered to have completed the study if they have completed all study visits, including the safety follow-up visit

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 in writing, 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

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

5.1. Inclusion Criteria

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

1. Ability to comprehend and willingness to sign a written ICF for the study.
2. Male or female participants age 18 years or above.
3. Diagnosis of HS based on clinical history and physical examination for at least 3 months before screening visit.
4. Diagnosis of HS (Hurley I or II) with the following:
   a. A total AN count of 3 to ≤ 10, with no draining tunnels at screening and baseline visits.
      AND
   b. The AN count at the screening AND baseline visits:
      – AN of 3 should affect at least 1 distinct anatomical area
      – AN of > 3 to ≤ 10 should affect at least 2 distinct anatomical areas

   Note: Anatomical areas include but are not limited to left and right axilla; or left and right inguinocrural fold or inframammary areas.

5. Baseline Skin Pain or Itch NRS score ≥ 1. Baseline Skin Pain or Itch NRS is defined as the 7-day average of Skin Pain or Itch NRS score before Day 1 (data from a minimum of 4 out of 7 days directly prior to Day 1 is needed).
6. Agreement to NOT use topical and systemic antibiotics for treatment of HS during the study.
7. Agreement to NOT use a diluted beach bath or topical antiseptic washes containing chlorhexidine gluconate or benzoyl peroxide on the areas affected by HS lesions during the study.
8. Willingness to avoid pregnancy or fathering children based on the criteria below.
    a. Male participants with reproductive potential must agree to take appropriate precautions to avoid fathering children from screening through 90 days (a spermatogenesis cycle) after the last application of ruxolitinib cream and must refrain from donating sperm during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    b. Female participants who are WOCBP must have a negative serum pregnancy test at screening and before the first application on Day 1 and must agree to take appropriate precautions to avoid pregnancy from screening through 30 days (1 menstrual cycle) after the last application of study ruxolitinib cream and must refrain from donating oocytes during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    c. Female participants not considered to be of childbearing potential as defined in Appendix A are eligible.

5.2. Exclusion Criteria

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

1. Presence of draining tunnels at screening or at baseline visits.
2. Total HS BSA affected (excluding scalp) is > 20%.
3. Participants with concurrent conditions and history of other diseases:
    a. Active ongoing inflammatory diseases of the skin other than HS that might confound the evaluation of HS.
    b. Any other concomitant skin disorder (eg, generalized erythroderma such as Netherton's syndrome), pigmentation, or extensive scarring that in the opinion of the investigator may interfere with the evaluation of HS AN or compromise participant safety.
    c. Active tuberculosis; or current and/or history of latent tuberculosis unless adequately treated.
    d. Immunocompromised (eg, lymphoma, acquired immunodeficiency syndrome, or Wiskott-Aldrich syndrome).
    e. Chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before baseline.

f. Active acute bacterial, fungal, or viral skin infection (eg, herpes simplex, herpes zoster, chicken pox, clinically infected AD, or impetigo) within 2 weeks before baseline.
g. Unstable asthma or COPD requiring systemic treatment (such as intravenous steroids) or hospital admission or emergency room treatment within 3 months from baseline; or stable asthma or COPD requiring more than 720 µg/day (2 puff BID of 180-ug dose) or fluticasone more than 440 µg/day (2 puffs BID of 110-ug dose) or other equivalent inhaled corticosteroids.

4. Any serious illness or medical, physical, or psychiatric condition(s) that, in the investigator's opinion, would interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data. For example:
   a. Clinically significant or uncontrolled cardiovascular disease, including unstable angina, acute myocardial infarction, or stroke within 6 months from Day 1 of study drug application, New York Heart Association Class III or IV congestive heart failure, and arrhythmia requiring therapy or persistent uncontrolled hypertension (blood pressure > 150/90 mmHg) unless approved by medical monitor/sponsor.
   b. Any malignancies or history of malignancies within 5 years before baseline with the exception of adequately treated or excised nonmetastatic basal cell or squamous cell cancer of the skin, or cervical carcinoma in situ.
   c. History of severe anemia, severe thrombocytopenia, or severe neutropenia.
5. Any of the following clinical laboratory test results at screening:
   a. Cytopenias at screening, defined as follows:
      – Hemoglobin < 100 g/L (ie, 10 g/dL)
      – ANC < 1.5×10^9/L (ie, 1500/µL)
      – Platelet count < 1×10^{11}/L (ie, 100,000/µL)
   b. Liver function tests:
      – AST or ALT ≥ 2.5 × ULN
      – Total bilirubin > 1.5 × ULN unless Gilbert's syndrome
   c. Estimated GFR < 30 mL/min/1.73 m^2 (using the Chronic Kidney Disease Epidemiology Collaboration equation).
   d. Positive serology test results at screening for HIV antibody.
   e. History or current of acute or chronic active HBV or HCV infection. Participants who have recovered or have been successfully treated with no evidence of active HBVor HCV infection, and those who are immune due to hepatitis B vaccination can enroll. Participants who are positive for the hepatitis B surface antigen will be eligible if they are negative for HBV-DNA; participants who are positive for the anti-HCV antibody will be eligible if they are negative for HCV-RNA.
   f. Any other clinically significant laboratory result that, in the opinion of the investigator, poses a significant risk to the participant.
6. History of treatment failure (as assessed by the investigator through study participant interview) for HS or any other inflammatory condition with any systemic or topical JAK or TYK2 inhibitor (eg, abrocitinib, baricitinib, brepocitinib, deucravacitinib, filgotinib, lestaurtinib, pacritinib, ruxolitinib, tofacitinib, upadacitinib).

7. Use of any of the following treatments within the indicated washout period before the baseline visit:
    a. 12 weeks or 5 half-lives (if known), whichever is longer, for systemic immunosuppressive or immunomodulating biologic drugs (eg, adalimumab, anakinra, bermekimab, bimekizumab, brodalumab, certolizumab, dupilumab, etanercept, golimumab, guselkumab, infliximab, iscalimab, ixekizumab, risankizumab, rituximab, secukinumab, vilobelimab, ustekinumab, etc).
    b. 4 weeks for any topical or systemic JAK or TYK2 inhibitor (eg, abrocitinib, baricitinib, brepocitinib, deucravacitinib, filgotinib, lestaurtinib, pacritinib, ruxolitinib, tofacitinib, upadacitinib, etc).
    c. 4 weeks – systemic corticosteroids or adrenocorticotropic hormone analogs, cyclosporin, methotrexate, azathioprine, or other systemic immunosuppressive or immunomodulating agents (eg, mycophenolate or tacrolimus).
    d. 2 weeks or 5 half-lives, whichever is longer - strong systemic CYP3A4 inhibitors.
    e. 2 weeks – systemic antibiotics and immunizations with live-attenuated vaccines, sedating antihistamines unless on a long-term stable regimen (nonsedating antihistamines are permitted).
    Note: Live-attenuated vaccines are prohibited during the DBVC period. COVID-19 vaccination is permitted.
    f. 2 weeks – topical therapy for HS (eg, topical antiseptics, topical antibiotics, topical corticosteroids, topical calcineurin inhibitors, other topicals).
    g. 2 weeks - any opioid treatment.
8. Current treatment or treatment within 30 days or 5 half-lives (whichever is longer) before the baseline visit with another investigational medication or current enrollment in another investigational drug Protocol.
9. Participant with known allergy or reaction to any of the components of the study cream.
10. History of alcoholism or drug addiction within 1 year before screening or current alcohol or drug use that, in the opinion of the investigator, will interfere with the participant's ability to comply with the administration schedule and study assessments.
11. Pregnant or lactating participants, or those considering pregnancy during the period of their study participation.
12. Participants with inadequate venous access in nonlesional areas or in lesional areas not treated by the study drug within the last 7 days.
13. Participants who are committed to a mental health institution by virtue of an order issued either by the judicial or the administrative authorities.
14. Participants who, in the opinion of the investigator, are unable or unlikely to comply with the administration schedule and study evaluations.
15. Employees of the sponsor or investigator or otherwise dependents of them.

5.3. Lifestyle Considerations

Participants should be cautioned to avoid exposure to artificial sunlight (including tanning booths, sun lamps, etc). If sunscreen or other cosmetics have been applied to the areas to be treated, participants should follow the guidance in Section 6.6 regarding concomitant medications.

It is recommended that bathing, showering, excessive sweating, or swimming should not take place within 2 hours before and after the planned study drug application.

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 at the discretion of the investigator (eg, when the investigator believes that previous borderline abnormal laboratory results may have resolved). Additionally, a participant who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status. Participants who rescreen must reconsent and be assigned a new participant ID number.

5.5. Replacement of Participants

No participants will be replaced at any time during this study. However, as noted in the COVID-19–related guidance (see Appendix B), due to the evolving situation of the COVID-19 pandemic, the sponsor may decide to recruit additional participants in the study beyond the expected number (eg, if a substantial number of participants withdraw early from the study).

6. STUDY TREATMENT

6.1. Study Treatment(s) Administered

Ruxolitinib 1.5% cream or matching vehicle cream will be applied as a thin film BID, with applications approximately 8 hours apart in the morning and in the evening at least 1 hour before bedtime.

At the baseline visit, an estimate of the %BSA (≤ 20%) affected by HS (total AN count 3 to ≤ 10) to be treated (excluding scalp) will be used by the IRT system to calculate the number of tubes of study drug to be dispensed. The participant will apply a thin film of study drug in front of site staff at the baseline/Day 1 visit by applying small amounts of study drug on each nodule and the surrounding area of the nodule (≈1 cm). All areas identified at baseline should continue to be treated through the end of the DBVC period (Week 16) unless the participant meets criteria for stopping study drug. If there are new AN to be treated, after consultation with the investigator, study drug should be applied to these AN in addition to the areas treated at baseline (maximum total affected areas ≤ 20% BSA), and the percentage of BSA to be treated will be recalculated and increased. This new estimate will be entered into the IRT system to calculate the number of tubes of study drug to be dispensed. Participants whose additional new areas to be treated in addition to the areas identified at the baseline visit exceed 20% BSA should be discontinued from study treatment and ET assessment should be completed.

At Week 16 and starting the OLE period, participants will be evaluated by the investigator to confirm whether they:

- require continuation of therapy due to AN count ≥ 1 and/or the presence of pain (Skin Pain NRS ≥ 1) or,
- can begin an observation/no treatment cycle due to AN count = 0 and no pain [Skin Pain NRS of 0]).

At Week 16, the IRT system will dispense a prespecified number of tubes according to the assessment of total BSA to be treated.

Between OLE study visits, participants will treat all areas identified with HS lesions (total affected area not to exceed 20% BSA). If all signs and symptoms of HS resolve between study visits, the participant will contact the investigator to confirm that study drug applications should be stopped 3 days after the HS lesion (AN count = 0) have disappeared. If this 3-day window is during a study visit and the AN count = 0, Skin Pain NRS = 0, as assessed by the investigator, treatment is to be stopped at the study visit.

Multiple cycles of treatment/no treatment may be utilized as needed and treatment start/stop dates should be recorded in the eDiary. If a participant has stopped treatment during the OLE period, treatment may be restarted after consultation with the investigator if the participant has an AN count ≥ 1 and/or pain (Skin Pain NRS score ≥ 1). Approval to treat additional areas may occur via telephone during the OLE period, although the investigator, at their discretion, may ask the participant to return for an unscheduled visit.

At any time during the OLE period, if a participant's new areas to be treated in addition to the areas already identified at the previous visit exceed 20% BSA, then the participant should be discontinued from study treatment and the ET assessment should be completed. The amount of

study drug used per application will be determined by weighing a tube before and after the participant applies study drug to the affected areas. All tubes (including caps) of study cream will be weighed before being dispensed. All returned tubes (including caps) of study cream will also be weighed.

Table 5 presents the study treatment information.

Table 5: Study Treatment Information

	Study Treatment 1	Study Treatment 2
Study treatment name:	Ruxolitinib	Vehicle
Mechanism of action:	JAK 1/2 inhibitor	Not applicable
Dosage formulation:	Cream	Cream
Treatment strength:	1.5%	Not applicable
Administration instructions:	DBVC period: Apply a thin film to affected areas identified at baseline in the morning and at least 1 hour before bedtime with applications approximately 8 hours apart for 16 weeks. OLE period: Apply a thin film to affected areas only in the morning and at least 1 hour before bedtime with applications approximately 8 hours apart as needed for 16 weeks.	
Packaging and labeling:	Ruxolitinib or vehicle cream will be provided in 60 g tubes. Each tube will be labeled as required per country requirement.	
Storage:	15°C-30°C (59°F-86°F)	
Status of treatment in participating countries:	Investigational	

6.2. Preparation, Handling, and Accountability

The investigator or designee must confirm appropriate temperature conditions (both ruxolitinib cream and vehicle cream are to be stored between 15°C and 30°C [59°F-86°F]) 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 study treatment. Refer to the Study Pharmacy Manual for participant instructions for handling of study cream. Participants should store study treatment at ambient temperature conditions.

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 the following:

- Delivery of study drug(s) to the study site.
- Inventory of study drug(s) at the site.
- Participant use of the study drug(s), including tube counts from each supply dispensed.
- Return of study drug(s) to the investigator or designee by participants.

The investigational product must be used only in accordance with the Protocol. The investigator or designee 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 the destruction of any remaining study drug according to institutional SOPs. If, however, local procedures do not allow on-site destruction, shipment of the study drug back to the sponsor is allowed. In this case, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to study treatment using an IRT system. The IRT system will assign in a 1:1 ratio, stratified by baseline AN count (≥ 3 to 4 or ≥ 5 to 10), participant study number, track participant visits, randomize according to the defined parameters, maintain the blinding, and manage study cream inventory. Full details will be provided in the IRT Manual.

Participants, investigators, and the sponsor will be blinded to each participant's treatment assignment during the DBVC period. During the OLE period, participants and investigators will remain blinded to the treatment assignment during the DBVC 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 9.7 and refer to the IRT Manual).

6.4. Study Treatment Compliance

Compliance with all study-related treatments should be emphasized to the participant by site staff, and appropriate steps should be taken to optimize compliance during the study. Compliance will be assessed for frequency of application of study cream by reviewing the participants' diaries. Participants will also be questioned regarding study cream application technique, missed applications, and use of any additional topical or systemic prescriptions of other products or over-the-counter products. Compliance with study treatment will be evaluated by the participant's adherence to the BID application regimen (evaluation of actual number vs prescribed number of applications), documented by the site staff, and monitored by the sponsor/designee.

Qualified clinical staff will review the diary entries for compliance. Participants will be considered compliant with the treatment regimen if they apply at least 80% but no more than 120% of the prescribed number of applications during participation in the DBVC and OLE periods of the study. Participants who are noncompliant during the DBVC period and OLE period (if on a treatment cycle) will be reinstructed by the investigator (or designee). Participants who are consistently noncompliant with study drug may be withdrawn from the study. The decision to withdrawal a participant based on noncompliance will be made by the investigator after consultation with the sponsor.

Drug accountability will be assessed by documenting the quantities of drug used between study visits (tube counts and weighing). At the first clinic visit and subsequent study visits, the amount of study cream to be applied is to be determined by weighing a tube (including the cap) before and after the participant applies a thin film of study cream to the affected areas. Participants will be instructed to bring all study cream with them to the study visits in order for site staff to assess study cream accountability.

6.5. Dose Modifications

There are no application adjustments/modifications allowed (decrease or increase in study drug frequency of application) except for drug interruption or permanent discontinuation, if needed (eg, for management of an AE).

Temporary interruption could be due to an AE in the DBVC or OLE period or clearance of the HS in the OLE period.

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

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

In some circumstances, it may be necessary to temporarily interrupt treatment with study drug (see Table 6). Changes to the study drug application frequency (eg, reduction to QD) are not allowed.

In the event that an AE is present at a specific site of study drug application, treatment may be temporarily withheld only at that application site and continued elsewhere. This should be recorded as a dose interruption on the AE eCRF page. Except in cases of emergency, it is recommended that any findings of concern (eg, AE) be confirmed and that the investigator

consult with the medical monitor before interrupting study drug applications. Additionally, the investigator must obtain approval from the medical monitor before restarting study drug. Participants who experience a recurrence of the initial AEs upon restarting the study drug may need to permanently discontinue treatment with the study drug.

Participants should be closely monitored for the development of signs and symptoms of infection during treatment with the study drug and up to the safety follow-up visit. Study drug should be interrupted if a participant develops a serious infection, an opportunistic infection, or sepsis. Study drug application should not be resumed until the infection is controlled.

Instructions for application interruptions of study drug–related to laboratory abnormalities are outlined in Table 6.

Table 6: Guidelines for Interruption and Restarting of Study Drug

Adverse Event Related to Study Drug	Action Taken
Any Grade 3 laboratory abnormality	• Laboratory abnormalities should be confirmed with repeat testing within 48-72 hours whenever possible and immediate delivery of the laboratory results should be requested. • Interrupt study drug, based on clinical judgment in consultation with the medical monitor (whenever possible), taking into account the relatedness of the AE to the study drug and the participant's underlying condition. • Interruption may occur after the initial test result or may be delayed until or unless the repeat test confirms the laboratory abnormality; however, if the repeat test does confirm the laboratory abnormality, the study drug must be interrupted unless the medical monitor approves continuation. • At the discretion of the investigator, after consultation with the sponsor, study drug application may be restarted once the laboratory abnormality has resolved.
Any Grade 4 laboratory abnormality	• Laboratory abnormalities should be confirmed with repeat testing within 48 hours whenever possible and immediate delivery of the laboratory results should be requested. • Interrupt study drug, based on clinical judgment in consultation with the medical monitor (whenever possible), taking into account the relatedness of the AE to the study drug and the participant's underlying condition. • Discontinue study drug permanently if laboratory abnormalities are confirmed and deemed related to study drug.

Note: Adverse event grades are based on CTCAE v5.

6.5.2. Criteria for Permanent Discontinuation of Study Drug to an Adverse Event

The occurrence of unacceptable severity of an AE, such that it would interfere with study drug treatment or study procedures and may require that the study drug be permanently discontinued. Unacceptable severity is defined as follows:

- Occurrence of an AE that is related to treatment with the study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromised 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 and/or surgical intervention (see Section 6.6.3).
- Adverse event requiring an interruption of study drug for more than 2 weeks.
- Participants with confirmed Grade 4 laboratory abnormalities deemed related to study drug.

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. Non-HS medications received up to 28 days before the first application of study treatment will be recorded in the eCRF. Any prior HS treatments received within 1 year of the first application of study drug will be collected, including the response to treatment and reason for stopping the treatment. All medications received from the first application through the follow-up period from the last application of study treatment will be recorded in the eCRF. Any addition, deletion, or change in the dose/regimen of these medications will also be recorded.

Other relevant medications or procedures received more than 28 days before the first dose of study drug may be recorded in the eCRF at the discretion of the investigator or at the request of the sponsor based on emerging events during the study.

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

6.6.1. Permitted Medications and Procedures

The following are permitted during the study if, in the judgement of the investigator, the intake of these medications and procedures will not impact the safety of the participant or efficacy of the treatment:

- [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 investigator.
- Inhaled corticosteroids for bronchial asthma or COPD is allowed with the dose equivalent of budesonide (not to exceed 720 µg/day or 2 puff BID of 180-ug dose) or fluticasone (not to exceed 440 µg/day or 2 puffs BID of 110-ug dose) or other equivalent inhaled corticosteroids.
- Use of any over-the-counter, nonprescription vitamins (excluding vitamin D and zinc), minerals, and phytotherapeutic, herbal, or plant-derived preparations.
- Wound Care
  - Concomitant use of wound care dressings on HS wounds is allowed.

6.6.2. Restricted Medications and Procedures

The use of following medications and procedures is restricted to specified conditions and if deemed acceptable by the investigator from 14 days before the baseline visit through follow-up visit:

- Use of any prescription medication to treat chronic medical conditions (such as hypertension) if on stable regimen in the judgement of the investigator

6.6.3. Prohibited Medications and Procedures

No rescue therapy and/or procedural intervention is allowed for HS during the study. In addition, the following rescue therapies are not permitted during the study:

- Treatment known to affect the course of HS.
- Current opioid treatment.
- Topical or systemic antibiotics, topical or intralesional corticosteroids, topical calcineurin inhibitors, systemic corticosteroids, methotrexate, dapsone, metformin, tretinoids/retinoids, aldactone, cyclosporine A, azathioprine and biological therapies, or other immunosuppressant/immunomodulators agents or any other topical or systemic treatment for HS.
- Any surgery for HS including, but are not limited to, the following:
  - Incision and drainage
  - Deroofing
  - Lesion ablation (electrosurgery)
  - Local excision
- Phototherapy (laser and pulsed light therapy) or tanning beds.
- Topical antiseptics (eg, diluted bleach bath or washes containing chlorhexidine gluconate or benzoyl peroxide).

In addition, the following therapies are not permitted during the study:

- Strong systemic CYP3A4 inhibitors.
- Live-attenuated vaccination during the DBVC period.

  Note: COVID-19 vaccination is permitted
- Any investigational medication other than the study drug.

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:

- Disease worsens during either the DBVC period or the OLE period, to the point where the extent of the affected area to be treated exceeds 20% BSA or there is a draining tunnel(s).
- Worsening HS and treatment with a prohibited medication and/or procedure as noted in Section 6.6.3.
- The participant becomes pregnant.
- Consent is withdrawn.

  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case, no further data, except data in the public domain, may be collected or solicited from the participant. Participants may choose to discontinue study treatment and remain in the study to be followed for progression and survival.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Unacceptable toxicity occurs (see Section 6.5.2).
- 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, after 2 consecutive study visits and reinforcement of study drug application by site staff, a participant who again fails to meet compliance benchmarks at a subsequent visit may be considered for withdrawal from the study. The medical monitor should be consulted for instruction on handling the participant.
- If, during the course of the study, a participant is found not to have met eligibility criteria at the time of enrollment, 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 application 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 prior to the Week 32 visit, the ET visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit. The last date of the last application of study cream and the reason for discontinuation of study cream 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 ET visit should be performed and the date recorded.
- The status of the participant should be updated to ET in the IRT system.
- 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 assessments.

7.2. Participant Withdrawal From the Study

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

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

See Table 3 for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are 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, they 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 their representative will explain the nature of the study to the participant or their 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. An ICF 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 including optional samples/procedures (eg, optional biopsy) and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the country(ies) in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that their personal data collected for the study will be used by the sponsor and/or their designee(s) in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that their 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 and must be assigned a new participant ID number.

8.1.2. Screening Procedures

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

Procedures conducted as part of the participant's routine clinical management (eg, blood counts or physical examinations) and obtained before signing of the ICF may be used for screening or baseline purposes provided that the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study (ie, within 28 days or less prior to Day 1). For participants who are enrolled in the study, information associated with eligibility requirements must be entered into the appropriate eCRF pages.

Results from the screening visit evaluations will be reviewed to confirm eligibility before randomization and 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 a country's abbreviation, the site ID, and the participant ID number. Site staff should contact the IRT to obtain the participant ID number during screening.

Upon determining that the participant is eligible for study entry, the IRT will be contacted to obtain the treatment assignment. Additionally, the IRT will be contacted at each regular study visit during both the DBVC period and the OLE period to update the study drug supply. Additional details are provided in the IRT Manual.

8.1.4. Distribution of Reminder Cards and/or Diaries

Participants will be provided with a reminder card starting on Day 1 and at all DBVC and all OLE visits through Week 32. The reminder card will indicate the date and time of the next visit.

Participants will be instructed on the use of the eDiary at the screening visit. The participant will start using the eDiary for completion of the Skin Pain NRS and Itch NRS at screening and for recording study drug applications on Day 1. [redacted]. Daily study drug administration will be recorded in the eDiary and verified by the study investigator/designee at study visits as shown in Table 3.

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. Medical history will include relevant medical and surgical treatments considered to be clinically significant by the investigator.

As race and/or ethnicity data are not to be analyzed from a scientific or medical perspective, but rather are to be reported in a descriptive format only in the CSR, data on race and/or ethnicity from France must not be collected as per GDPR and local data protection law and requirements.

8.1.5.2. Disease Characteristics and Treatment History

A disease-targeted medical and treatment history will be collected at screening. Details regarding the participant's HS, including date of diagnosis, relevant disease characteristics, and prior treatments, and the reason for stopping treatments, including systemic treatments, and surgical procedures, will be recorded.

8.2. Efficacy Assessments

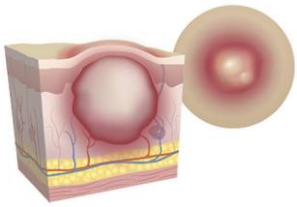
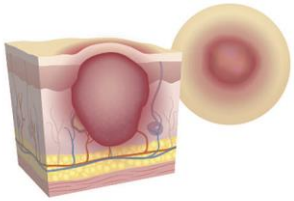
8.2.1. Lesion Counts

The HS lesion counts will be assessed at each study visit (Table 3) by the investigator and used for calculation of efficacy parameters as follows: AN counts (Section 8.2.1.1), HiSCR (Section 8.2.1.2), IHS4 (Section 8.2.1.3), [redacted].

[redacted]

Definitions and schematics of various HS lesions (Frew et al 2021) are provided in Table 7 to aid in the identification of the different morphologies.

Table 7: Definition of Hidradenitis Suppurativa Lesions

HS Lesion	Definition	Schematic
Abscess	A tender, fluctuant (compressible), palpable lesion, with erythema.	
Inflammatory nodule	A solid, spherical, palpable lesion >1 cm; tender and/or erythematous. Note: a noninflammatory nodule is defined as nontender, nonerythematous nodule.	
Tunnel (nondraining)	Compression of surrounding structures does not elicit drainage of contents.	
Tunnel (draining)[a]	A linear tract that may open onto the skin surface; drainage expressed at rest or with compression of surrounding structures.	

Note: Definitions and lesion schematics obtained from Frew et al 2021 ("tunnels may include connection to a hollow organ (eg, bladder, intestine) (A), blind ending (B), 2 skin-to-skin openings (C), and no opening to the surface (D). The original artwork was created by Bradley Winters, Penn State University").

[a] Excluded from this study.

8.2.1.1. Abscess and Inflammatory Nodule Counts

The AN 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.

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 2016, 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. In this study, participants with draining fistulas (tunnels) will be excluded from the study. Should a randomized participant develop a draining tunnel during the study, the participant will be discontinued from the study.

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 (Example: IHS4 score equals the number of inflammatory nodules

[multiplied by 1] plus the number of abscesses [multiplied by 2] plus the number of draining tunnels [multiplied by 4]).

[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 Table 8). Participants who have been diagnosed with HS, Hurley Stage I or II as per inclusion criterion, will be enrolled into the study. The investigator (or designee) will determine the Global Hurley Stage in each affected anatomical region at the designated study visits listed in Table 3.

Table 8: 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.

8.2.3. Body Surface Area

Total %BSA affected by HS will be used to determine the number of tubes of study drug dispensed at each visit. Total %BSA affected will be estimated at each visit as outlined in the SoA (see Table 3). Body surface area assessment will be approximated to the nearest 0.1% using the Palmar Method as a guide, with the palm plus 5 digits, with fingers tucked together and thumb tucked to the side (handprint), considered as 1% BSA and the thumb as 0.1% BSA.

8.2.4. Patient-Reported Outcomes

Patient-reported outcomes will be assessed as outlined in the SoA (see Table 3).

All PROs will be collected via electronic eCOA solution. Sites will be provided with training materials and instructions on the use of eCOA solution and will be responsible to train participants on eDiary use and eCOA completion. Further details on use of the eCOA devices will be provided in respective study documentation.

For PROs scheduled to be completed at study visits: At Day 1, participants will complete PROs after eligibility is met. For subsequent visits after randomization, questionnaires will be completed by the participant before site personnel perform any clinic assessments to avoid biasing the participant's response

8.2.4.1. eDiary Assessments: Skin Pain and Itch Numeric Rating Scales

The participant will be instructed to complete and record the Skin Pain and Itch NRS via an eDiary, daily, in the evening beginning on the day of screening through Week 32 or ET (see Table 3).

Both the Skin Pain and Itch NRS are a daily participant-reported measure (24-hour recall) of the worst level of skin pain and itch intensity related to HS.

The participants will rate the following:

- Skin Pain NRS: Pain severity of their HS by selecting a number from 0 (no pain) to 10 (worst imaginable pain) that best describes their worst level of pain in the past 24 hours.
- Itch NRS: Itch severity of their HS by selecting a number from 0 (no itch) to 10 (worst imaginable itch) that best describes their worst level of itching in the past 24 hours.

The baseline Skin Pain NRS and the Itch NRS is established prior to the first dose of study drug as follows:

- The average of the 7-day Itch NRS score prior to the baseline visit (minimum 4 out of the 7 days' data required) will be collected.

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted] [redacted]

[redacted]

[redacted] [redacted]

[redacted]

8.3. Safety Assessments

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

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

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 30 days after the last application of study drug. Adverse events for enrolled participants 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, that are considered related to the study drug/procedures, or that caused the participant to discontinue the study drug. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant, such as "How are you feeling?", is the preferred method to inquire about AE occurrences. Adverse events may also be detected when they are volunteered by the participant during the screening process or between visits or through physical examinations, laboratory tests, or other assessments. The definition, reporting, and recording requirements for AEs are described in Section 9.

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

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

8.3.2. Physical Examinations

At the screening visit and the Week 32/ET2 visit, a comprehensive physical examination should be conducted. The comprehensive physical examination will include assessment(s) of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes; as well as a brief neurological examination. In addition, a participant's height and weight will be obtained during the screening visit.

During the study, a targeted physical examination may be conducted by the investigator or medically qualified designee (per institutional policies and local standard of care) to assess AEs, symptoms/signs, laboratory abnormalities, or other findings. Findings from the targeted physical examination should be reported on the AE eCRF.

8.3.3. Vital Signs

Vital sign measurements (to be taken at each study visit and before blood collection for laboratory tests) include blood pressure, pulse, respiratory rate, and body temperature. Blood pressure and pulse will be taken with the participant in the sitting position after 5 minutes of rest. Abnormal vital signs can be repeated after a rest period at the discretion of the investigator. Abnormal vital sign results identified after the first dose of study treatment, 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) are to be reported as an AE.

8.3.4. Laboratory Assessments

See Table 9 for the list of clinical laboratory tests to be performed and Table 3 for the timing and frequency. A central laboratory will perform all clinical laboratory assessments for safety (eg, blood chemistries or hematology assessments) [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. 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 30 days after the last application of the study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significantly abnormal by the investigator or medical monitor.

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

Table 9: Required Laboratory Analytes

Chemistry	Hematology	Serology	Pregnancy Testing
ALT AST Glucose Creatine kinase Creatinine Total bilirubin Direct bilirubin (if total bilirubin is elevated above ULN)	Complete blood count, including: • Hemoglobin • Hematocrit • Platelet count • Red blood cell count • White blood cell count Differential count, including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	Hepatitis B surface antigen HCV antibody HIV antibody HBV-DNA[a] HCV-RNA[b] **Other** hsCRP	Human chorionic gonadotropin (WOCBP only) FSH (women of nonchildbearing potential only) Female participants of childbearing potential only require a serum test at screening and a urine pregnancy test at all other visits. A positive urine test will be confirmed by a serum test.

Note: Additional tests may be required, as agreed by investigator and sponsor, based on emerging safety data or to rule out a diagnosis.
[a] Reflex testing if Hepatitis B surface antigen is positive.
[b] Reflex testing if HCV antibody is positive.

8.3.4.1. Pregnancy Testing

A serum pregnancy test will be required for all WOCBP during screening. Urine pregnancy tests will be performed locally, as outlined in the SoA (see Table 3), and as medically indicated (eg, in case of loss of menstrual cycle or when pregnancy is suspected).

If a urine pregnancy test is positive, the results must 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 9.8 for reporting requirements.

8.3.4.2. Serology

HIV and hepatitis screening assessment will be performed at the screening visit (see Table 3). Generally, virology and serology 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.

[redacted]

[redacted]

8.5. [redacted] Translational Assessments

[redacted]

8.5.2. Photography

At select sites, photographs of the HS lesion (identified as target lesion), will be taken at visits indicated in Table 3. Detailed methods for capturing photographs will be provided in the Study Manual.

8.6. Unscheduled Visits

Unscheduled visits may occur at any time medically warranted, including when participants develop new lesions of HS. Any assessments performed at those visits should be recorded in the eCRF.

8.7. End of Treatment and Early Termination

The EOT coincides with the Week 32 visit. A participant that completes the Week 32 visit will have reached the EOT with study drug.

If a decision is made that the participant will permanently discontinue study drug prior to the Week 32 visit, then the ET visit should be conducted. If the ET visit coincides with a regular study visit, then the ET evaluations will supersede those of that scheduled visit, and the data should be entered in the ET page in the eCRF. If this decision does not coincide with a regular visit, reasonable efforts should be made to have the participant return to the site to complete the ET procedures.

8.8. Follow-Up

8.8.1. Safety Follow-Up

The safety follow-up period is the interval between the Week 32/ET visit and the scheduled follow-up visit, which should occur 30 days (+ 7 days' visit window) after the Week 32/ET visit (or 30 days after the last application of study drug if the Week 32/ET visit was not performed). Participants who have been in an observation/no treatment cycle from Week 28 or earlier until Week 32 do not need to complete the safety follow-up visit.

Adverse events and SAEs must be reported up until 1) at least 30 days after the last application 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.

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 it is considered drug-related. • An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.
Additional Guidance for 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) are to be reported as an AE. • Abnormal laboratory test results are to be reported as 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/disease, including either an increase in the frequency and/or intensity of the condition, is to be reported as an AE. • New conditions detected or diagnosed after the start of study drug administration are to be reported as an AE. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction are to be reported as an AE. • Signs and/or symptoms from dose administration errors of a study drug (eg, overdose) or a concomitant medication are to be reported as an AE. • "Lack of efficacy," "disease progression," or "failure of expected pharmacological action" 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. • A condition that leads to a medical or surgical procedure (eg, endoscopy or appendectomy) will be reported as an AE if it occurs after obtaining informed consent. If the condition is present before entering the study, then it should be captured as medical history. • Pre-existing diseases or conditions with expected fluctuations in signs or symptoms should be reported as an AE only if the investigator judges the fluctuation to have worsened more than expected during study participation.

9.2. Definition of Serious Adverse Event

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

A serious adverse event is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an adverse drug experience that places the participant, in the opinion of the initial reporter, at immediate risk of death from the adverse experience as it occurs. 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 (involving at least an overnight stay) at the hospital or emergency department 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 or planned surgery (eg, stent replacement, hip surgery) is not considered an SAE. Hospitalization for medical interventions in which no unfavorable medical occurrence occurred (ie, elective procedures or routine medical visits) is not considered an SAE.
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. Is an important medical event An important medical event is an event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such events include 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; development of drug dependency or drug abuse; or suspected transmission of an infectious agent via a medicinal product.

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 Events Form in the eCRF. All AEs/SAEs should be reported for enrolled participants, but only SAEs need to be reported for screen failure participants. For enrolled participants, conditions that were present at the time informed consent was given should be recorded on the Medical History Form in the eCRF. For detailed information, refer to the eCRF guidelines.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator (or designee) 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 Adverse Events Form in the eCRF.
- There may be rare instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant ID number, will be redacted by the site staff on the copies of the medical records before submission. These records can be submitted to Incyte Pharmacovigilance by email/fax per the contact information listed as per SAE completing guidelines.
- 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 following:

- The severity grade (CTCAE v5.0 Grade 1 to 5). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study drug: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at the final safety follow-up visit.
- The action taken with regard to study drug as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the Adverse Events 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 v5.0 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 drug and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are medical 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 possibility of a relationship.
- The investigator will also consult the RSI in the IB for study drug, in making their assessment.
- Alternative causes, such as underlying or concurrent disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that they have reviewed the AE/SAE and have 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 based on the available information for every event before the initial transmission of the SAE.**
  - The investigator may change their opinion of causality in light of follow-up information and submit 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.
- Once an AE is detected, it should be followed in the Adverse Events Form in the eCRF 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.
- 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.

- Updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance (either via email/fax if paper SAE form is used or in the SAE EDC CRF) until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
- Any updated SAE data (including SAEs being downgraded to nonserious) will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study drug or study procedure[s]), all SAEs occurring after the participant has signed the ICF through the last study visit or at least 30 days after the last application of study drug must be reported to the sponsor (or designee) immediately, without undue delay but not later than within **24 hours** of obtaining knowledge 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 but not later than within 24 hours of it being available.

Investigators are not obligated to actively seek SAE information after the safety follow-up visit or more than 30 days after the last dose of study drug. If the investigator learns of any SAE, including death, at any time during this period, and they consider the event to be reasonably related to the study drug or study participation, then the investigator must notify the sponsor (or designee) within 24 hours of becoming aware of the event.

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

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

If the SAE is not documented in the RSI of the IB (new occurrence) and is thought to be related to the study drug, the sponsor or its designee may urgently require further information from the investigator for expedited 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 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 drug 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 Events Form in the eCRF.
- The investigator must report within 24 hours of learning of its occurrence any SAE via the EDC system (primary method) or by completing the Serious Adverse Event Report Form in English (only if the EDC system is not available). The contact information for Incyte Pharmacovigilance by email/fax is listed in the Study Reference Manual or the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.
- In circumstances where the EDC system is not accessible for reporting SAE information (initial and/or follow-up SAE information) to the sponsor within 24 hours, refer to the Incyte Reference Guide for Completing the Serious Adverse Report Form. Once the EDC system is functional, the SAE report should be retrospectively added to the EDC system and follow-up should be completed through the EDC. The original copy of the Serious Adverse Event Report Form and the email or facsimile confirmation sheet must be kept at the study site (refer to the Incyte Reference Guide for Completing the Serious Adverse Report Form or Study Reference Manual for details and for the email address or fax number).
- Follow-up information is also recorded in the eCRF and transmitted to Incyte Pharmacovigilance via the EDC system. The follow-up report should include information that was not provided previously, such as the outcome of the event, 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.

9.5. Potential Drug-Induced Liver Injury

Not applicable.

9.6. Events of Clinical Interest

Not applicable.

9.7. Emergency Unblinding of Treatment Assignment

In case of a medical emergency, for a participant's safety management, the procedure for emergency unblinding is provided to the investigator in the IRT Manual. The IRT system has an option to select for "Emergency Code Break" action for a given participant. After entering the study drug tube number and verification of the unmasking information, the investigator/subinvestigator will proceed to either final confirmation or cancellation of the code break procedure.

If a participant's treatment assignment is unblinded, the sponsor or its designee should be notified immediately by telephone for awareness.

If an investigator, the site staff performing assessments, or a participant is inadvertently unblinded, then the participant must discontinue study drug 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.

9.8. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that the 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 evaluations. 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 the pregnancy of a study participant must be recorded and reported as described in Section 9.4.

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.

9.9. 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.

9.10. 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 their 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, they will return a copy of the product complaint communication with the product.

9.11. Treatment of Overdose

There has been no clinical experience with overdose resulting from excessive use of ruxolitinib cream. Treatment of overdose should consist of general supportive measures.

10. STATISTICS

10.1. Sample Size Determination

Approximately 60 participants will be randomized 1:1 to ruxolitinib cream 1.5% BID or vehicle BID. The sample size was not calculated based on statistical power calculations, but for demonstration of preliminary findings of clinical response. It is anticipated that a sample size of approximately 60 participants will permit sufficient data to be generated to assess whether ruxolitinib cream warrants further investigation in HS. Also, the sample size is considered sufficient to provide enough data for an initial evaluation of the safety profile.

10.2. Populations for Analysis

The populations for analysis are provided in Table 10.

Table 10: Populations for Analysis

Population	Description
ITT	The ITT population includes all randomized participants. Treatment groups for this population will be defined according to treatment assignment at randomization.
Safety	The safety population includes all participants who applied study drug at least once. Treatment groups for this population will be determined according to the actual treatment the participant received on Day 1.
[redacted]	

10.3. Level of Significance

Given that the sample size is not based on the statistical power, the significance level for primary efficacy analysis will be 0.1 for a two-sided test.

10.4. Statistical Analyses

10.4.1. Primary Analysis

The primary analysis will be based on the ITT population. The summary of primary endpoint analysis is provided in Table 11.

Table 11: Summary of Primary Analysis

Parameter	Definition
Treatment effect	Ruxolitinib 1.5% cream compared with vehicle cream
Population	ITT Population
Variable	Change from baseline in AN count at Week 16
Population-level summary	Mean Change from baseline in AN count at Week 16

Note: All randomized participants, including those with missing Week 16 data, and those who discontinue study treatment at any time before the timepoint of interest, or discontinue from the study for any reason, will be included for the primary analysis. No rescue therapy or treatment switch is allowed in this study.

The primary efficacy analysis will compare ruxolitinib 1.5% cream versus vehicle cream in the mean change from baseline in AN count using a MMRM. The MMRM will include the fixed effect of treatment group (ruxolitinib 1.5% and vehicle cream), stratification factor (AN count ≥ 3 to 4 or AN count ≥ 5 to 10 at baseline), visit, and visit by treatment interaction. The variance-covariance matrix of the within-participant errors in MMRM will be modeled as unstructured.

The primary alternative hypothesis (superiority of active ruxolitinib 1.5% cream BID group compared with vehicle) will be tested at a 2 sided $\alpha = 0.1$ level using the least square mean estimate of the change from baseline in AN count at Week 16 from the MMRM specified above. Subgroup analysis by baseline characteristics will be performed.

10.4.2. Secondary Analysis

All secondary and [redacted] efficacy variables will be summarized using descriptive statistics based on the ITT population. For categorical measurements, summary statistics will include sample size, frequency, and percentages. For continuous measurements, summary statistics will include sample size, mean, median, standard deviation, standard error of the mean, minimum, and maximum. Summary statistics for continuous measures will be provided for baseline, the actual measurements at each visit, and the change and percentage change from baseline at each visit, if applicable. The Skin Pain NRS score for each visit will be determined by averaging the 7 daily Skin Pain NRS scores before the corresponding visit day. If 4 or more daily scores are missing (out of the 7), the Skin Pain NRS score at the visit will be set to missing. The Itch NRS score for each visit will be determined using a similar approach.

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 application of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study drug administration. Adverse events will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the National Cancer Institute CTCAE v5.0 using Grades 1 through 5.

The subset of AEs considered by the investigator to have a causal relationship to study drug will be considered 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 (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time.

10.5. Interim Analysis

There is no planned interim analysis for the study. There are 2 formal planned analyses:

- The primary analysis will occur after the primary database lock, when all participants have completed the DBVC period. [redacted]
- The final analysis will occur when all participants have completed or withdrawn from the 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 and health authorities, 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 during the retention period 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 will be appointed by the sponsor before the end of the study. As part of his or 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 the following:

- 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 the following:

- 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], photographs, diary data) or as otherwise specified in the Protocol.

- Maintaining adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source data are, in general, all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
- 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, 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 and available at the investigator's site. Examples of source documents are original documents, data, and records (eg, hospital records; electronic hospital records; clinical and office charts; laboratory notes; memoranda; participants' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives; microfilm or magnetic media; x-rays; participants' files; and e-records/records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).
  - 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.
- Sending participants' data, either as unique samples, copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
  - As required by privacy and data protection regulations and Incyte's privacy policies, if any photographs of participants are to be taken, the photographs must be limited to the area of the face or the body that is strictly necessary and the photographs should be masked (ie, identifying features such as eyes, mouth, scars, tattoos, or unique markings or features should be either obscured with a black bar or digitally pixelated so as to not permit the reidentification of the participants and preserve their confidentiality) by a specially designated photography vendor prior to sending the photographs to Incyte or any other third-party vendors for analysis or further processing.

  - In accordance with French regulations, sites in France must perform the masking before the photographs are transferred, including to any specially designated photography vendor, Incyte, or any other third-party vendors for analysis or further processing. In addition, the participant's specific consent for photographs shall be collected.

- 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 Quality Assurance

The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations). The sponsor or designee is responsible for the data management of this study, including quality checking of the data. Further, monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues, Protocol deviations, and monitoring techniques (eg, central, remote, or on-site monitoring) are provided in the Data Management Plan and the Monitoring Plan.

Quality tolerance limits will be predefined in the Integrated Project Management Plan to identify systematic issues that can impact participant’s safety, efficacy results and analysis, and/or reliability of study results. These predefined parameters will be monitored during the study and can be adjusted during the study upon data review. Important deviations from the QTLs and remedial actions taken, including reporting to IRBs/ECs and health authorities if applicable, will be summarized in the clinical study report.

11.4. 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 personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable. Appropriate notice, or notice and consent (as may be required by each applicable jurisdiction), for collection, use, 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.

11.5. 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.

11.6. Publication Policy

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

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

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

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

11.7. 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 AND DEFINITIONS

Definitions

WOCBP: A woman who is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal with 1 of the following:[a]
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.

Female participants on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal, highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

For male participants of reproductive potential[b]

The following methods during the Protocol-defined timeframe in Section 5.1 are highly effective:

- Use of a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant
- Vasectomy with medical assessment of the surgical success (verified by site personnel's review of the participant's medical records)
- Sexual abstinence[c]
  - Abstinence from penile-vaginal intercourse

The following are **not** acceptable methods of contraception:

- Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method
- Male condom with cap, diaphragm, or sponge with spermicide
- Male and female condom used together

Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

For female participants who are WOCBP

The following methods during the Protocol-defined timeframe in Section 5.1 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[d]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[d]
  - oral
  - injectable
  - implantable[e]
- Intrauterine device[e]
- Intrauterine hormone-releasing system[e]
- Bilateral tubal occlusion[e]
- Vasectomized partner[e,f]
- Sexual abstinence[c]

[a] Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
[b] If the male participant has a partner of childbearing potential, the partner should also use contraceptives.
[c] 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 treatment. 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.
[d] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method. In this case, 2 methods of contraception should be used.
[e] Contraception methods that in the context of this guidance are considered to have low user dependency.
[f] Vasectomized partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has received medical assessment of the surgical success.
Source: Clinical Trials Facilitation and Coordination Group 2020.

APPENDIX B. COVID-19 PANDEMIC MITIGATION STRATEGIES AND INSTRUCTIONS

The COVID-19 global pandemic is an evolving situation and presents numerous challenges to the ongoing conduct of clinical trials. The sponsor has issued the following Protocol considerations to ensure participant safety is maintained and adequate benefit/risk analyses are applied relative to the completion of study procedures and maintaining the investigational product supply chain.

Recognizing the flexibility required to manage the impact of the pandemic on this clinical trial, additional details will be added as needed to respective study manuals and project plan documents and communicated to the investigative sites as needed.

Number of Study Participants

The evolving situation of the pandemic may result in a substantial number of participants' early dropout from the study, which could affect the data integrity of the trial. Because of this risk and in order to mitigate it, the sponsor may decide to recruit additional participants in the study, beyond the expected number.

Study Visits

Remote Site Visit Guidelines:

In addition to the remote visits already specified in the Protocol, the evolving situation of the pandemic may require further travel restrictions and isolation requirements, or the investigator's benefit/risk assessment may determine it to be unsafe for participants to attend study visits at the investigational site. In such cases, the site staff may elect to pursue the following:

- In order to minimize participant risk, study visits may be conducted via telemedicine modalities (phone or video calls). At a minimum, a review of AEs, concomitant medications, and study drug compliance must be completed. Periodic on-site visits should be conducted whenever feasible, in addition to the mandatory on-site visits outlined below.
- No efficacy assessments can be performed via telemedicine (video call or phone call).
- Laboratory sampling: in order to support investigator oversight of participant safety and disease management, off-site laboratory sampling (in accordance with the SoA, see Table 3) may be allowed in 1 of 2 ways:
  - Use of home nursing services.
  - Instruct the participant to undergo some laboratory tests at a local (nearby) hospital laboratory or facility closer to the participant's residence rather than at the investigational site. In this case, the study physician will provide the participant with the list of parameters to be checked. These tests should be performed at certified laboratories and copies of results provided to the site.

Mandatory On-Site Visits:

The visits outlined below **must be performed in person** in order to capture the investigator's efficacy assessments and the patient-reported outcomes, even if the date that the participant eventually comes into the clinic deviates from the visit window.

No efficacy assessments can be performed via telemedicine (video call, phone call, or photography).

The visit window deviation must be documented, and the sponsor's representative must be informed of when it is believed that the participant can come into the clinic. Further instructions will be provided if needed.

During the DBVC period, the following visits must be performed in person:

- Screening
- Day 1 (baseline)
- Week 16 visit

During the OLE period, the following visits must be performed in person:

- Week 32 visit

Investigational Medicinal Product Dispensing and Distribution

In order to ensure the continuity of providing their participants' clinical supplies within the constraints imparted by the pandemic, the site staff can decide to supply study drug via shipment to participants.

If the participant cannot attend a visit at the study site, adequate supplies of study drug determined by the investigator can be shipped to the participant by the investigator or appropriately delegated staff (eg, the study pharmacy staff) using a third-party service if duly authorized by the participant.

The study site may use their own preferred courier, provided the courier adheres to certain standards (eg, use of personal protection equipment, maintenance of temperature-controlled transit environment), or one centrally contracted by the sponsor.

Clinical Trial Monitoring

Study monitoring visits may be postponed due to documented COVID-19–related reasons; however, the site monitor will continue to employ off-site monitoring practices such as routine communication methods (eg, phone calls, e-mails, video visits) with the sites to get information on trial progress, participant status, and information on issue resolution. The study monitor may remotely review data entered into the EDC for accuracy and completeness. If allowed by local regulations, remote source data verification may be implemented with agreement of the principal investigator and institution, as applicable.

If the study-site monitor cannot be on-site to perform the final drug accountability for reconciliation purposes and the operation cannot be postponed, it may be performed by a pharmacist from the hospital pharmacy or by the study coordinator/data manager with suitable

training. The study drug can be returned to the sponsor by the hospital pharmacy directly or destroyed in accordance with local practices, if applicable, and with sponsor approval.

Other Considerations

If necessary, direct contracts can be established with third-party local physicians to conduct activities related to the clinical management of participants for whom the investigator is responsible and maintains oversight. In such situations, the investigator is required to provide the local physician with a delegation letter listing all delegated activities. The sponsor, through the study investigator or institution, will reimburse the local physician for the tests/procedures conducted outside of the standard of care.

- In case of need, participants may refer to the local health care provider. Participants will be requested to obtain certified copies of the source data at the local health facility with the outcome of the contact and provide those to the investigator for appropriate oversight. The investigator/delegate will be requested to enter any relevant information into the EDC.
- Should COVID-19–related restrictions be localized and have an effect on a limited number of sites, the affected sites may utilize direct contracting of third parties to support continuous study conduct (eg, home nursing services, couriers, etc).

Reimbursement of Extraordinary Expenses

The sponsor will arrange to reimburse participants for any extraordinary expenses, keeping appropriate documentation as evidence (eg, travel expenses for the local laboratory visit[s], the costs of local [nearby] laboratory tests).

APPENDIX C. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Not applicable.

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Approval Task	[redacted] Approver [redacted]
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