Official Title: A Randomized, Double-Blind, Vehicle-Controlled Study of the Efficacy and Safety of Ruxolitinib Cream in Participants With Cutaneous Lichen Planus

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Clinical Study Protocol

INCB 18424-216

A Phase 2, Randomized, Double-Blind, Vehicle-Controlled Study of the Efficacy and Safety of Ruxolitinib Cream in Participants With Cutaneous Lichen Planus

Product:	**Ruxolitinib Cream**
IND Number:	**77101**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803 USA**
Original Protocol:	**02 MAY 2022**
Protocol Amendment 1:	**27 MAR 2023**

INVESTIGATOR'S AGREEMENT

I have read the INCB 18424-216 Protocol Amendment 1 (dated 27 MAR 2023) 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
AST	aspartate aminotransferase
BID	twice daily
BSA	body surface area
CCL	C-C motif chemokine ligand
CCR	C-C motif chemokine receptor
CFR	Code of Federal Regulations
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CXCL	C-X-C chemokine ligand
CXCR	C-X-C chemokine receptor
CYP	cytochrome P450
DBVC	double-blind, vehicle-controlled
[redacted]	[redacted]
DNA	deoxyribonucleic acid
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HBV	hepatitis B virus
HCV	hepatitis C virus

Abbreviations and Special Terms	Definition
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
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
IFN	interferon
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
IRB	institutional review board
IRT	interactive response technology
ITCH4	≥ 4-point improvement in WI-NRS score
ITT	intent-to-treat
JAK	Janus kinase
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
NRS	numeric rating scale
OLE	open-label extension
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
RNA	ribonucleic acid
RSI	Reference Safety Information
SAE	serious adverse event
SAP	Statistical Analysis Plan
SoA	schedule of activities

Abbreviations and Special Terms	Definition
SOP	standard operating procedure
STAT	signal transducer and activator of transcription
STD	standard deviation
TEAE	treatment-emergent adverse event, AEs reported for the first time or worsening of a pre-existing event after first dose of study treatment
ULN	upper limit of normal
VC	vehicle-controlled
WBC	white blood cell
WOCBP	women of childbearing potential

1. PROTOCOL SUMMARY

Protocol Title:

A Phase 2, Randomized, Double-Blind, Vehicle-Controlled Study of the Efficacy and Safety of Ruxolitinib Cream in Participants with Cutaneous Lichen Planus

Protocol Number: INCB 18424-216

Objectives and Endpoints:

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

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To establish the efficacy of ruxolitinib 1.5% cream BID in participants with cutaneous LP.	IGA-TS response (defined as an IGA score of 0 or 1 with ≥ 2-grade improvement from baseline) at Week 16. [Proportion of participants achieving IGA-TS at Week 16]
Secondary	
To further assess the treatment effects of ruxolitinib 1.5% cream BID in participants with cutaneous LP.	• IGA-TS response at each scheduled postbaseline visit up to and including Week 32. [Proportion of participants achieving IGA-TS at each scheduled postbaseline visit] • ITCH4 response (defined as a ≥ 4-point improvement in Itch NRS score from baseline) at each scheduled postbaseline visit up to and including Week 32. [Proportion of participants with ITCH4 at each scheduled postbaseline visit] • Time to achieve ITCH4. • Change from baseline in the Skin Pain NRS score at each scheduled postbaseline visit up to and including Week 32.
To evaluate the safety and tolerability of ruxolitinib 1.5% cream BID.	• The type, frequency, and severity of AEs, including changes in vital signs and clinical laboratory blood samples.

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 cutaneous LP
Population	Male and female participants at least 18 years of age who have predominantly cutaneous LP (covering ≤ 20% BSA) and baseline IGA score ≥ 3.
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 16-week, randomized, DBVC study with a 16-week OLE period with a crossover to active treatment for participants who complete the 16-week DBVC period (vehicle cream), followed by a 30-day post-treatment, safety follow-up visit. Participants initially randomized to the active treatment arm will continue with ruxolitinib 1.5% cream during the OLE period.
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

Treatment Groups and Duration:

This is a Phase 2, randomized, DBVC study with a DBVC period of 16 weeks followed by an OLE period of 16 weeks. Participants who were initially assigned to ruxolitinib 1.5% cream will continue with active treatment during the OLE period, while those participants who were initially assigned to vehicle will cross over to active treatment.

Approximately 60 participants will be randomized 1:1 to either ruxolitinib 1.5% cream or vehicle cream (see Figure 1). Participants will be stratified by baseline IGA score (3 or 4). Participants will apply either ruxolitinib 1.5% cream or vehicle cream (both BID) through Week 16 to 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 in the VC period will be crossed over to ruxolitinib 1.5% cream, and participants randomized to ruxolitinib 1.5% cream at baseline will continue to apply ruxolitinib cream through Week 32. In the OLE period, participants will only treat active lesions. At Week 16, the LP treatment area will be evaluated by the investigator to assess the disease and confirm whether treatment continuation is required (IGA score ≥ 1) during the OLE period or can otherwise (re)enter an observation/no treatment cycle (IGA score = 0). Treatment assignment during the DBVC period will remain blinded until all participants have completed treatment or discontinued.

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.

Figure 1: Study Design Schema

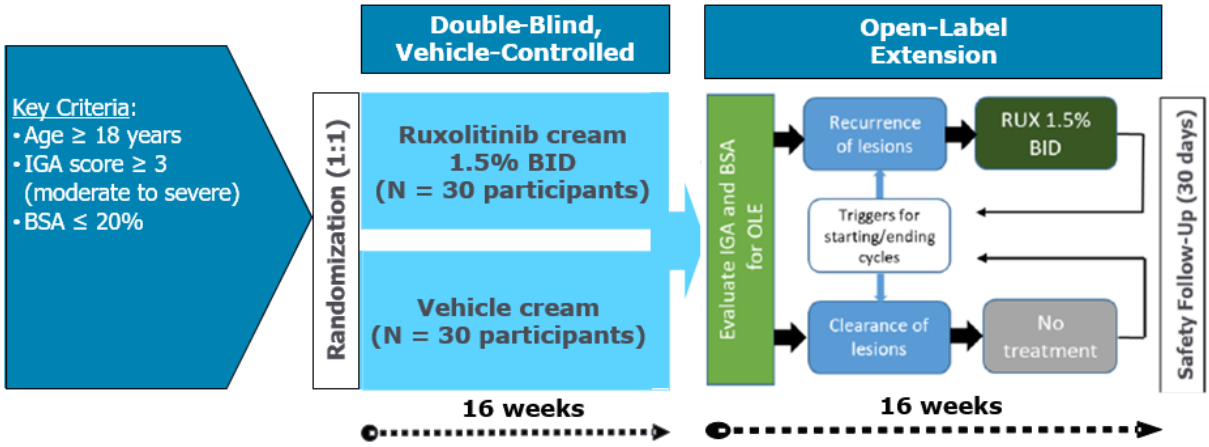

Table 3: Schedule of Activities

	Days −28 to −1	DBVC Period						OLE Period						Safety Follow-Up
Visit Day (Range)	**Screening**	**Baseline/ Day 1**	**Wk 2[a] (± 3 d)**	**Wk 4[a] (± 3 d)**	**Wk 8[a] (± 3 d**	**Wk 12[a] (± 3 d)**	**Wk 16/ EOT1[b] (± 3 d)**	**Wk 18[a] (± 3 d)**	**Wk 20[a] (± 3 d)**	**Wk 24[a] (± 3 d)**	**Wk 28[a] (± 3 d)**	**Wk 32 EOT2/ET[c] (± 3 d)**	**Unscheduled Visit**	**30 Days (+ 7 Days After Last Application)**
Administrative procedures														
Informed consent	X													
Inclusion/exclusion criteria review	X	X												
Demography and medical history	X													
Prior/concomitant medications	X	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	X		
Distribute reminder cards	X	X	X	X	X	X	X	X	X	X	X	X		
Distribute eDiary	X													
Apply study drug in clinic		X	X	X	X	X	X	X	X	X	X			
Weigh/dispense study drug		X	X	X	X	X	X	X	X	X	X			
Collect/weigh study drug			X	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	X
Comprehensive physical examination[d]	X											X		
Height and body weight	X											X		
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physician-reported outcomes														
IGA	X	X	X	X	X	X	X	X	X	X	X	X		
[redacted]														
%BSA[e]	X	X	X	X	X	X	X	X	X	X	X	X		
Target lesion assessment[f]		X	[redacted]											

Table 3: Schedule of Activities (Continued)

	Days −28 to −1	DBVC Period						OLE Period						Safety Follow-Up
Visit Day (Range)	**Screening**	**Baseline/ Day 1**	**Wk 2[a] (± 3 d)**	**Wk 4[a] (± 3 d)**	**Wk 8[a] (± 3 d**	**Wk 12[a] (± 3 d)**	**Wk 16/ EOT1[b] (± 3 d)**	**Wk 18[a] (± 3 d)**	**Wk 20[a] (± 3 d)**	**Wk 24[a] (± 3 d)**	**Wk 28[a] (± 3 d)**	**Wk 32 EOT2/ET[c] (± 3 d)**	**Unscheduled Visit**	**30 Days (+ 7 Days After Last Application)**
Patient-reported outcomes														
Itch NRS	Completed each evening through the last application of study drug.													
Skin Pain NRS														
[redacted]														
Laboratory assessments														
Chemistry assessments	X	X[h]			X		X			X		X	X[i]	X
Hematology assessments	X	X[h]			X		X			X		X	X[i]	X
FSH[j]	X													
Serum pregnancy test[k]	X													
Urine pregnancy test[k]		X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis/HIV serology	X													
[redacted]														
Drug exposure assessments														
[redacted]														

[a] Visits at Weeks 2, 4, 8, 12, 18, 20, 24, and 28 can be performed virtually (through telemedicine if applicable) only due to COVID-19–related reasons. No efficacy assessments can be performed virtually (see Appendix B).

[b] All Week 16 assessments must be completed before the participant can continue in the OLE period. Study drug will not be applied in the clinic at Week 16 for participants not continuing into the OLE period.

[c] Participants who withdraw from the study early should complete the ET and the safety follow-up visits.

[d] Targeted physical examinations can be performed for assessment of AEs and during other visits, including unscheduled visits, as per discretion of the investigator.

[e] The total %BSA affected should be ≤ 20% to be eligible for study entry and continued participation.
[f] Target lesions typical of LP (3 or more) will be identified at baseline.
[redacted]
[h] Not necessary if screening assessment is performed within 14 days of Day 1.
[i] Laboratory assessments are optional during unscheduled visits based on investigator's discretion and clinical judgment.
[j] Women of nonchildbearing potential only. FSH is not needed in women with documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.
[k] Female participants of childbearing potential will have a serum test at screening, a urine pregnancy test before Day 1 study cream application, and a urine test at other visits noted. A positive urine test must be confirmed by a serum test.
[redacted]

2. INTRODUCTION

2.1. Background

Lichen planus is an inflammatory skin condition characterized by purple, polygonal, pruritic papules, and plaques. The lesions are often covered by lacy, reticular, white lines known as Wickham striae. Lichen planus can affect any ectodermally derived tissues, including the skin (most commonly), nails, and mucous membranes. Onset is usually acute, affecting the flexor surfaces of the wrists, forearms, and legs. Oral LP can be the sole clinical presentation of the disease or accompanied by cutaneous or other mucosal manifestations, including the genital area, gastrointestinal tract, and eyes. Classic cases of LP may be diagnosed clinically, but a biopsy is often helpful and is required for more atypical cases (Usatine and Tinitigan 2011). Itch is present in most patients and is considered the most bothersome symptoms of LP (Welz-Kubiak and Reich 2013). Lichen planus is associated with relatively high rates of depression and anxiety. A recent meta-analysis showed a high prevalence of signs of depression (27%) and anxiety (28%) in patients with LP (Jalenques et al 2020).

The prevalence of LP is 0.89% in the general population and 0.98% in patients seeking dermatological care, according to a recent meta-analysis of 46 studies (Li et al 2020). The prevalence of cutaneous LP is reported to range between 0.2% and 1.0% of the adult population, and it is outnumbered by oral LP in most study populations (Boyd and Neldner 1991, Le Cleach and Chosidow 2012). Patients with LP are usually between the ages of 30 and 60 years, and there appears to be a slightly higher prevalence in women (60%; Axéll and Rundquist 1987). While oral LP affects females more frequently than males (Axéll and Rundquist 1987, Li et al 2020), cutaneous LP does not demonstrate a prominent sex predilection (Irvine et al 1991). Cutaneous LP tends to manifest during the fifth and sixth decades of life, with almost two-thirds of patients presenting with the disease between the ages of 30 and 60 years (Schwager et al 2019, Wagner et al 2013). The majority of cutaneous LP lesions resolve spontaneously over 1 to 2 years, often with a residual hyperpigmented macule (Weston and Payette 2015).

Lichen planus is a T cell–mediated disease affecting the stratified squamous epithelia of the skin and/or mucous membrane. Histologically, the disease is characterized by a lichenoid inflammatory infiltrate and vacuolar degeneration of the basal layer of the epidermis. Several alterations in the expression of cytokines and chemokines in lesions or serum of patients with LP have been described. Serum levels of IL-5, IL-6, IL-8, IL-9, IL-10, IL-12 IL-17, IL-22, tumor necrosis factor α, transforming growth factor β, IFN-γ, CXCR-3, CXCR-4, CXCL-10, CXCL-12, CCR1, CCR3, CCR4, CCL5-CCR5, and CCL17-CCR4 have been found to be elevated (Chen et al 2013, Kurago 2016, Weber et al 2017, Zychowska et al 2020). Recent studies demonstrated that the inflammation in cutaneous LP is dominated by IFN-γ, IL-6, and IL-21 and the proinflammatory milieu is dominated by STAT1 activation (Boch et al 2021, Shao et al 2019). All of these cytokines, IL-21, IFN-γ, IL-6, and Type I IFN, use JAK1 for signal transduction. Of note, JAK1 has been reported to be overexpressed in dermal skin of LP (Alves de Medeiros et al 2016). Therefore, JAK1 blockade could be beneficial for cutaneous LP.

Patients with LP currently have limited treatment options, which include irritant avoidance and first-line treatment with topical corticosteroids. Topical calcineurin inhibitors are the second line of choice when topical corticosteroids are not effective or not tolerated.

Ruxolitinib is a small molecule inhibitor of the JAKs, which play an important role in signal transduction following cytokine and growth factor binding to their receptors. Increased production of cytokines and growth factors has been associated with a number of chronic inflammatory conditions, including AD, vitiligo, and other autoimmune diseases of the skin. Therefore, JAK inhibition may be expected to be efficacious in these diseases (refer to the IB for more information).

The efficacy of ruxolitinib cream, a JAK1/2 inhibitor, has been demonstrated in inflammatory dermatoses such as 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% affected BSA (excluding the scalp; Papp et al 2020). In both AD Phase 3 studies, more than 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 score of 0 or 1 with ≥ 2-grade improvement from baseline) compared with 15.1% and 7.9% of participants who applied vehicle cream, respectively. 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 vs 16.3% and 15.4% for vehicle cream, respectively). 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 in the US as Opzelura™ for the topical short-term and noncontinuous chronic 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.

Ruxolitinib 1.5% cream has demonstrated efficacy in vitiligo. Studies INCB 18424-306 and -307 were identically designed randomized, VC, Phase 3 studies 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 studies 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 Face Vitiligo Area Scoring Index at Week 24 compared to participants treated with a vehicle control. In addition, ruxolitinib 1.5% cream was safe and well-tolerated in both adolescents and adults with vitiligo.

Recently, the potential benefit of ruxolitinib 1.5% cream BID was reported in a single-arm, open-label study in participants with cutaneous LP treated for 8 weeks (Mangold et al 2021). Twelve patients with a median age of 63 years (range: 34-81 years) participated in the study. At Week 4 (primary endpoint), total body lesion number decreased by a median of 50 lesions (interquartile range: 25-723; $p < 0.001$). Mean (STD) mCAILS scores decreased by 11.0 (6.2) in index treatment lesions and 3.4 (5.6) in index controls, for a mean difference of 7.6 (8.8; $p = 0.016$). Ten of 12 index treatment lesions (83.3%) achieved treatment response, as defined by ≥ 50% reduction in mCAILS score, compared to 4 of 12 controls (33.3%; $p = 0.077$). Post hoc analysis, which excluded 4 participants who unintentionally treated their control lesions at any point during the study, revealed response of 7 of 8 treatment lesions (87.5%) compared to 1 of 8 control lesions (12.5%; $p = 0.04$). All participants were responsive (≥ 50% improvement) based on Patient Global Assessment score at Week 4; 2 of 12 were 100% clear, 5 of 12 had ≥ 90% improvement, 4 of 12 had marked (≥ 75% to 90%) improvement, and 1 of 12 had

moderate (≥ 50% to 75%) improvement. A significant reduction (p = 0.006) in mean pruritus NRS scores was reported at Week 4. Only 1 AE was deemed to be possibly related to the study treatment ("abnormal taste" reported at Week 1) and was classified as mild. All other AEs were judged as mild to moderate and were determined to be unrelated to the study medication.

This study is designed to evaluate the efficacy and safety of ruxolitinib 1.5% cream in participants with cutaneous LP.

2.1.1. Scientific Rationale for Study Design

Similar to AD and vitiligo, LP is considered to be an inflammatory dermatosis. The pathogenesis of LP involves autoimmunity and several cytokines that are dependent on the JAK-STAT pathway for signal transduction. Similar to AD and vitiligo, JAK1- and JAK2-associated cytokines are involved in the pathogenesis of cutaneous LP. Prior studies have shown overexpression of IFN-γ, IL-21, IL-4, IL-12A, and tumor necrosis factor in LP (Pietschke et al 2021, Shao et al 2019). Ruxolitinib is a selective inhibitor of JAK1 and JAK2, and based on its demonstrated efficacy in both AD and vitiligo in well-designed pivotal Phase 3 trials (INCB 18424-303/-304 and INCB 18424-306/-307) and data from Mangold et al (2021), ruxolitinib 1.5% cream is expected to have potential activity in cutaneous LP.

While the study by Mangold et al (2021) provides preliminary evidence of the efficacy of ruxolitinib 1.5% cream in patients with LP, this was a single-arm study with a small sample size, and these findings need to be replicated in a larger randomized controlled trial as a proof of concept. Lichen planus lesions mostly resolve spontaneously over a period of 1 to 2 years, and the aim of treatment is to hasten recovery and reduce associated symptoms such as itching. Given the high rate of spontaneous resolution, it is important to demonstrate the efficacy of ruxolitinib 1.5% cream against a VC arm. Although ruxolitinib 1.5% cream has been demonstrated to improve AD at 8 weeks, LP lesions involve significantly more skin changes. Mangold et al (2021) demonstrated reduction in lesion count by 50% after 4 weeks of open-label treatment with ruxolitinib 1.5% cream. However, concern with spontaneous resolution of LP remains. In the study by Mangold et al (2021), approximately 33% of control lesions achieved treatment response, as defined by ≥ 50% reduction in mCAILS score at Week 4. Based on these findings, it is crucial to demonstrate the efficacy of ruxolitinib 1.5% cream in participants with cutaneous LP as a proof-of-concept Phase 2 study with a longer treatment period (16 weeks was chosen for this study) before moving to confirmatory Phase 3 studies. In addition, there is a need to demonstrate the long-term safety and efficacy of ruxolitinib 1.5% cream in LP by including an OLE period.

This study will evaluate the efficacy and safety of ruxolitinib 1.5% cream BID versus vehicle in participants with LP. The VC period is 16 weeks. Participants who are randomly assigned to ruxolitinib 1.5% cream will continue to treat active LP areas during the OLE period for an additional 16 weeks. Participants assigned to vehicle initially will then be crossed over to receive active treatment for an additional 16 weeks. This design will provide a well-controlled assessment of the efficacy of ruxolitinib 1.5% cream in participants with LP compared to vehicle.

2.1.2. Justification for Dose

The ruxolitinib cream strength and application frequency for this study (ruxolitinib 1.5% cream BID) was selected primarily based on preliminary evidence from the open-label study by Mangold et al (2021) and 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. Overall, ruxolitinib 1.5% cream was found to be more efficacious than ruxolitinib 0.75% cream, while the safety and tolerability profiles of both treatment arms were comparable and nondifferentiating. Of note, the Phase 3 efficacy and safety findings were on par and thus fully confirmatory of the outcomes of the earlier Phase 2 (INCB 18424-206) dose range–finding study. Similarly, Phase 3 pivotal studies in vitiligo (INCB 18424-306 and -307) provide further support for the superior efficacy of ruxolitinib 1.5% cream versus vehicle cream.

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

2.2. 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 itch (Papp et al 2020). Given that LP has an itch component to the disease, it is likely that participants with LP will benefit from ruxolitinib cream in treating itch.

Safety data from the Phase 3 AD studies (INCB 18424-303 and-304) demonstrated that ruxolitinib 1.5% cream BID applied continuously for 8 weeks followed by prolonged (44 weeks) intermittent use is 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.

In the study by Mangold et al (2021), all AEs were mild to moderate in severity and, with 1 exception, all were unrelated to the study medication. This provides some evidence of the safety of ruxolitinib 1.5% cream in participants with LP.

Results from dermal safety studies in healthy adult participants (INCB 18424-104, -105, -106, -107, and -108) to evaluate local tolerability demonstrated that ruxolitinib 1.5% cream did not cause sensitization and was only slightly irritating under exaggerated testing conditions (occlusive application). In addition, ruxolitinib 1.5% cream was not phototoxic and did not induce photosensitization. This was further confirmed by the Phase 3 (INCB 18424-303 and -304) safety data, where ruxolitinib 1.5% cream BID was well-tolerated at the application sites with infrequently reported application site reactions. The most frequently reported application site reaction events were application site pain (lowest-level terms were primarily application site burning or application site stinging) and application site pruritus. Each of these events occurred in a lower proportion of participants in the ruxolitinib 1.5% cream BID treatment group (< 1%) compared with the vehicle cream treatment group (3%-5%) during the 8-week VC period, which

may be attributable to worsening of the underlying disease in the absence of active drug treatment. More detailed information about the known and expected benefits and risks and reasonably expected AEs of ruxolitinib cream may be found in the IB.

The efficacy and safety data from AD and vitiligo studies as well as data from the study by Mangold et al (2021) in cutaneous LP provide support of the expected positive benefit-risk ratio of ruxolitinib cream in LP. Furthermore, given that LP has an itch component to the disease, it is anticipated that participants with LP will benefit from ruxolitinib cream in treating itch.

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 cutaneous LP.	IGA-TS response (defined as an IGA score of 0 or 1 with ≥ 2-grade improvement from baseline) at Week 16. [Proportion of participants achieving IGA-TS at Week 16]
Secondary	
To further assess the treatment effects of ruxolitinib 1.5% cream BID in participants with cutaneous LP.	• IGA-TS response at each scheduled postbaseline visit up to and including Week 32. [Proportion of participants achieving IGA-TS at each scheduled postbaseline visit] • ITCH4 response (defined as a ≥ 4-point improvement in Itch NRS score from baseline) at each scheduled postbaseline visit up to and including Week 32. [Proportion of participants with ITCH4 at each scheduled post-baseline visit] • Time to achieve ITCH4. • Change from baseline in the Skin Pain NRS score at each scheduled postbaseline visit up to and including Week 32.
To evaluate the safety and tolerability of ruxolitinib 1.5% cream BID.	The type, frequency, and severity of AEs, including changes in vital signs and clinical laboratory blood samples.

Table 4: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, randomized, DBVC study in participants at least 18 years of age who have predominantly cutaneous LP (covering ≤ 20% BSA) and baseline IGA score ≥ 3. The study will consist of a 16-week DBVC period followed by a 16-week OLE period. Participants who were initially assigned to ruxolitinib 1.5% cream will continue with active treatment during the OLE period, while those participants who were initially assigned to vehicle will cross over to active treatment.

Approximately 60 participants will be randomized 1:1 to either ruxolitinib 1.5% cream or vehicle cream (see Figure 1). Participants will be stratified by baseline IGA score (3 or 4). Participants will apply either ruxolitinib 1.5% cream or vehicle cream (both BID) through Week 16 to 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 in the VC period will be crossed over to ruxolitinib 1.5% cream, and participants randomized to ruxolitinib 1.5% cream at baseline will continue to apply ruxolitinib cream through Week 32. In the OLE period, participants will only treat lesions that are symptomatic. At Week 16, the LP treatment area will be evaluated by the investigator to assess the disease and confirm whether treatment continuation is required (IGA score ≥ 1) during the OLE period or can otherwise (re)enter an observation/no treatment cycle (IGA score = 0; see also Section 6.1). Treatment assignment during the DBVC period will remain blinded until all participants have completed treatment or discontinued. Table 3 presents the SoA.

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 aged 18 years or older.
3. Clinical diagnosis of LP with predominant cutaneous involvement.
4. IGA score of 3 or 4 at screening and baseline.
5. LP affecting ≤ 20% of the BSA at screening and baseline.
6. Baseline LP-related Itch NRS score ≥ 4. Baseline Itch NRS is defined as the 7-day average of Itch NRS score before Day 1 (data from a minimum of 4 out of 7 days directly prior to Day 1 is needed).
7. 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 study treatment 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 a negative urine pregnancy test before the first study cream 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 treatment 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. A female participant not considered to be of childbearing potential as defined in Appendix A is eligible.

5.2. Exclusion Criteria

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

1. Concurrent conditions and history of other diseases:
    a. Variants of LP deemed by the investigators to be inappropriate for topical treatment, including but not limited to predominant mucosal (such as oral or vaginal) LP.

        Note: Participants with mucosal LP can be eligible if they have predominant cutaneous LP and agree to not treat mucosal LP during the study.
    b. Active ongoing inflammatory diseases of the skin other than LP that might confound the evaluation of LP lesions or compromise participant safety.
    c. 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 LP lesions or compromise participant safety.
    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, chickenpox, clinically infected AD, or impetigo) within 1 week before baseline.
2. Participants with the following conditions:
    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 mm Hg) unless approved by the medical monitor/sponsor.
    b. Current or previous malignancy within 5 years of study entry, except for adequately treated nonmetastatic nonmelanoma skin cancer.
    c. Unstable asthma or COPD requiring systemic treatment (such as intravenous steroids) or hospital admission or emergency department treatment within 3 months from baseline or stable asthma or COPD requiring budesonide more than 720 µg/day (2 puffs BID of 180-µg dose) or fluticasone more than 440 µg/day (2 puffs BID of 110-µg dose) or other equivalent inhaled corticosteroids.
    d. Current and/or history of arterial or venous thrombosis, including deep venous thrombosis and pulmonary embolism.
    e. Current and/or history of active tuberculosis or current and/or history of latent tuberculosis unless adequately treated.
    f. History of severe anemia, severe thrombocytopenia, or severe neutropenia.
    g. 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. Investigator should consult with the medical monitor to clarify eligibility when in doubt.

3. Any of the following clinical laboratory test results at screening:
   a. Cytopenias, defined as follows:
      – Hemoglobin < 100 g/L (ie, 10 g/dL)
      – Absolute neutrophil count < 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 glomerular filtration rate < 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 of acute or chronic active hepatitis B or C virus infection. Participants who have recovered or have been successfully treated with no evidence of active hepatitis B or C 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.
4. Use of any of the following treatments within the indicated washout period before the baseline visit:
   a. 5 half-lives or 12 weeks, whichever is longer – biologic agents (eg, dupilumab). For biologic agents with washout periods longer than 12 weeks (eg, rituximab), consult the medical monitor.
   b. 4 weeks – systemic corticosteroids or adrenocorticotropic hormone analogs, cyclosporine, methotrexate, azathioprine, or other systemic immunosuppressive or immunomodulating agents (eg, mycophenolate or tacrolimus).
   c. 2 weeks or 5 half-lives, whichever is longer – strong systemic CYP3A4 inhibitors.
   d. 2 weeks – systemic antibiotics and immunizations with live-attenuated vaccines, sedating antihistamines unless on a long-term stable regimen (nonsedating antihistamines are permitted).
   e. *Note:* Live-attenuated vaccines are prohibited during the DBVC period. COVID-19 vaccination is permitted.
   f. 2 weeks – treatment with topical therapy (eg, topical corticosteroids, pimecrolimus, and tacrolimus).
5. 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.
6. Pregnant or lactating participants, or those considering pregnancy during the period of their study participation.
7. 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.

8. Previous treatment with systemic or topical JAK inhibitors (eg, ruxolitinib, tofacitinib, baricitinib, filgotinib, lestaurtinib, pacritinib).
9. Inadequate venous access in nonlesional areas or in areas not treated by the study drug.
10. Known allergy or reaction to any of the components of the study drug.
11. In the opinion of the investigator, are unable or unlikely to comply with the administration schedule and study evaluations.
12. Committed to a mental health institution by virtue of an order issued either by the judicial or the administrative authorities.
13. Employees of the sponsor or investigator or otherwise dependents of them.

5.3. Lifestyle Considerations

Participants should be cautioned to avoid excessive 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 1 hour before or 2 hours after the planned study drug application. Participants should not wash the area where study cream has been applied for at least 2 hours after application of study cream.

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 Treatments Administered

Ruxolitinib cream or matching vehicle will be applied as a thin film BID, with applications approximately 8 to 12 hours apart in the morning and in the evening at least 1 hour before bedtime.

At the baseline visit, an estimate of the %BSA to be treated will be used by the IRT system to calculate the number of tubes of study cream to be dispensed. During clinic visits, the participant should apply a thin film of study cream in front of site staff until all the affected areas to be treated are covered. This supervised application will be limited to 1 application of the study drug during the clinic visit. 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 cream. If there are new areas to be treated, including expansion of existing areas or development of new areas, after consultation with the investigator, study cream should be applied to these areas in addition to the areas treated at baseline (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 cream to be dispensed. Participants whose 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 the EOT assessment should be completed.

During the OLE period, starting at the Week 16 visit, the LP treatment areas will be evaluated by the investigator to assess if they still have disease and confirm whether the participant requires continuation of therapy (IGA score ≥ 1) or can otherwise (re)enter the observation/no treatment cycle (IGA score = 0). Participants will stop treatment applications 3 days after all LP signs and symptoms have resolved. Multiple cycles of treatment/no treatment may be utilized as needed and treatment start/stop dates should be recorded by the participant in their eDiary. At any time during the OLE period, if a participant's new areas to be treated in addition to the areas identified at the previous visit exceed 20% BSA, then the participant should be discontinued from study treatment and the EOT assessment should be completed.

The amount of study cream 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

	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 8-12 hours apart for 16 weeks. OLE period: Apply a thin film to affected areas in the morning and at least 1 hour before bedtime with applications approximately 8-12 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.

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. Participants should store study treatment at ambient temperature conditions.

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 IGA score (3, 4), 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 period 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), and the sponsor should be consulted by the investigator for instruction on the proper handling of the participant.

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 study drug interruption or permanent discontinuation if needed (eg, for management of an AE).

Temporary interruption could be due to an AE during the DB VC or OLE period or clearance of the LP during the OLE period.

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

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

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of AEs or laboratory abnormalities that may have an unclear relationship to study drug (see Table 6). 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 should 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.

Table 6: Guidelines for Interruption of Study Drug for Treatment-Related Adverse Events 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 Due to an Adverse Event

The occurrence of unacceptable severity of an AE, such that it would interfere with study drug treatment or study procedures, 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, compromises the participant's ability to continue study-specific procedures, or continuing in the study is considered to not be in the participant's best interest.
- Worsening of LP that requires treatment with a prohibited concomitant medication.
- Adverse event requiring an interruption of study drug for more than 2 weeks.
- 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-LP medications received up to 28 days before the first application of study treatment will be recorded in the eCRF. Any prior LP 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 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 application 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 judgment of the investigator, the intake of these medications and procedures will not impact the safety of the participant or efficacy of the treatment:

- Participants may use/continue to use bland emollients. Participants may not change or introduce a new emollient within 4 weeks of the baseline visit.

  Note: Emollients should not be used within 2 hours before and 1 hour after application of study drug.

- Participants may use nonsedating, over-the-counter antihistamines.
- Established and stable treatment with sedating antihistamines (≥ 28 days prior to baseline) may be continued.
- Use of inhaled corticosteroids for bronchial asthma or COPD is allowed with the dose equivalent of budesonide (not to exceed 720 µg/day or 2 puffs BID of a 180-µg dose) or fluticasone (not to exceed 440 µg/day or 2 puffs BID of a 110-µg dose) or other equivalent inhaled corticosteroids.
- Use of any over-the-counter, nonprescription vitamins, minerals, and phytotherapeutic, herbal, or plant-derived preparations is permitted.

6.6.2. Restricted Use 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 the follow-up visit:

- Use of any prescription medication to treat chronic medical conditions (such as hypertension) if on a stable regimen in the judgment of the investigator.
- Short course of topical anti-infectives (including antibacterial, antifungal, and antivirals) if used ≤ 5 days on active LP lesions to treat skin infection. Anti-infective treatment should not be used for at least 2 hours before and 1 hour after application of study cream.

6.6.3. Prohibited Medications and Procedures

No rescue treatment or therapy is allowed during the study. In addition, the following are not permitted during the study:

- Any investigational medication other than the study drug.
- Medications to treat LP (such as retinoids, methotrexate, thalidomide, heparin, griseofulvin, cyclosporine, sulfasalazine, mycophenolate, hydroxychloroquine or metronidazole, etc). Other treatments known to affect the course of LP are also prohibited.
- Topical corticosteroids or calcineurin inhibitors.
- Systemic corticosteroids, methotrexate, cyclosporin A, azathioprine and biological therapies, or other immunosuppressant/immunomodulator agents.
- Any other topical or systemic treatment for LP.
- Concomitant use of strong inhibitors of CYP3A4.
- Phototherapy (such as ultraviolet B) or tanning beds.
- Live-attenuated vaccination during the DBVC period.

  Note: COVID-19 vaccination (not live-attenuated) is permitted.

6.7. Treatment After the End of the Study

There will be no treatment provided after the end of the study.

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.
- Worsening LP and treatment with a prohibited medication 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 for the following reasons:

- 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 administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the participant.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment prior to the Week 32/EOT2 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 [example only; not applicable to this Protocol]) 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 study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that 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 eDiaries

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 and will also remind the participant that their morning application of study cream (if applicable)

will take place at the clinic under site supervision after blood draws for [redacted] safety evaluations have been completed.

Participants will be provided with a handheld device at the screening visit. The participant will start using the eDiary function of the handheld device on Day 1. The date and time of the last application of study drug [redacted] will be recorded in the eDiary. 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 or surgical treatment within the last 2 years that are considered to be clinically significant by the investigator.

8.1.5.2. Disease Characteristics and Treatment History

Relevant medical and treatment history for the past year will be collected at screening by the investigator or qualified designee. Details regarding the participant's history of LP, including date of diagnosis, relevant disease characteristics, and prior treatments with outcome (eg, inadequate response) and reason for stopping treatment, will be recorded.

8.2. Efficacy Assessments

8.2.1. Health Economics

Health economics parameters are not evaluated in this study.

8.2.2. Investigator's Global Assessment

The IGA to assess cutaneous LP has been modified by the sponsor to appropriately assess LP. The investigator/rater will assess the lesions at the study visits indicated in Table 3 by using the descriptors [redacted] that best describe the overall appearance of the lesions at a given timepoint. It is not necessary that all characteristics under the morphological description be present.

IGA-TS is defined as an IGA score of 0 or 1 with ≥ 2-grade improvement from baseline.

[redacted]

[redacted]

8.2.8. Patient-Reported Outcomes

Patient-reported outcomes will be collected and assessed as outlined in the SoA (see Table 3). For all patient-reported outcome assessments conducted at the study site, in order to avoid bias in the participants' responses to the questionnaires, assessments should be completed before any other evaluations or study procedures on the day of the study visit and prior to treatment-related discussions with the investigator or study site staff.

8.2.8.1. eDiary Assessments

The participant will be instructed to complete and record their Itch NRS and Skin Pain NRS scores via eDiary every evening beginning on the day of screening through Week 32 or ET.

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

The participants will rate the following:

- Itch NRS: Itch severity of their LP 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.
- Skin Pain NRS: Pain severity of their LP 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.

The average of the 7-day Itch NRS score prior to the baseline visit (minimum 4 out of 7 days' data required) will be used to determine if a participant meets the inclusion criteria.

Detailed directions for the administration of the eDiary will be provided in the Study Manual.

[redacted]

8.3. Safety Assessments

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

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

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until 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 (EOT2)/ET 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. Fitzpatrick skin classification will be included as part of the physical examination at screening.

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.

Height and body weight will be assessed at screening and the Week 32 (EOT2)/ET visit.

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 8 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) and will store the samples for [redacted] PD analysis. 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 8: Schedule of Laboratory Assessments

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

Note: Additional tests may be required, as agreed upon by the 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.
[c] A negative urine pregnancy test at baseline is required prior to initiating Day 1 study cream application.

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 and Table 8). 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]

8.6. Unscheduled Visits

Unscheduled visits may occur at any time medically warranted, including when participants develop new areas of LP. 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/EOT2 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/EOT2 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 (EOT2)/ET visit and the scheduled follow-up visit, which should occur 30 days (+ 7 days' visit window) after the Week 32 (EOT2)/ET visit (or 30 days after the last application of study drug if the Week 32 (EOT2)/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 or 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 or thrombocytopenia) should be recorded in the eCRF rather than the abnormal laboratory test result (eg, low hemoglobin or 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, or diagnostic reports) related to the event.
- The investigator (or delegate) will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completing the 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 Grades 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, or unknown).
- The seriousness, 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 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 Event 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 Event 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.

There are no study-specific warnings or precautions in this study.

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 1.5% cream BID or vehicle cream BID. The sample size calculation is based on the Fisher exact test for the primary efficacy endpoint, the proportion of participants achieving IGA-TS at Week 16. Based on previous studies (INCB 18424-303 and -304) and the results from an investigator sponsored trial (Mangold et al 2021) with topical ruxolitinib (NCT03697460), the preliminary assumption of response rates is 58% for ruxolitinib 1.5% cream and 20% for vehicle cream. Using a 2-sided alpha of 0.05, the sample size based on the current setup will have > 80% power to detect a difference between active treatment and vehicle.

In addition to providing adequate power for efficacy variables, the sample size is determined to provide an adequate database for safety evaluations.

10.2. Populations for Analysis

The populations for analysis are provided in Table 9.

Table 9: Populations for Analysis

Population	Description
ITT	The ITT population includes all randomized participants.
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.
OLE evaluable	All analyses for the OLE period will be conducted with the OLE evaluable population, which includes all participants who applied ruxolitinib 1.5% cream at least once during the OLE period.
[redacted]	[redacted]
[redacted]	[redacted]

10.3. Level of Significance

The significance level for primary efficacy analysis will be 0.05 for a 2-sided test.

10.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

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 10.

Table 10: Summary of Primary Analysis

Parameter	Definition
Treatment	Ruxolitinib 1.5% cream compared with vehicle cream
Population	ITT population
Variable	IGA-TS response at Week 16: achieving an IGA score of 0 or 1 with ≥ 2-grade improvement from baseline at Week 16
Population-level summary	IGA-TS response rate difference with 95% CI

Note: Participants with missing Week 16 data, as well as all participants who discontinue study treatment at any time before the timepoint of interest, or discontinue from the study for any reason, will be defined as nonresponders. No rescue therapy or treatment switch is allowed in this study.

The primary alternative hypothesis (superiority of ruxolitinib 1.5% cream BID compared with vehicle) will be tested at a 2 sided $\alpha = 0.05$ level using a Cochran-Mantel-Haenszel test stratified by baseline IGA score (3 or 4). The p-value and stratum-adjusted IGA-TS response rate difference with 95% CI will be provided. A summary of IGA-TS rates will be reported for each treatment group. Subgroup analysis by baseline characteristics will be performed. Details will be provided in the SAP.

10.4.2. Secondary Analysis

All secondary [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, STD, 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 Itch NRS score as well as the Skin Pain NRS score for each visit will be determined by averaging the 7 daily scores for Itch or Skin Pain before the corresponding visit day. If 4 or more daily scores are missing (out of the 7), the Itch NRS or Skin Pain NRS score at the visit will be set to missing.

For the time to achieve ITCH4, a log-rank test stratified by randomization stratification factor will be used for between-treatment group comparisons. The hazard ratio and its 95% CI will be estimated based on the stratified Cox regression model using Efron's method accounting for ties. Kaplan-Meier curves will be presented by treatment groups. The number of participants, number of events, and number of censorings will be summarized by treatment groups. The Kaplan-Meier estimate of median time will be presented with its 95% CI. The 95% CI will be calculated using the method by Brookmeyer and Crowley (1982).

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. The sponsor will be unblinded after the primary database lock; however, investigators and participants will remain blinded to the individual study treatment assignment.
- 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 the 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 their 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], 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; [redacted] 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, [redacted], 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, [redacted]

- 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/or the Monitoring Plan.

Quality tolerance limits will be predefined in the Quality Risk Management Plan or Integrated Project Management Plan to identify systematic issues that can impact participants' 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 quality tolerance limits and remedial actions taken, including reporting to IRBs/IECs and health authorities if applicable, will be summarized in the CSR.

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, and the sponsor operates comprehensive data privacy and data security programs that are applicable to this study. 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. Appropriate data protection terms that comply with applicable laws will be included in relevant study agreements.

To ensure confidentiality of records and protect personal data, 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.

In the event of a data breach involving participant data, the sponsor or its designee will follow the sponsor's incident response procedures. The precise definition of a data breach varies in accordance with applicable law but may generally be understood as a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data. In accordance with its incident response procedures, the sponsor will assess the breach to consider its notification and remediation obligations under applicable law.

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 Clinical 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 woman of childbearing potential 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, post ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea 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, [redacted]).

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, subject 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

Document	Date
Amendment 1	27 MAR 2023

Amendment 1 (27 MAR 2023)

Overall Rationale for the Amendment:

[redacted]

2. **Section 5.1, Inclusion Criteria (Criterion 7b)**

   Description of change: Updated to include that WOCBP must have a negative serum pregnancy test at screening and a negative urine pregnancy test before the first study drug application on Day 1.

   Rationale for change: To be consistent with the pregnancy test requirements in the SoA.

3. **Section 5.2, Exclusion Criteria (Criterion 2b)**

   Description of change: Updated to cover current or previous malignancy within 5 years of study entry, except for adequately treated nonmetastatic nonmelanoma skin cancer.

   Rationale for change: To be consistent with other ruxolitinib cream study protocols.

4. **Section 5.2, Exclusion Criteria (Criterion 2g)**

   Description of change: Updated exclusion criterion 2 to relocate the investigator's opinion of conditions into new criterion 2g as one of the listed conditions.

   Rationale for change: To allow the investigator's opinion to determine additional exclusions.

5. **Section 10.4.2, Secondary Analysis**

   Description of change: Updated to include Skin Pain NRS analysis from daily diary data.

   Rationale for change: Not specified in the original protocol.

6. **Incorporation of administrative changes.** Other regulatory guidance and administrative changes have been incorporated in the Protocol and are noted in the redline version of the amendment.

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Approval Task	[redacted]
Approval Task	[redacted]
Approval Task	[redacted]
Approval Task	[redacted] Approver [redacted]
Approval Task	[redacted] Approver [redacted]

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