Official Title: A Phase 3, Double-Blind, Randomized, Vehicle-Controlled, Efficacy and Safety Study of Ruxolitinib Cream in Participants With Prurigo Nodularis

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Clinical Study Protocol

INCB 18424-319

A Phase 3, Double-Blind, Randomized, Vehicle-Controlled, Efficacy and Safety Study of Ruxolitinib Cream in Participants With Prurigo Nodularis

Topical **Ru**xolitinib **E**valuation in **P**rurigo **N**odularis (TRuE-PN1)

Product:	**Ruxolitinib Cream**
IND Number:	**77101**
EU CT Number:	**2022-501621-20-00**
Phase of Study:	**3**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803 USA**
Original Protocol:	**20 APR 2022**
Amendment 1:	**14 NOV 2022**
Amendment 2:	**01 DEC 2022**
Amendment 3:	**14 JUN 2023**
Amendment 4:	**21 FEB 2024**

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (Brazil 2013) and conducted in adherence to the study Protocol, applicable Good Clinical Practices, and applicable laws and country-specific regulations, including WMO (Medical Research Involving Human Participants Act) and Clinical Trials Regulation (EU) No. 536/2014, in which the study is being conducted.

INVESTIGATOR'S AGREEMENT

I have read the INCB 18424-319 Protocol Amendment 4 (dated 21 FEB 2024) 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
CFR	Code of Federal Regulations
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMH	Cochran-Mantel-Haenszel
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CP	conditional power
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P450
DBVC	double-blind, vehicle-controlled
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EASI	Eczema Area and Severity Index
EASI75	75% reduction from baseline in Eczema Area and Severity Index
EC	Executive Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EOT	end of treatment
ET	early termination
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone

Abbreviations and Special Terms	Definition
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HADS	Hospital Anxiety and Depression Scale
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HRQoL	health related quality of life
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
IGA	Investigator's Global Assessment
IGA-CPG-A	Investigator Global Assessment for Activity of Chronic Prurigo
IGA-CPG-S-TS	Investigator's Global Assessment for Stage of Chronic Prurigo Treatment Success is defined as an IGA-CPG-S score of 0 or 1 with ≥ 2-grade improvement from baseline
IGA-CPG-S	Investigator Global Assessment for Stage of Chronic Prurigo
IL	interleukin
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
JAK	Janus kinase
MedDRA	Medical Dictionary for Regulatory Activities
NRS	numeric rating scale
OLE	open-label extension
PAS	Prurigo Activity Score
PCR	polymerase chain reaction
PD	pharmacodynamic(s)

Abbreviations and Special Terms	Definition
PDE	phosphodiesterase
[redacted]	
PK	pharmacokinetic(s)
PN	prurigo nodularis
PP	per protocol
PRO	patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System®
QALY	quality-adjusted life-year
RNA	ribonucleic acid
RSI	Reference Safety Information
SAE	serious adverse event
SAP	Statistical Analysis Plan
SNRI	serotonin and norepinephrine reuptake inhibitor
SoA	schedule of activities
SOP	standard operating procedure
SPF	sun protection factor
SSRI	selective serotonin reuptake inhibitor
STAT	signal transducer and activator of transcription
TCI	topical calcineurin inhibitors
TCS	topical corticosteroids
TEAE	treatment-emergent adverse event
Th	T helper
TYK	tyrosine kinase
ULN	upper limit of normal
VAS	visual analog scale
WI-NRS	Worst-Itch Numeric Rating Scale
WI-NRS4	≥ 4-point improvement in WI-NRS score
WPAI	Work Productivity Index
WOCBP	women of childbearing potential

1. PROTOCOL SUMMARY

Protocol Title:

A Phase 3, Double-Blind, Randomized, Vehicle-Controlled, Efficacy and Safety Study of Ruxolitinib Cream in Participants With Prurigo Nodularis

Topical **Ru**xolitinib **E**valuation in **P**rurigo **N**odularis (TRuE-PN1)

Protocol Number: INCB 18424-319

Objectives and Endpoints:

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

Table 1: Primary and Key Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To demonstrate the efficacy of ruxolitinib 1.5% cream BID in participants with PN.	WI-NRS4 response at Week 12, defined as achieving a ≥ 4-point improvement (reduction) in WI-NRS score from baseline.
Key Secondary	
To further demonstrate the treatment effects of ruxolitinib 1.5% cream BID in participants with PN.	• WI-NRS4 response at Week 4. • Overall-TS at Week 12, defined as achieving both a WI-NRS4 response and an IGA-CPG-S-TS. (IGA-CPG-S-TS is defined as an IGA-CPG-S score of 0 or 1 with a ≥ 2 grade improvement from baseline.) • IGA-CPG-S-TS at Week 12. • WI-NRS4 response on Day 7.

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 3
Clinical Indication	Treatment of adults with PN
Population	Male and female participants at least 18 years of age who have a clinical diagnosis of PN for at least 3 months, IGA-CPG-S score of ≥ 2, ≥ 6 pruriginous lesions on ≥ 2 different body areas, and PN-related WI-NRS score ≥ 7. Note: The total estimated BSA treatment area must be ≤ 20%. Treatment area is defined as the area affected by pruriginous lesions plus an ~ 1 cm area surrounding each lesion.
Number of Participants	Approximately 180 participants will be randomized 1:1 to 1 of 2 treatment groups (ruxolitinib 1.5% cream BID or vehicle cream BID) stratified by baseline IGA-CPG-S score and geographic region. Participants with an IGA-CPG-S score of 2 will constitute up to approximately 20% of the overall study population.
Study Design	This is a randomized, 12-week, DBVC study with a 40-week OLE period with active treatment for participants who complete 12 weeks of treatment during the DBVC period followed by a 30-day post-treatment safety follow-up visit.
Estimated Duration of Study Participation	Up to approximately 60 weeks, including up to 4 weeks for screening, up to 52 weeks for treatment, and 30 days for safety follow-up.
DMC	No (see Section 5.6)
Coordinating Principal Investigator	To be determined

Treatment Groups and Duration:

Approximately 180 adults with PN (≥ 6 pruriginous lesions [defined as: papules, nodules, plaques, umbilicated lesions, and linear lesions] on ≥ 2 different body areas) will be randomized 1:1 to either ruxolitinib 1.5% cream or vehicle cream. The total estimated BSA treatment area must be ≤ 20%. Treatment area is defined as the area affected by pruriginous lesions plus an ~ 1 cm area surrounding each lesion. During the DBVC period, eligible participants will apply either ruxolitinib 1.5% cream or vehicle cream (both BID) to all pruriginous lesions identified at baseline (including ~ 1 cm area surrounding each lesion). The BID applications should continue through the end of the DBVC period (Week 12) unless the participant meets criteria for stopping study cream.

At Week 12, participants who have completed 12 weeks of treatment with no safety concerns will enter the 40-week OLE period. Affected areas will be treated intermittently based on the presence of pruriginous lesions and/or PN-related itch. The investigator will assess whether the participant requires continuation of therapy (IGA-CPG-S score ≥ 1 and/or the presence of PN-related itching). During the OLE period, all participants will apply ruxolitinib 1.5% cream BID, to PN affected areas only plus an ~ 1 cm area around each pruriginous lesion and/or to areas of PN-related itching.

The safety follow-up period should occur 30 days (+ 7-day visit window) after the Week 52/EOT2 or ET visit (or 30 days after the last application of study cream if the

Week 52/EOT2 or ET visit was not performed). If the participant is in the OLE period and has been in an observation/no-treatment cycle with an IGA-CPG-S score of 0 and a WI-NRS score of 0 for at least 30 days prior to the Week 52/EOT2 visit, then the Week 52/EOT2 visit will also count as the safety follow-up visit.

Figure 1 presents the study design schema, and Table 3 and Table 4 present the SoA. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Figure 1: Study Design Schema

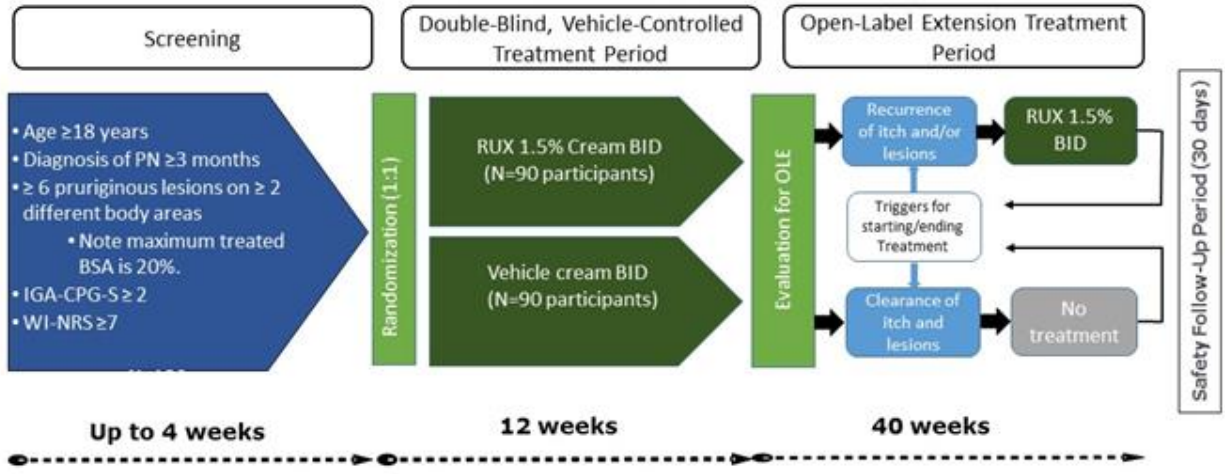


Table 3: Schedule of Activities for the Double-Blind Vehicle-Controlled Period

Visit Day (Range)	Screening	DBVC Period					Notes
	Days −28 to −1	Baseline/Day 1	Week 2 (± 3 d)	Week 4 (± 3 d)	Week 8 (± 3 d)	Week 12/EOT1 (± 3 d)	
Administrative procedures							
Informed consent (including photographic and skin tape ICF, as applicable)	X						Section 8.1.1
Informed consent for optional qualitative [redacted] Note: A subgroup of participants at sponsor-selected sites will be included in a substudy involving [redacted]	X						Section 8.1.6 If consent to provide [redacted] was not obtained at screening, it can be obtained at any visit prior to Week 12.
Contact IRT	X	X	X	X	X	X	Section 8.1.3
Inclusion/exclusion criteria review	X	X					Section 5.1, Section 5.2
Demography and medical history (general and disease, including Fitzpatrick Skin Type)	X						Section 8.1.5
Prior/concomitant medications	X	X	X	X	X	X	Section 6.6
Apply study cream in clinic under site supervision		X				X	Section 6.1
Weigh/dispense study cream		X	X	X	X	X	Section 6.1
Distribute reminder cards	X	X	X	X	X	X	Section 8.1.4
Collect/weigh study cream			X	X	X	X	Section 6.2
Issue eDiary	X						Section 8.1.4, Section 8.3.1
Assess eDiary study cream application compliance		X	X	X	X	X	Section 6.4
Assess eDiary PRO compliance	X	X	X	X	X	X	Section 8.3, Section 8.3.1
Contact participant 1 week prior to each study visit to confirm compliance with WI-NRS assessment		X	X	X	X	X	Section 8.2.1, Section 8.3.1

Table 3: Schedule of Activities for the Double-Blind Vehicle-Controlled Period (Continued)

Visit Day (Range)	Screening	DBVC Period					Notes
	Days −28 to −1	Baseline/Day 1	Week 2 (± 3 d)	Week 4 (± 3 d)	Week 8 (± 3 d)	Week 12/EOT1 (± 3 d)	
Safety assessments							
AE assessments	X	X	X	X	X	X	Section 8.4.1 If an AE is noted, that body system should be physically examined
Comprehensive physical examination	X						Section 8.4.2
Targeted physical examination (as needed based on AEs)		X	X	X	X	X	Section 8.4.2
Height and body weight	X						Section 8.4.2
Vital signs	X	X	X	X	X	X	Section 8.4.3
12-lead ECG	X						Section 8.4.4
Efficacy assessments							
WI-NRS	eDiary is completed each evening from screening through the last application of study cream.						Section 8.2.1
%BSA of estimated treatment area*†	X	X	X	X	X	X	Section 8.2.4 *Total estimated BSA treatment area (excluding the scalp) must be ≤ 20% to be eligible for study entry and continued participation †Treatment area is defined as the area affected by pruriginous lesions plus an ~ 1 cm area surrounding each lesion
IGA-CPG-S	X	X	X	X	X	X	Section 8.2.2.1
IGA-CPG-A	X	X	X	X	X	X	Section 8.2.2.2
PAS	X	X	X	X	X	X	Section 8.2.3
[redacted]		X	X	X	X	X	Section 8.2.5

Table 3: Schedule of Activities for the Double-Blind Vehicle-Controlled Period (Continued)

Visit Day (Range)	Screening	DBVC Period					Notes
	Days −28 to −1	Baseline/Day 1	Week 2 (± 3 d)	Week 4 (± 3 d)	Week 8 (± 3 d)	Week 12/EOT1 (± 3 d)	
Patient-reported outcomes							
Skin Pain NRS	eDiary is completed each evening from screening through the last application of study cream.						Section 8.3.2
DLQI		X	X	X	X	X	Section 8.3.3
EQ-5D-5L		X	X	X	X	X	Section 8.3.9.1
HADS		X	X	X	X	X	Section 8.3.6
[redacted]		X	X	X	X	X	[redacted]
[redacted]			X	X	X	X	[redacted]
FACIT-Fatigue		X	X	X	X	X	Section 8.3.7
PROMIS Sleep		X	X	X	X	X	Section 8.3.8
WPAI		X	X	X	X	X	Section 8.3.9.2
Laboratory assessments							
Chemistry assessments	X	X*				X	Section 8.4.5 *Not necessary if screening assessment is performed within 14 days of Day 1
Hematology assessments	X	X*				X	
FSH	X						Section 8.4.5 Women of nonchildbearing potential only
Serum pregnancy test	X						Section 8.4.5.1 WOCBP only; positive urine test to be confirmed by serum test
Urine pregnancy test		X		X	X	X	
HIV serology	X						Section 8.4.5.2
Hepatitis testing	X						Section 8.4.5.3 Participants who enrolled prior to Protocol Amendment 3 should have hepatitis testing performed at the next scheduled or unscheduled visit.
Thyroid test	X						Section 8.4.5

Table 3: Schedule of Activities for the Double-Blind Vehicle-Controlled Period (Continued)

Visit Day (Range)	Screening	DBVC Period					Notes
	Days −28 to −1	Baseline/Day 1	Week 2 (± 3 d)	Week 4 (± 3 d)	Week 8 (± 3 d)	Week 12/EOT1 (± 3 d)	
PK and translational laboratory assessments							
PK blood			X			X	Section 8.5
Serum for biomarkers		X				X	Section 8.6.1
Skin tapes at selected sites:							Section 8.6.2
Target lesion		X				X	Section 8.6.2.1
Normal skin		X					Section 8.6.2.1

Note: All Week 12 assessments must be completed before the participant can continue into the OLE period. Study cream will not be applied in the clinic at Week 12 for participants not continuing into the OLE period.
Note: Patient-reported outcomes (with the exception of the WI-NRS and Skin Pain NRS) must be conducted before any other assessments.
Note: Blood draw for clinical laboratory tests must be performed before the in-clinic study cream application.
Note: Pharmacokinetic assessments must be performed before study cream application.

Table 4: Schedule of Activities for the Open-Label Extension Period

Visit Day (Range)	OLE Period					Safety Follow-Up	Notes
	Week 14 (± 3 d)	Week 16, 20, 24 (± 3 d)	Week 28, 32, 36 (± 3 d)	Week 40, 44, 48 (± 3 d)	Week 52/EOT2, ET (± 3 d)	30 Days (+ 7 d) After Last Dose	
Administrative procedures							
Contact IRT	X	X	X	X	X		Section 8.1.3
Prior/concomitant medications	X	X	X	X	X	X	Section 6.6
Weigh/dispense study cream	X	X	X	X			Section 6.1
Distribute reminder cards	X	X	X	X	X		Section 8.1.4
Collect/weigh study cream	X	X	X	X	X		Section 6.2
Assess eDiary study cream application compliance	X	X	X	X	X		Section 6.4
Assess eDiary PRO compliance	X	X	X	X	X		Section 8.3, Section 8.3.1
Contact participant 1 week prior to each study visit to confirm compliance with WI-NRS assessment	X	X	X	X	X		Section 8.2.1, Section 8.3.1
Safety assessments							
AE assessments*	X	X	X	X	X	X	Section 8.4.1 *If an AE is noted, that body system should be physically examined
Comprehensive physical examination						X	Section 8.4.2
Targeted physical examination (as needed; based on AEs)	X	X	X	X	X	X	Section 8.4.2
Vital signs	X	X	X	X	X	X	Section 8.4.3

Table 4: Schedule of Activities for the Open-Label Extension Period (Continued)

Visit Day (Range)	OLE Period					Safety Follow-Up	Notes
	Week 14 (± 3 d)	Week 16, 20, 24 (± 3 d)	Week 28, 32, 36 (± 3 d)	Week 40, 44, 48 (± 3 d)	Week 52/EOT2, ET (± 3 d)	30 Days (+ 7 d) After Last Dose	
Efficacy assessments							
WI-NRS	eDiary is completed each evening from screening through the last application of study cream.						Section 8.2.1
%BSA of treatment area*	X	X	X	X	X	X	Section 8.2.4 Total estimated BSA treatment area (excluding the scalp) must be ≤ 20% for continued participation *Treatment area is defined as the area affected by pruriginous lesions plus an ~ 1 cm area surrounding each lesion
IGA-CPG-S	X	X	X	X	X	X	Section 8.2.2.1
IGA-CPG-A	X	X	X	X	X	X	Section 8.2.2.2
PAS	X	X	X	X	X	X	Section 8.2.3
[redacted]	X	X*	X†	X‡	X		Section 8.2.5 *Week 20 only †Weeks 28 and 36 only ‡Week 44 only
Patient-reported outcomes							
Skin Pain NRS	eDiary is completed each evening from screening through the last application of study cream.						Section 8.3.2
DLQI	X	X	X	X	X	X	Section 8.3.3
EQ-5D-5L	X	X	X	X	X		Section 8.3.9.1
HADS	X	X	X	X	X	X	Section 8.3.6
[redacted]	X	X	X	X	X	X	[redacted]
	X	X	X	X	X	X	
FACIT-Fatigue	X	X	X	X	X	X	Section 8.3.7
PROMIS Sleep	X	X	X	X	X	X	Section 8.3.8
WPAI	X	X	X	X	X	X	Section 8.3.9.2

Table 4: Schedule of Activities for the Open-Label Extension Period (Continued)

Visit Day (Range)	OLE Period					Safety Follow-Up	Notes
	Week 14 (± 3 d)	Week 16, 20, 24 (± 3 d)	Week 28, 32, 36 (± 3 d)	Week 40, 44, 48 (± 3 d)	Week 52/EOT2, ET (± 3 d)	30 Days (+ 7 d) After Last Dose	
Laboratory assessments							
Chemistry assessments		X			X	X	Section 8.4.5
Hematology assessments		X			X	X	Section 8.4.5
Urine pregnancy test	X	X	X	X	X	X	Section 8.4.5.1 WOCBP only; positive urine test to be confirmed by serum test
PK assessments							
PK blood					X		Section 8.5

Note: Participants who withdraw from the study early should complete the ET and safety follow-up visits.
Note: Patient-reported outcomes must be conducted before any other assessments.
Note: For participants in the OLE period who have been in an observation/no-treatment cycle with an IGA-CPG-S score of 0 and a WI-NRS score of 0 for at least 30 days prior to the Week 52/EOT2 visit, then the Week 52/EOT2 visit will also count as the safety follow-up visit.

2. INTRODUCTION

2.1. Background

2.1.1. Ruxolitinib Cream

Ruxolitinib cream is a topical formulation of ruxolitinib phosphate under development for a variety of dermatological conditions. Ruxolitinib (1.5%) cream is approved by the US FDA 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. More recently, ruxolitinib has been approved for the topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older (Opzelura™ 2022). Ruxolitinib phosphate is an inhibitor of the JAK family of protein TYKs. Inflammatory cytokines are strongly implicated in the pathogenesis of a number of inflammatory dermatoses. Because JAKs serve to translate extracellular signals from a number of relevant cytokines and growth factors upregulated in these inflammatory diseases, JAK inhibitors represent potential therapeutic agents for these disease states (Chapman et al 2022).

2.1.2. Prurigo Nodularis

Prurigo nodularis is a chronic inflammatory skin disorder characterized by symmetrically distributed severely pruritic nodules most commonly found on the extensor surface of the arms and legs and on the trunk (Huang et al 2020b). Typically, the upper back is spared, as this is an area that patients cannot reach (Watsky 2021). Prurigo nodularis presents as firm, dome-shaped, itchy nodules (also referred to as lesions) ranging in size from a few millimeters to several centimeters with pruritus lasting ≥ 6 weeks and signs of repeated scratching, picking, or rubbing (Pereira et al 2018). In addition to pruritus, patients may experience burning, stinging, and pain sensation (Elmariah et al 2021). The exact pathogenesis of PN remains unknown; however, there is evidence of a significant interaction and dysregulation between immune cells (eg, T cells, mast cells, and eosinophilic granulocytes; Almeida et al 2004, Zeidler et al 2018) and nerve fibers leading to a cutaneous reaction pattern causing endless cycles of chronic itch followed by repeated scratching (Kwatra 2020). The itch generally precedes the nodules, and in a subset of patients with chronic pruritus, PN occurs as a result of continuous scratching.

Kwatra (2022) describes classic PN as a unique inflammatory skin disease. Transcriptomic studies have supported this by finding that PN has a unique transcriptome compared with both psoriasis and AD, with dysregulation of cutaneous fibroproliferative and neurovascular function (Kwatra 2022, Sutaria et al 2022). The exact incidence and prevalence of PN are not known; however, based on insurance claims data, PN has an estimated prevalence of 72 per 100,000 among 18- to 64-year-old people in the United States (Huang et al 2020b). In England, a retrospective data analysis gathered from the English National Health Service showed an estimated prevalence of 3.27 per 10,000, equating to 18,471 patients living with PN in 2018 (Morgan et al 2022). Reports vary on whether it is more prevalent in women versus men (Huang et al 2020b) or occurs equally in men and women (Elmariah et al 2021, Pereira et al 2018). An epidemiologic study of 7095 patients with PN in the United States showed that older adults (mean age, 50.9 years) are affected by the disease with a slightly higher diagnosis in women

(53.1%) versus men (46.9%; Huang et al 2020b). Furthermore, Black patients are substantially more likely to have PN than White patients (McColl et al 2021). In particular, 1 study found that African American patients were 3.4 times more likely to have PN than White patients (Boozalis et al 2018).

Prurigo nodularis has substantial negative effects on quality of life (Kwatra 2020) and is associated with sleep disturbance, impact on job performance, and avoidance of social activities (Todberg et al 2020). In addition, the burden of systemic comorbidities in PN often exceeds that of other inflammatory skin disorders (ie, AD or psoriasis). Prurigo nodularis is associated with increased rates of mental health (specifically anxiety and depression) and endocrine, cardiovascular, and renal disorders as well as HIV and malignancy (Dazzi et al 2011, Huang et al 2020a, Kowalski et al 2019). Approximately half of all patients with PN report a history of AD (Iking et al 2013).

In SEP 2022, Dupixent® was approved by the FDA for the treatment of adult patients with PN (Dupixent 2022). The overall goal in treating PN, topically or systemically, is to stop the itch-scratch cycle and reduce the pruritus to allow flattening of the skin nodules/lesions. Current therapies focus on targeting the immunological and/or the neural mechanism of the disease (Williams et al 2021). Based on clinical experience and small observational studies, superpotent topical corticosteroids (eg, clobetasol) and intralesional steroids (eg, triamcinolone) are considered first-line therapy (Williams et al 2020) with some limited success in targeting the itch. Other topical treatments including capsaicin, TCIs (eg, tacrolimus, pimecrolimus), and topical vitamin D analogs (eg, calcipotriol, tacalcitol) are also used for the treatment of PN. Sedating antihistamines (eg, hydroxyzine, diphenhydramine) administered at bedtime may be useful in controlling nocturnal pruritus. Both selective serotonin reuptake inhibitors and tricyclic antidepressants are also used for treatment of chronic pruritus, especially when a component of depression is present (Watsky 2021).

Patients with widespread disease may be given phototherapy (Kowalski et al 2019). Patients with recalcitrant PN may be given systemic treatments including systemic immunosuppressants, thalidomide, lenalidomide, and anticonvulsants (Tsianakas et al 2016). However, long-term use can be associated with potential significant toxicity, and their efficacy in patients with recalcitrant PN has not been established (Elmariah et al 2021, Watsky 2021).

2.2. Study Rationale

Inflammatory cells, including T cells, eosinophils, and mast cells, are increased in patients with PN and secrete neurotrophins that promote neurogenic inflammation (Kwatra 2020, Perez et al 1993). Central to the pathogenesis of PN is a robust inflammatory response and intense itch associated with release of mediators such as IL-31, tryptase, eosinophil cationic protein, histamine, prostaglandins, and neuropeptides (Almeida et al 2004, Zeidler et al 2018).

Although the exact initial pathogenesis or itch trigger in PN remains unknown, there is evidence of Th1 and Th2 cytokine involvement (Watsky 2021). Ruxolitinib cream, a JAK1/JAK2 inhibitor, mediates the production of key proinflammatory cytokines involved in inflammation and transmission of itch at the intracellular level (Kim et al 2020). The role of Th1 and Th2 cytokines in the pathogenesis of PN also has been evaluated by examining the cytokine signatures in the epidermis in 22 cases of PN, using STAT1, STAT3, and STAT6 (Fukushi et al 2011). In 19 of 22 cases, the entire epidermis stained with anti-pSTAT6, a marker for the Th2 cytokines IL-4,

IL-5, and IL-13. Only 8 cases showed scattered staining with anti-pSTAT1, a marker for the Th1 cytokines interferon gamma and IL-27. These findings suggest that Th2 cytokines play a principal role in the pathogenesis of PN (Watsky 2021).

Ruxolitinib cream in 2 Phase 3 studies (INCB 18424-303 and INCB 18424-304) showed anti-inflammatory and rapid antipruritic effects with superior efficacy versus vehicle cream in participants with mild to moderate AD (Papp et al 2021). Given that JAKs and Th1 and/or Th2 cytokines play an important role in PN, ruxolitinib (1.5%) cream may be a good candidate for the treatment of this disease, particularly the itch component.

2.2.1. Scientific Rationale for Study Design

This Phase 3 study will investigate the efficacy and safety of ruxolitinib 1.5% cream BID versus vehicle cream BID in participants with PN (IGA-CPG-S score of ≥ 2, ≥ 6 pruriginous lesions on ≥ 2 different body areas, and PN-related WI-NRS score ≥ 7). The total estimated BSA treatment area must be ≤ 20%. This design will provide a well-controlled assessment of the efficacy of ruxolitinib 1.5% cream in participants with PN while minimizing the treatment duration for participants assigned to vehicle cream. Further, the 40-week OLE period will provide the participants who are initially randomized to vehicle cream the opportunity to receive ruxolitinib 1.5% cream, and it is an adequate duration to assess the safety and efficacy of intermittent dosing with ruxolitinib 1.5% cream.

Based on 2 Phase 3 pivotal studies (INCB 18424-303 and -304) in participants ≥ 12 years of age with mild to moderate AD affecting 1% to 20% BSA (excluding the scalp), ruxolitinib 1.5% cream BID was statistically significantly superior to vehicle cream after 8 weeks of treatment for the primary endpoint, IGA-TS (IGA score of 0 or 1 with ≥ 2-grade improvement from baseline). Furthermore, statistically significant improvement was observed on the key secondary endpoints, including EASI75 and ≥ 4-point improvement in Itch NRS score (Papp et al 2021).

In PN, disease healing is characterized by flattening of the lesions, with the base of the lesions remaining unchanged. A white or colored scar may remain after lesion clearance. In a static assessment of lesions, the stage of elevation or flattening for multiple lesions cannot be compared with previous visits.

Zeidler (2021) reported that for chronic prurigo, the number of lesions is representative of the stage of the disease. The presence of excoriation to the lesion(s) reflect(s) scratching activity, which is an early sign of CPG improvement (ie, the resolution of crusts and erosions from the top of the lesions). Two IGAs were validated to assess the stage (number of lesions) and the scratching activity of chronic prurigo, IGA-CPG stage, and IGA-CPG activity.

2.2.2. Justification for Dose

Study data from the 2 Phase 3 registrational studies (INCB 18424-303 and -304) in participants ≥ 12 years of age with AD supports the selection of the 1.5% BID regimen in this study. Overall, ruxolitinib 1.5% cream was found to be more efficacious than the 0.75% strength, while the safety and tolerability profiles of both treatment regimens were comparable and nondifferentiating. Of note, the Phase 3 efficacy and safety findings were consistent with and confirmatory of the outcomes of the earlier Phase 2 (INCB 18424-206) dose range–finding study. Given these data, and the fact that high potency topical corticosteroids are recommenced

as first line therapy over less potent corticosteroids, ruxolitinib 1.5% cream BID was selected as the treatment regimen for this study.

2.2.3. Justification for Vehicle Control

The comparison to vehicle cream is relevant to better understand the effect of ruxolitinib cream in the treatment of PN. The use of vehicle cream is justified considering: the 12-week duration of the DBVC period; the recent approval of Dupixent by the FDA, which was based on a population with more severe prurigo nodularis (≥ 20 nodular lesions); there are no other approved PN-specific therapies to be used as a comparator; and delaying treatment does not pose excessive harm to patients (Millum and Grady 2013). After the 12-week, vehicle-controlled period, all participants who complete visits (through Week 12) will receive ruxolitinib cream 1.5% for up to 40 weeks in the OLE period.

2.3. Benefit/Risk Assessment

In the Phase 3 AD studies, ruxolitinib 1.5% cream BID rapidly and effectively improved both the signs and symptoms of AD in adults and adolescents. The antipruritic effect of ruxolitinib 1.5% cream BID showed a rapid onset, with evidence of a treatment effect on daily Itch NRS scores as early as Day 1 (ie, within 12 hours after the first application of study cream). The disease course (assessed by IGA scores and %BSA affected by AD at study visits during Weeks 8 through 52) was well-controlled throughout the entirety of the long-term safety period of the study. The treatment effects of ruxolitinib 1.5% cream BID on IGA-TS, EASI75, and Itch NRS score were consistently observed across both adult and adolescent subgroups.

Safety data from the Phase 3 AD studies demonstrated that use of ruxolitinib 1.5% cream BID continuously for 8 weeks followed by prolonged (44 weeks) intermittent use was safe and well-tolerated. The TEAEs were generally Grade 1 or 2 in severity and were most often events of nasopharyngitis and upper respiratory tract infection. Frequencies of these events were within the expected range for the general AD population. There were no meaningful differences in the TEAE profile of ruxolitinib 1.5% cream BID between the adult and adolescent subgroups.

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, which showed that 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 (application site pain, 0.7%; application site pruritus, 0.6%) compared with the vehicle cream treatment group (application site pain, 4.8%; application site pruritus, 2.8%) during the 8-week, vehicle-controlled period, which may be attributable to worsening of the underlying disease in the absence of active cream treatment.

The overall benefit/risk assessment of ruxolitinib 1.5% cream BID favors its use in both adolescent and adult patients with PN affecting areas up to and including 20% BSA.

Furthermore, given that PN has an itch component to the disease, it is likely that participants with PN will benefit from treatment with ruxolitinib cream for itch.

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

3. OBJECTIVES AND ENDPOINTS

Table 5 presents the objectives and endpoints.

Table 5: Objectives and Endpoints

Objectives	Endpoints
Primary	
To demonstrate the efficacy of ruxolitinib 1.5% cream BID in participants with PN.	• WI-NRS4 response at Week 12, defined as achieving a ≥ 4-point improvement (reduction) in WI-NRS score from baseline.
Key Secondary	
To further demonstrate the treatment effects of ruxolitinib 1.5% cream BID in participants with PN.	• WI-NRS4 response at Week 4. • Overall-TS at Week 12, defined as achieving both a WI-NRS4 response and an IGA-CPG-S-TS. (IGA-CPG-S-TS is defined as an IGA-CPG-S score of 0 or 1 with a ≥ 2 grade improvement from baseline) • IGA-CPG-S-TS at Week 12. • WI-NRS4 response on Day 7.
Secondary	
To further demonstrate the treatment effects of ruxolitinib 1.5% cream BID in participants with PN.	• WI-NRS4 response at each postbaseline visit. • Change from baseline in WI-NRS score at each postbaseline visit. • Time to ≥ 2-point improvement from baseline in WI-NRS score. • Time to ≥ 4-point improvement from baseline in WI-NRS score. • Achieving a ≥ 2-point improvement (reduction) in Skin Pain NRS score from baseline. • Change from baseline in Skin Pain NRS score at each postbaseline visit. • IGA-CPG-S-TS at each postbaseline visit. • IGA-CPG-A score of 0 or 1 with at least a 2 grade improvement (reduction) at each postbaseline visit. • Achieving > 75% healed lesions from PAS at each postbaseline visit.

Table 5: Objectives and Endpoints (Continued)

Objectives	Endpoints
To evaluate the effect of ruxolitinib 1.5% cream BID on QOL.	• Change from baseline in DLQI score at each postbaseline visit. • Change from baseline in EQ-5D-5L score at each postbaseline visit.
To evaluate the safety and tolerability of ruxolitinib 1.5% cream BID in participants with PN.	The type, frequency, and severity of AEs, including changes in vital signs and clinical laboratory blood samples.
Exploratory	
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, multicenter, randomized, DBVC, parallel-group study in adults with PN (IGA-CPG-S score of ≥ 2; ≥ 6 pruriginous lesions on ≥ 2 different body areas; and PN-related WI-NRS score ≥ 7). The total estimated BSA treatment area must be ≤ 20%. Treatment area is defined as the area affected by pruriginous lesions plus an ~ 1 cm area surrounding each lesion. Eligible participants will be randomized 1:1 to ruxolitinib 1.5% cream or vehicle cream. Participants will apply either ruxolitinib 1.5% cream or vehicle cream (both BID) through Week 12 to all pruriginous lesions identified at baseline plus an ~ 1 cm surrounding area each lesion.

At Week 12, participants who have completed 12 weeks of treatment with no safety concerns will enter the 40-week OLE period. The investigator will assess whether the participant requires continuation of therapy (IGA-CPG-S score ≥ 1 and/or the presence of PN-related itching). During the OLE period, all participants will apply ruxolitinib 1.5% cream BID to PN affected areas plus an ~ 1 cm area surrounding each pruriginous lesion and/or areas of PN-related itching. After the last application of study cream, participants will be followed for safety; the safety visit will occur at least 30 days after the last application of study cream.

The treatment assignment a participant received during the DBVC period will be blinded to investigators and participants until after all participants have completed treatment or discontinued treatment and completed the safety follow-up period.

Figure 1 presents the study design schema. The SoA for the DBVC and OLE periods are presented in Table 3 and Table 4, respectively.

The COVID-19 global pandemic may present challenges to the normal conduct of this study (including AE and laboratory assessments), requiring the outline of potential mitigation strategies described in Appendix B. Participants do not need to stop treatment in the study to receive a COVID-19 vaccine.

4.2. Overall Study Duration

The study begins when the first participant signs the study ICF. The end of the study is defined as the date of the last visit of the last participant in the study or the last scheduled procedure shown in the SoA for the last participant in the study globally. Estimated total duration of participation for an individual is up to approximately 60 weeks, including up to 4 weeks for screening, up to 52 weeks for treatment, and 30 days for safety follow-up.

4.3. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study site 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. Age ≥ 18 years at the time of signing the ICF.
3. Clinical diagnosis of PN ≥ 3 months before screening.
4. There are ≥ 6 pruriginous lesions on ≥ 2 different body areas (such as right and left leg) at screening and baseline. Note: The total estimated BSA treatment area must be ≤ 20%.
5. IGA-CPG-S score of ≥ 2 at screening and baseline.
6. Baseline PN-related WI-NRS score ≥ 7. Baseline WI-NRS score is defined as the 7-day average of WI-NRS scores before Day 1 (data from a minimum of 4 out of 7 days prior to Day 1 is needed).
7. Removed during Protocol Amendment 2.
8. Willingness to avoid pregnancy or fathering children based on the criteria below.
    a. Male participants with reproductive potential must agree to take appropriate precautions to avoid fathering children from screening through 90 days (a spermatogenesis cycle) after the last application of study cream and must refrain from donating sperm during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    b. Female participants who are WOCBP must have a negative serum pregnancy test at screening and negative urine pregnancy test before the first application of study cream 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 cream and must refrain from donating oocytes during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    c. 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. Acute or chronic pruritus due to a condition other than PN. (Conditions such as: scabies, insect bite, lichen simplex chronicus, psoriasis, acne, folliculitis, habitual picking, lymphomatoid papulosis, chronic actinic dermatitis, dermatitis herpetiformis, sporotrichosis, bullous disease, excoriation syndrome, venous stasis; systemic hematologic disorders [iron-deficiency anemia, polycythemia rubra vera, lymphoma, leukemia]; gastrointestinal disorders [celiac disease, gastric malignancy, obstructive biliary disease; α-1 antitrypsin deficiency]; infections [HIV, hepatitis B and C, mycobacterial]; endocrine disorders [hyperthyroidism]; psychosocial disorders [depression, anxiety], and chronic renal failure.)
2. Total estimated BSA treatment area (excluding the scalp) > 20%.
3. Neuropathic and psychogenic pruritus, such as but not limited to notalgia paresthetica, brachioradial pruritus, small fiber neuropathy, skin picking syndrome, or delusional parasitosis.
4. Active AD lesions (signs and symptoms other than dry skin) within 6 months of screening and baseline.
5. Uncontrolled hypothyroidism or hyperthyroidism at screening as determined by the investigator. Note: If the participant has a history of thyroid disease and is on treatment, the participant must be on a stable thyroid regimen for at least 6 weeks prior to Day 1.
6. Concurrent conditions and history of other diseases:
    a. 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 pruriginous lesions or assessments of efficacy or compromise participant safety.
    b. Immunocompromised (eg, lymphoma, acquired immunodeficiency syndrome, Wiskott-Aldrich syndrome).
    c. Chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before baseline.
    d. Active acute bacterial, fungal, or viral skin infection (eg, herpes simplex, herpes zoster, chickenpox, clinically infected AD, or impetigo) within 1 week before baseline.
    e. Unstable asthma or COPD requiring systemic treatment (such as intravenous steroids) or hospital admission or treatment in the emergency department within 3 months of baseline

       or

       Stable asthma or COPD requiring the dose equivalent of budesonide more than 720 µg/day (2 puffs BID of a 180-µg dose) or fluticasone more than 440 µg/day (2 puffs BID of a 110-µg dose) or other equivalent inhaled corticosteroids.

f. Acute or chronic active HBV or HCV infection (see Section 8.4.5.3). Participants who have recovered or have been successfully treated with no evidence of active HBV or HCV infection and those who are immune due to HBV vaccination can enroll.

g. Any underlying condition known to be associated with the clinical presentation of PN that is not under control (stable) prior to the baseline visit.

7. 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 application of study cream and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data. For example:

   a. Clinically significant or uncontrolled cardiovascular disease, including unstable angina, acute myocardial infarction or stroke within 6 months from Day 1, New York Heart Association Class III or IV congestive heart failure, and arrhythmia requiring therapy or uncontrolled hypertension (blood pressure > 150/90 mmHg) unless approved by the medical monitor/sponsor.

   b. Participants with or a history of malignancy in the 5 years preceding the baseline visit, except for adequately treated, nonmetastatic nonmelanoma skin cancer.

   c. Current and/or history of arterial or venous thrombosis, including deep vein thrombosis and pulmonary embolism.

   d. Current and/or history of active tuberculosis or current and/or history of latent tuberculosis unless adequately treated.

   e. History of severe anemia, severe thrombocytopenia, or severe neutropenia.

8. 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 CKD-EPI 2021 Creatinine Equation).

   d. Positive serology test results at screening for HIV antibody.

   e. Any other clinically significant laboratory result that, in the opinion of the investigator, poses a significant risk to the participant.

9. Use of any of the following treatments within the indicated washout period before the baseline visit:
    a. Five 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. Current treatment or treatment within 30 days or 5 half-lives (whichever is longer) before baseline with another investigational medication or current enrollment in another investigational drug protocol.
    c. Four weeks for any topical or systemic JAK or TYK2 inhibitor (eg, abrocitinib, baricitinib, deucravacitinib, filgotinib, lestaurtinib, pacritinib, ruxolitinib, tofacitinib, or upadacitinib).
    d. Four weeks – systemic or intralesional corticosteroids or adrenocorticotropic hormone analogs, cyclosporine, methotrexate, azathioprine, or other systemic immunosuppressive or immunomodulating agents (eg, mycophenolate or tacrolimus).
    e. Four weeks for opioid antagonists (eg, naloxone and naltrexone).
    f. Four weeks for gabapentin, pregabalin, or thalidomide.
    g. Four weeks for the following:
        – Paroxetine, fluvoxamine, or other SSRIs
        – SNRIs
        – Tricyclic antidepressants
    h. Four weeks – recreational or medicinal use (topical, inhaled, oral, sublingual, or any other route) of cannabis or cannabinoids (eg, THC, CBD).
    i. Two weeks – systemic antibiotics and immunizations with live-attenuated vaccines.

        Note: Live-attenuated vaccines are prohibited during the DBVC period. COVID-19 vaccination is permitted.
    j. Two weeks – sedating antihistamines.
    k. Two weeks or 5 half-lives, whichever is longer – strong systemic CYP3A4 inhibitors.
    l. Two weeks – any topical treatments for PN (other than bland emollients, eg, Aveeno® creams, ointments, sprays, and soap substitutes), such as corticosteroids, calcineurin inhibitors, topical antipruritics (eg, doxepin cream), PDE4 inhibitors, coal tar (shampoo), topical antibiotics, and antibacterial cleansing body wash/soap.
    m. One week – nonsedating antihistamines used for the treatment of PN.
10. Current use of a medication known to cause pruritus.
11. History of treatment failure (as assessed by the investigator through study participant interview) for PN or any inflammatory condition with any systemic or topical JAK inhibitors (eg, abrocitinib, baricitinib, deucravacitinib, filgotinib, lestaurtinib, pacritinib, ruxolitinib, tofacitinib, or upadacitinib).

12. Psoralen and ultraviolet A or ultraviolet B therapy within 4 weeks before baseline

    or

    Ultraviolet light therapy or prolonged exposure to natural or artificial sources of ultraviolet radiation (eg, sunlight or tanning booth) within 2 weeks before baseline and/or intention to have such exposure during the study that is thought by the investigator to potentially impact the participant's PN.
13. Pregnant or lactating, or considering pregnancy during study participation.
14. 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 application schedule and study assessments.
15. Removed during Protocol Amendment 1.
16. Known allergy or reaction to any of the components of the study cream.
17. In the opinion of the investigator, unable or unlikely to comply with the application schedule and study evaluations.
18. Committed to a mental health institution by virtue of an order issued either by the judicial or the administrative authorities.
19. Employees of the sponsor or investigator or otherwise dependents of them.
20. The following participants are excluded in France:
    a. Vulnerable populations according to article L.1121-6 of the French Public Health Code.
    b. Adults under legal protection or who are unable to express their consent per article L.1121-8 of the French Public Health Code.
    c. Individuals not affiliated with the social security system.

5.3. Lifestyle Considerations

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

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

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study treatment. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the result to be in error. Additionally, a participant who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status. Participants who rescreen must reconsent and be assigned a new participant number.

5.5. Replacement of Participants

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).

5.6. Data Monitoring Committee

A DMC or Data Safety Monitoring Board will not be used in this study because the primary objective is to evaluate relief of itch due to PN, which does not involve the treatment any of the following: a life-threatening disease; the reduction of risk of a major adverse health outcome; or a comparison of the rates of mortality or major morbidity. The primary endpoint analysis will be conducted after all participants complete Week 12. The long-term safety of ruxolitinib 1.5% cream was assessed in 2 indications approved by the FDA (Sections 2.2.1 and 2.2.2). In this study, the population is not a medically fragile population and may include elderly participants. The exclusion criteria excludes participants at with any serious illness or medical, physical, or psychiatric condition(s) that, in the investigator's opinion, would pose a significant risk to the participant. For example, elevated risk of death or other serious outcomes. Moreover, this multicenter study is not large (n = 180) and the duration of the study (ie, primary endpoint) is 12 weeks (FDA 2006, EMA 2005).

6. STUDY TREATMENT

6.1. Study Treatments Administered

Ruxolitinib 1.5% cream or matching vehicle cream will be applied as a thin film BID on each pruriginous lesion and the surrounding area of the lesion (~ 1 cm), with applications at least 8 hours apart in the morning and in the evening at least 1 hour before bedtime.

On Day 1 and at Week 12 (if applicable), the participant will apply a thin film of study cream to the treatment area under the supervision of site staff. The treatment area is defined as the area affected by pruriginous lesions plus an ~ 1 cm area surrounding each lesion. During the DBVC period, all other applications of study cream will be applied by the participant to the treatment area identified at baseline. The total BSA treatment area must be ≤ 20%. Participants should not apply the application of study cream at home prior to clinic visits at Week 2, Week 12/EOT1, and Week 52/EOT2 (see Section 8.5).

At the baseline visit, an estimate of the %BSA treatment area will be used by the IRT system to calculate the number of tubes of study cream to be dispensed. All areas identified at baseline should continue to be treated through the end of the DBVC period (Week 12) unless the participant meets criteria for stopping study cream (see Section 6.5.2). If there are new pruriginous lesions to be treated, after consultation with the investigator, study cream should be applied to these lesions in addition to the areas treated at baseline (total BSA treatment area must be ≤ 20%), 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.

During the OLE period starting at the Week 12 visit, pruriginous lesions will be evaluated by the investigator to confirm whether the participant still requires continuation of therapy (ie, IGA-CPG-S score ≥ 1 and/or the presence of itching related to PN). Participants with an IGA-CPG-S score of 0 may continue or restart therapy if there is itch associated with underlying PN, or they can otherwise (re)enter the observation/no-treatment cycle (ie, IGA score of 0 and WI-NRS score of 0). At Week 12, the IRT system will dispense a prespecified number of tubes according to the assessment of total BSA treatment area.

Between OLE study visits, participants will treat all areas identified with pruriginous lesions and/or itch associated with PN (total BSA treatment area must be ≤ 20%). If all signs and symptoms of PN resolve between study visits, the participant will contact the investigator to confirm that study cream applications should be stopped 3 days after the lesions and itch have disappeared. If this 3-day window is during a study visit, and the IGA-CPG-S score is 0 and itch has resolved, as assessed by the investigator, treatment is to be stopped at the study visit.

If a participant has stopped treatment during the OLE period, treatment may be restarted after consultation with the investigator that the participant has an IGA-CPG-S score ≥ 1 and/or the presence of PN-related itching (WI-NRS score > 0). In the event that new pruriginous lesions are outside of the usual location and/or are more widespread than at the prior visit, the participant is required to contact the site for approval. Approval to treat additional areas may occur via telephone or other modes of communication during the OLE period; however, the investigator, at their discretion, may ask the participant to return for an unscheduled visit.

The amount of study cream used per application will be determined by weighing a tube (including the cap) before and after the participant applies study cream to the affected areas at Day 1. 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.

Application instructions will be provided by the site staff, and the participant will record their daily applications in the eDiary. Refer to the Pharmacy Manual for participant instructions for handling study cream.

Table 6 presents the study treatment information.

Table 6: Study Treatment Information

	Ruxolitinib	Vehicle
Mechanism of action	JAK1/2 inhibitor	Not applicable
Dosage formulation	Cream	Cream
Unit dose strength(s)/dosage level(s)	1.5%	Not applicable
Application instructions	DBVC period: Apply a thin film to pruriginous lesions identified at baseline (plus an ~ 1 cm area surrounding each lesion) in the morning and at least 1 hour before bedtime with applications at least 8 hours apart for 12 weeks. OLE period: Apply a thin film to pruriginous lesions (plus an ~ 1 cm area surrounding each lesion) in the morning and at least 1 hour before bedtime with applications at least 8 hours apart as needed for 40 weeks.	
Packaging and labeling	Ruxolitinib or vehicle cream will be provided in a 60-g tube. 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 have been maintained during transit for all study treatments received and any discrepancies are reported and resolved before use of the study treatment.

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

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

- Delivery of study cream to the study site
- Inventory of study cream at the site
- Participant use of the study cream, including tube counts and weight from each supply dispensed
- Return of study cream 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 cream. 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 cream 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 cream according to institutional SOPs. If, however, local procedures do not allow on-site destruction, shipment of the study cream 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 cream is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

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

The COVID-19 global pandemic may present challenges to the normal conduct of this study, requiring the outline of potential mitigation strategies described in Appendix B. Participants do not need to interrupt study cream to receive the COVID-19 vaccine.

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-CPG-S score (2 or ≥ 3), and geographic region (North America or outside of North America), the participant study number; track participant visits; randomize according to the defined parameters; maintain the blinding; and manage study cream inventory. Enrollment for participants with an IGA-CPG-S score of 2 will be up to approximately 20% of the overall study population. Full details will be provided in the IRT Manual.

Participants, investigators, and the sponsor will remain blinded to each participant's treatment assignment throughout 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 Section 9.7; refer to the IRT Manual). The investigator has the right to unblind the study treatment in the case of a medical emergency.

6.4. Study Treatment Compliance

Compliance with all study-related treatments should be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance will be assessed for frequency of application of study cream by reviewing the participants' eDiaries. 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 cream 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 eDiary entries for compliance. Participants will be considered compliant with the treatment regimen if they apply and report at least 80% of the prescribed number of applications during participation in the DBVC period of the study. Participants who are noncompliant during the DBVC and/or OLE periods (if on a treatment cycle) will be reinstructed by the investigator (or designee); the sponsor should be consulted by the investigator for instruction on the proper handling of the participant who fails to comply with study treatment despite re-enforcement.

Study cream accountability will be assessed by documenting the quantities of study cream used between study visits (tube counts and weighing). At the first clinic visit, 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 or modifications allowed (decrease or increase in study cream strength or frequency of application) except for interruption or permanent discontinuation if needed (eg, for management of an AE). Temporary interruption could be due to an AE during the DBVC or OLE period (see Section 6.5.1) or due to IGA-CPG-S score of 0 and no itch related to PN during the OLE period (see Section 6.1).

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

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 cream. In the event that an AE is present at a specific site of study cream 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 cream applications. Additionally, the investigator must obtain approval from the medical monitor before restarting study cream. Participants who experience a recurrence of the initial AEs upon restarting the study cream may need to permanently discontinue treatment with the study cream.

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

Instructions for application interruptions of study cream related to laboratory abnormalities are outlined in Table 7.

Table 7: Guidelines for Interruption of Study Cream for Treatment-Related Adverse Events and Restarting of Study Cream

Adverse Event	Action Taken
Any Grade 3[a] 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 cream, based on clinical judgment in consultation with the medical monitor (whenever possible), taking into account the relatedness of the AE to the study cream 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 cream must be interrupted unless the medical monitor approves continuation. • At the discretion of the investigator, after consultation with the sponsor, study cream application may be restarted once the laboratory abnormalities have resolved or returned to the baseline level.
Any Grade 4[a] 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. • Discontinue study cream permanently if laboratory abnormalities are confirmed, laboratory abnormalities are considered related to study cream, and no alternative cause is found.

[a] Adverse event grades are based on CTCAE v5.0.

6.5.2. Criteria for Permanent Discontinuation of Study Cream

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

- Occurrence of an AE that is related to treatment with the study cream that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.
- Worsening of PN that requires treatment with a prohibited concomitant medication.
- An AE requiring an interruption of study cream for more than 2 weeks.
- Grade 4 laboratory abnormalities deemed related to study cream and confirmed on repeat testing (see Table 7).

See Section 7.1.1 for reasons for discontinuation.

6.6. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. Any prior medication (other than PN medications) received up to 28 days before the first application of study treatment will be recorded in the eCRF. Any prior PN treatments received at least 1 year before the first application of study cream will be recorded, including the reason for stopping the treatment (eg, inadequate response or intolerance or contraindication). All medications received from the first application of study cream through 30 days after the last application of study cream 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 cream 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.

Concomitant medications administered within 30 days after the last application of study cream 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:

- Participants may use/continue to use bland emollients (eg, Aveeno® creams, ointments, sprays, or soap substitutes). Participants may not change or introduce a new emollient within 4 weeks of the baseline visit through the end of the study.

  Note: Emollients should not be used within 4 hours before and 30 minutes after study cream application.

- If sunscreen is needed, a mineral-based sunscreen (such as zinc oxide or titanium oxide–based) with an SPF of at least 30 is preferred and may be used not less than 4 hours before and at least 1 hour after study cream application.
- Participants may use nonsedating, over-the-counter antihistamines except for the treatment of PN.
- 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.

6.6.2. Restricted Medications and Procedures

The use of the following medications and procedures is restricted as specified below:

- Use of any over-the-counter, nonprescription preparations (including vitamins, minerals, and phytotherapeutic, herbal, or plant-derived preparations) within 7 days before the baseline visit through the safety follow-up visit unless deemed acceptable by the investigator.
  - Use of any prescription medication within 7 days before the baseline visit through the safety follow-up visit unless deemed acceptable by the investigator.
  - Use of topical anti-infectives applied to pruriginous lesions to treat concurrent infection should be limited to 5 days or less. Furthermore, the use of topical anti-infectives should not be used for at least 4 hours before and 1 hour after application of study cream.

6.6.3. Prohibited Medications and Procedures

The following are not permitted during the study:

- Any investigational medication other than the study cream.
- Systemic or topical agents for PN (except bland emollients as noted in Section 6.6.1).
- Treatment known to affect the course of PN.
- Any topical or systemic JAK or TYK2 inhibitor other than ruxolitinib cream (eg, ruxolitinib, tofacitinib, baricitinib, filgotinib, lestaurtinib, pacritinib, abrocitinib, brepocitinib).
- Systemic immunosuppressive or immunomodulating biologic drugs (eg, adalimumab, dupilumab, etanercept, infliximab, golimumab, certolizumab, ustekinumab, secukinumab, brodalumab, ixekizumab, risankizumab, guselkumab, bimekizumab, iscalimab, bermekimab, rituximab, anakinra).
- Systemic immunosuppressive or immunomodulating small-molecule drugs (eg, oral, injectable, or intralesional corticosteroids; methotrexate; cyclosporine; dapsone; azathioprine).
- Any opioid antagonist.
- Gabapentin, pregabalin, and thalidomide.
- Paroxetine, fluvoxamine, or other SSRIs.
- SNRIs
- Tricyclic antidepressants.
- Sedating antihistamines.
- Nonsedating antihistamines for the treatment of PN.
- Recreational or medicinal use (topical, inhaled, oral, sublingual or any other route) of cannabis or cannabinoids (eg, THC, CBD).
- Topical corticosteroids, tacrolimus, pimecrolimus, and PDE4 inhibitors (Eucrisa®).
- Systemic corticosteroids, methotrexate, cyclosporine A, azathioprine and biological therapies, or other immunosuppressant agents.
- Phototherapy or tanning beds.
- Immunizations with live-attenuated vaccines during the DBVC period.

  Note: COVID-19 vaccination is permitted.
- Strong systemic CYP3A4 inhibitors.

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:

- 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 solicited from or collected on the participant. Consent may also be partial. Participants may choose to discontinue study treatment and remain in the study to be followed for safety.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Unacceptable toxicity as noted in Section 6.5.2.
- Worsening PN and the need for treatment with a prohibited medication as noted in Section 6.6.3.
- Worsening PN during either the DBVC period or the OLE period, in which the extent of PN to be treated (ie, all areas excluding the scalp plus 1 cm surrounding pruriginous lesion[s]) exceeds 20% BSA.
- If a participant is found after randomization not to have met eligibility criteria at the time of enrollment.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.
- Development of AD lesions.

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

- If, after 2 consecutive study visits and reinforcement of study cream application by site staff, a participant's cream usage exceeds one 60-g tube every 4 days, 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 a participant is noncompliant with study procedures or study cream application in the investigator's opinion, the sponsor should be consulted for instruction on handling the participant.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment prior to the Week 52/EOT2 visit, the ET visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit. If a participant is in the OLE period and has been in an observation/no-treatment cycle with an IGA-CPG-S score of 0 and a WI-NRS score of 0 for at least 30 days prior to the Week 52/EOT2 visit, then the Week 52/EOT2 visit will also count as the safety follow-up visit. These visits are described in Table 3 and Table 4. 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 date recorded.
- The status of the participant should be updated to ET in the IRT.
- Participants must be followed for safety until the time of the follow-up visit or until study cream–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

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

7.2. Participant Withdrawal From the Study

A participant may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. When a participant is withdrawn from the study, the ET visit procedures should be performed; if possible, the safety follow-up visit should also be conducted within 30 days of the last application of study cream.

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 and Table 4 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, and all site-specific changes must be approved by the IRB/IEC and the sponsor or its designee. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF must contain all required elements, including optional samples/procedures (eg, optional biopsy), and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the countries in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that their personal data collected for the study will be used by the sponsor and/or their designee(s) in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must provide consent to the most current version of the ICF during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and the day the participant is randomized 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.

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

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

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of the country's abbreviation, the site ID, and the participant number. Site staff should contact the IRT to obtain the participant ID number during screening. Upon determining that the participant is eligible for randomization, the IRT will be contacted to obtain the treatment assignment. Additionally, the IRT will be contacted at the study visits indicated in Table 3 and Table 4 to update the study cream supply. Additional details will be provided in the IRT Manual.

8.1.4. Distribution of Reminder Cards and/or eDiaries

Participants will be provided with a reminder card at each visit except the safety follow-up visit. The reminder card will indicate the date/time of the next visit and will also remind the participant that they should not apply their application of study cream before the Week 2, Week 12/EOT1, and Week 52/EOT2 visits. Study cream will be applied after blood draws for PK and safety assessments have been completed on Week 2 and Week 12 (see Section 8.5).

Participants will be instructed on the use of the eDiary at screening. The date and time of the last application of study cream preceding each PK sample collection visit (Week 2, Week 12/EOT1, and Week 52/EOT2/ET) will be recorded in the eDiary. Daily study cream application will be recorded in the eDiary and verified by the study investigator/designee at study visits as shown in Table 3 and Table 4.

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, Fitzpatrick Skin Type, medical and surgical history, history of atopy (eg, AD, allergic rhinitis/rhinoconjunctivitis, asthma, or food allergy), and current illnesses. Medical history will include relevant medical and surgical treatments considered to be clinically significant by the investigator.

As race and/or ethnicity data are not to be analyzed from a scientific or medical perspective, but rather are to be reported in a descriptive format only in the CSR, data on race and/or ethnicity

from France (or other countries as per local law) must not be collected as per GDPR and local data protection law and requirements.

8.1.5.2. Disease Characteristics and Treatment History

A PN-targeted medical and treatment history will be collected at screening. Details regarding the participant's PN, including date of diagnosis, relevant disease characteristics, and prior treatments with outcome (eg, inadequate response), and the reason for stopping treatments, including systemic treatments, surgical procedures, and phototherapy, will be recorded. A medical or surgical history of other conditions related to PN or relevant to the conduct of this clinical trial will also be collected at screening.

In addition, information about prescription PN treatments (eg, name, start/end dates, regimen) used within 12 months prior to screening, and the reason for discontinuation (eg, inadequate response, intolerance) will be collected.

Acceptable documentation for the use of prescription treatments (within 12 months prior to screening) include any of the following:

- Medical records
- Communication with the participant's treating physician
- Investigator documentation based on any of the following:
  - An interview with the participant or legal representative
  - Review of participant- or legal representative–reported medication history.

[redacted]

8.2. Efficacy Assessments

8.2.1. Worst-Itch Numeric Rating Scale

The WI-NRS is a PRO comprised of a single item rated on a scale from 0 ("No itch") to 10 ("Worst imaginable itch"). Each evening beginning on the day of screening through Week 52 or ET, the participant will assess their worst level of PN-related itch during the past 24 hours on a scale of 0 to 10 in an eDiary (see Section 8.3.1).

An average of the 7-day WI-NRS scores, 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. The study staff should contact the participant 1 week prior to each visit to confirm the participant's compliance with completion of the WI-NRS assessment.

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

8.2.2. Investigator's Global Assessment

The severity and the activity of PN will be assessed via the IGA-CPG-S and the IGA-CPG-A, respectively.

8.2.2.1. Investigator Global Assessment for Stage of Chronic Prurigo (IGA-CPG-S)

The IGA-CPG-S is an overall severity rating on a scale of 0 to 4 (see Table 8).

The IGA-CPG-S will be performed at the visits noted in the SoA (see Table 3 and Table 4).

Table 8: IGA-CPG-S

Score	Category	Description: Stage (IGA-CPG-S)
0	Clear	No lesions (0 lesions)
1	Almost clear	Rare palpable pruriginous lesions (approximately 1-5 lesions)
2	Mild	Few palpable pruriginous lesions (approximately 6-19 lesions)
3	Moderate	Many palpable pruriginous lesions (approximately 20-100 lesions)
4	Severe	Abundant palpable pruriginous lesions (over 100 lesions)

Source: Zeidler et al 2021.

For a participant to be eligible for enrollment, their IGA-CPG-S score must be ≥ 2 at screening and baseline. Note: The total BSA treatment area must be ≤ 20%. The IGA-CPG-S-TS is defined as an IGA-CPG-S score of 0 or 1 with ≥ 2 grade improvement from baseline.

8.2.2.2. Investigator Global Assessment for Activity of Chronic Prurigo (IGA-CPG-A)

The IGA-CPG-A is an overall severity rating on a scale of 0 to 4 (see Table 9). The IGA will be performed at the visits noted in the SoA (see Table 3 and Table 4).

Table 9: IGA-CPG Activity

Score	Category	Description: Activity (IGA-CPG A)
0	Clear	No pruriginous lesions have excoriations or crusts
1	Almost clear	Very small proportion of pruriginous lesions have excoriations or crusts (up to approximately 10% of all pruriginous lesions)
2	Mild	Minority of pruriginous lesions have excoriations or crusts (approximately 11-25% of all pruriginous lesions)
3	Moderate	Many pruriginous lesions have excoriations or crusts (approximately 26-75% of all pruriginous lesions)
4	Severe	Majority of pruriginous lesions have excoriations or crusts (approximately 76-100% of all pruriginous lesions)

Source: Zeidler et al 2021.

8.2.3. Prurigo Activity Score

The extent and severity of PN will also be assessed via the PAS (v1.2) and will be determined at the visits noted in the SoA (see Table 3 and Table 4). The first 3 items are descriptive of the type, predominant type, distribution, and quantity of pruriginous lesions. The remaining 2 items of the PAS will assess disease activity in terms of percentage (ie, 0%, 1%-25%, 26%-50%, 51%-75%, 76%-100%) of pruriginous lesions with excoriations/crusts on top (to reflect active scratching), and the percentage (100%, 76%-99%, 51%-75%, 26%-50%, 0%-25%) of healed pruriginous lesions, in order to quantify change of PN skin lesions. In addition, the total number of pruriginous lesions in a representative area will be identified at screening and followed throughout the study.

8.2.4. Body Surface Area

Total estimation of the %BSA treatment area will be used to determine the number of tubes of study cream dispensed at each visit (see Section 6.1). Treatment area is defined as the area affected by pruriginous lesions plus an ~ 1 cm area surrounding each lesion. Total %BSA treatment area will be estimated at each visit as outlined in the SoA (see Table 3 and Table 4). Body surface area assessment will be approximated to the nearest 0.1% using the Palmar Method as a guide. The Palmar Method is the palm plus 5 digits, with fingers tucked together and thumb tucked to the side (handprint), which is considered as 1% BSA and, the thumb, as 0.1% BSA, respectively.

8.3. Patient-Reported Outcomes

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.

8.3.1. Electronic Diary Assessments: Worse-Itch Numeric Rating Scale and Skin Pain Numeric Rating Scale

Participants will either bring and use their own device or be issued a handheld device (eDiary) at the screening visit. Each participant will be instructed to complete the eDiary each evening beginning on the day of screening through Week 52 or treatment discontinuation. Compliance with the eDiary is calculated electronically in real time via the vendor portal. If the participant is frequently not completing the eDiary, the site staff will be informed so compliance can be addressed in a timely manner. Note: Completion of the WI-NRS a minimum of 4 out of 7 days before study visits is required for the analysis.

Study sites will contact participants 1 week before the baseline visit to confirm compliance with eDiary assessments to ensure information is available to allow randomization if appropriate. The WI-NRS is depicted Section 8.2.1.

8.3.2. Skin Pain Numeric Rating Scale

Each evening, the participant will assess their worst level of PN-related skin pain during the past 24 hours on a scale of 0 to 10.

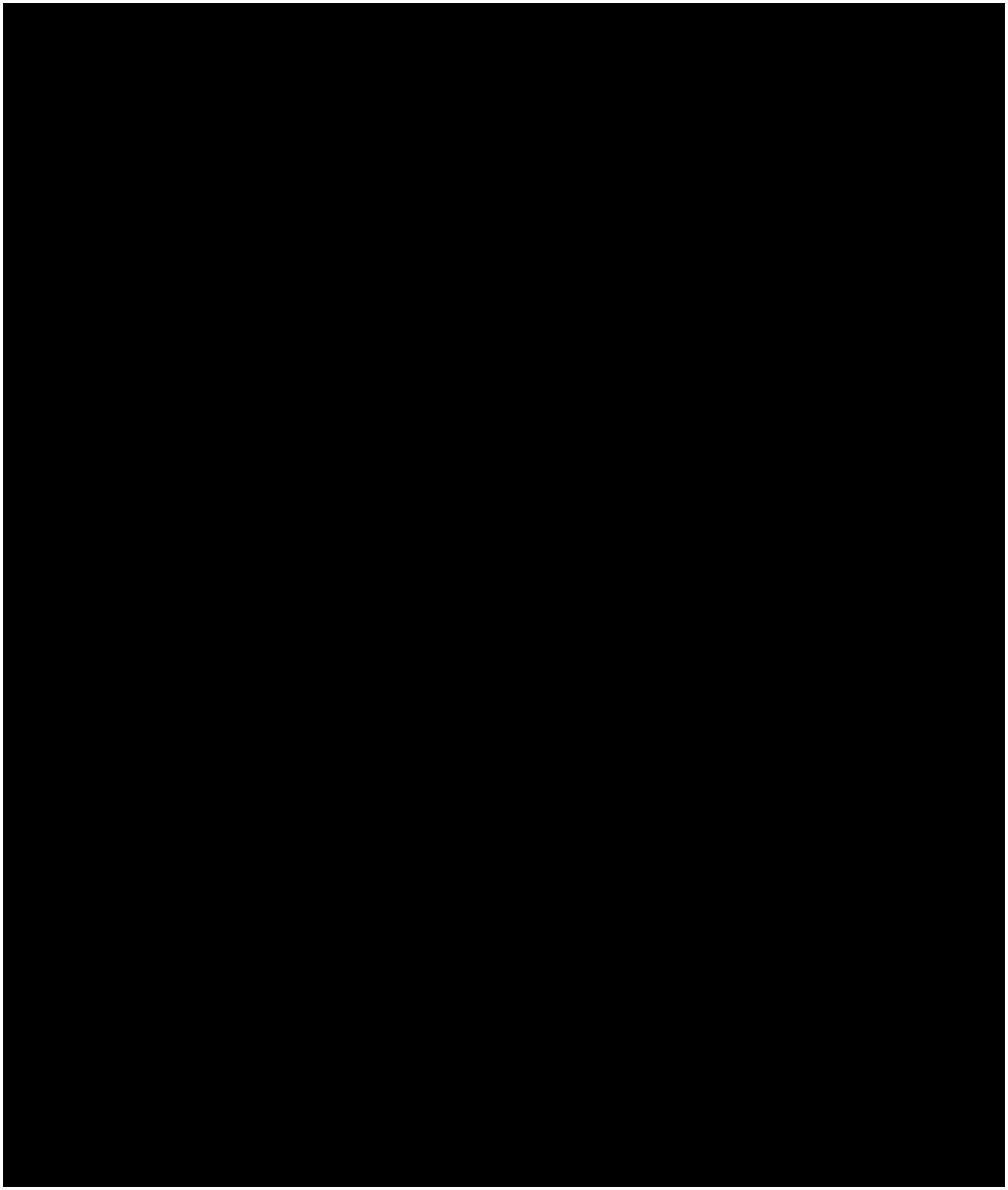
8.3.3. Dermatology Life Quality Index

The DLQI is a simple, 10-question validated questionnaire to measure how much the skin problem has affected the participant over the previous 7 days and will be completed as outlined in the SoA (see Table 3 and Table 4; Finlay and Khan 1994). The participant will answer the questionnaire as follows: (1) very much, (2) a lot, (3) a little, or (4) not at all.

The questionnaire is analyzed under 6 headings as follows:

- Symptoms and feelings (Questions 1 and 2)
- Daily activities (Questions 3 and 4)
- Leisure (Questions 5 and 6)
- Work and school (Question 7)
- Personal relations (Questions 8 and 9)
- Treatment (Question 10)

Overall scoring ranges from 0 to 30, with a high score indicative of poor HRQoL.



[redacted]

8.3.9. Health Economics

8.3.9.1. EQ-5D-5L

Participants will complete the EQ-5D-5L questionnaire at the designated study visits listed in the SoA (see Table 3 and Table 4). The EQ-5D-5L questionnaire is a standardized, validated instrument for use as a measure of health outcome (Herdman et al 2011). The EQ-5D-5L questionnaire will provide data for use in economic models and analyses, including developing health utilities or QALYs. The EQ-5D-5L questionnaire consists of the following 2 sections: the EQ-5D descriptive system and the EQ VAS. The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

Each dimension has 5 levels: Level 1 = no problems, Level 2 = slight problems, Level 3 = moderate problems, Level 4 = severe problems, and Level 5 = extreme problems. This part of the EQ-5D-5L questionnaire provides a descriptive profile that can be used to generate a health state profile. For example, a participant in "health state 12345" would have no problems with mobility, slight problems with self-care (washing or dressing), moderate problems with doing usual activities, severe pain or discomfort, and extreme anxiety or depression. Each health state can potentially be assigned a summary index score based on societal preference weights for the health state. These weights, sometimes referred to as utilities, are often used to compute QALYs for use in health economic analyses. Health state index scores generally range from < 0 (where 0 is the value of a health state equivalent to dead; negative values represent values as worse than dead) to 1 (the value of full health), with higher scores indicating higher health utility. The health state preferences often represent national or regional values and can therefore differ between countries/regions. The EQ VAS records the participant's self-rated health on a vertical VAS (0-100), where the endpoints are labeled "the best health you can imagine" (100 score) and "the worst health you can imagine" (0 score).

[redacted]

8.4. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA in Table 3 and Table 4. See Section 6.5 for guidelines regarding the management of relevant laboratory or other safety assessment abnormalities.

8.4.1. 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 cream. 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 cream. 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 cream/procedures, or that caused the participant to discontinue the study cream. 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 by the investigator immediately without undue delay and not later than 24 hours (or immediately as mandated per local country regulations) of obtaining knowledge of the events. The investigator will also submit any updated SAE data to the sponsor immediately without undue delay and not later than 24 hours of obtaining knowledge of the update.

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).

8.4.2. Physical Examinations

Physical examinations must be performed by a medically qualified individual, such as a licensed physician, a physician assistant, or an advanced practice registered nurse, as local law permits. Abnormalities identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study cream. Investigators should pay special attention to clinical signs related to previous serious illnesses.

At the screening visit, a comprehensive physical examination should be conducted. The comprehensive physical examination will include height and body weight and 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.

During the study, participants will have targeted physical examinations. Participants will be assessed by the investigator or medically qualified designee per institutional standard of care. These assessments should be an evaluation as indicated by participant symptoms, AEs, or other findings and documented on the Adverse Events Form in the eCRF.

8.4.3. Vital Signs

Vital sign measurements (to be taken before blood collection for laboratory tests) will be performed at each study visit and include blood pressure, pulse, respiratory rate, and body temperature. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after 5 minutes of rest.

If vital signs cannot be taken before blood collection for laboratory tests, there must be a minimum of 30 minutes from the completion of the blood collection procedures to the beginning of the vital signs collection. Abnormal vital sign results identified after the first application of study cream constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study cream.

8.4.4. Electrocardiograms

A single 12-lead ECG will be obtained at the screening visit as outlined in the SoA (see Table 3 and Table 4) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. The 12-lead ECG will be performed with the participant in a recumbent or semirecumbent position after 5 minutes of rest. An ECG is acceptable if performed within 2 months of the baseline visit.

The decision to include or exclude a participant or discontinue study treatment based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate. Any safety assessments, including ECGs that are considered clinically significant in the judgment of the investigator, are to be reported as AEs.

8.4.5. Laboratory Assessments

See Table 10 for the list of clinical laboratory tests to be performed, and Table 3 and Table 4 for the timing and frequency. A central laboratory will perform all clinical laboratory assessments

for safety (ie, blood chemistries, hematology assessments). The sponsor or designee will perform all PK and translational sample analyses. 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 study cream should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

Screening laboratory assessments must be performed within 28 days before Day 1. If performed more than 28 days before Day 1, then the test must be repeated and eligibility confirmed before study cream application on Day 1.

Table 10: Required Laboratory Analytes

Chemistry	Hematology	Serology	Pregnancy Testing
Albumin 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	• HIV • HBsAg • HBsAb[a] • HBcAb[a] • HCVAb[b] • HBV DNA (reflex)[a] • HCV RNA (reflex)[b]	• Human chorionic gonadotropin (WOCBP only) • FSH (women of nonchildbearing potential only) • WOCBP require a serum test at screening and a urine pregnancy test at all other visits. A positive urine test will be confirmed by a serum test. • Pregnancy tests (serum or urine) should be repeated if required by local regulations. **Thyroid Function Markers** • Thyroid-stimulating hormone • Free thyroxine

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] If either HBsAb or HBcAb is positive, a reflexive HBV DNA must be obtained (see Section 8.4.5.3.1).
[b] If HCVAb is positive, a reflexive HCV RNA must be obtained (see Section 8.4.5.3.2).

8.4.5.1. Pregnancy Testing

A serum pregnancy test will be required for all WOCBP during screening. Urine pregnancy tests will be performed locally as outlined in Table 3 and Table 4, as medically indicated (eg, in case of loss of menstrual cycle, when pregnancy is suspected), or per country-specific requirement (note that country-required urine pregnancy testing will be outlined and communicated to investigational sites under separate cover). If a urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test.

If the serum pregnancy test result is negative after a urine test result 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 cream and continue participation in the study.

If a pregnancy is confirmed by a serum pregnancy test result, see Section 9.8 for reporting requirements.

8.4.5.2. HIV Testing

HIV screening assessments will be performed at the screening visit to rule out HIV infection (see Table 10). Generally, HIV tests should be performed early in the screening process due to the length of time needed to obtain the results. Additional tests may be performed if clinically indicated.

8.4.5.3. Hepatitis Testing

All participants will be tested for the presence of HBV and HCV at screening. Participants enrolled prior to Protocol Amendment 3 should have hepatitis testing performed at the next scheduled or unscheduled visit.

8.4.5.3.1. Hepatitis B Virus

Participants must undergo HBV testing at screening. This includes testing for HBsAg, HBcAb, and HBsAb with reflex HBV DNA testing.

A diagram is shown in Table 11 with further explanation below.

Table 11: Interpretation and Management of HBV Serologic Test Results

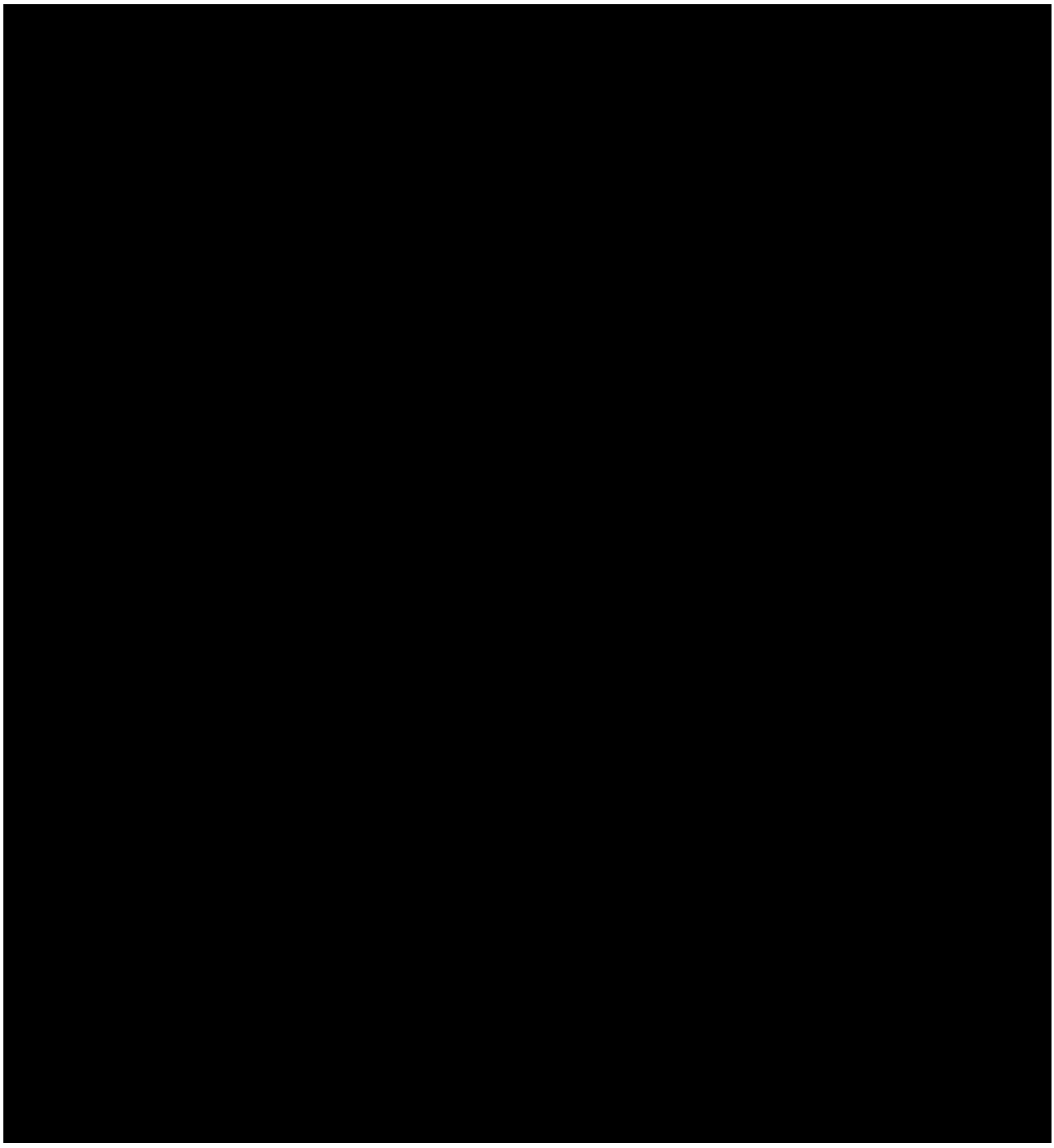
Scenario	HBsAg	HBcAb	HBsAb	Status
A	Positive or indeterminate	Negative or positive	Negative or positive	Not eligible
B	Negative	Negative	Negative	Eligible
C	Negative	Negative	Positive	**HBV DNA PCR required** Positive results: not eligible Negative results: eligible
D	Negative	Positive	Positive	
E	Negative	Positive	Negative	

For participants in Scenarios C, D, and E:

- If the HBV DNA PCR test is negative, the participant is eligible and may be randomized.
- If the HBV DNA PCR test is positive, the participant is **not** eligible and will be screen failed.
- In the event the HBV DNA PCR test cannot be performed, the participant is **not** eligible and will be screen failed.

8.4.5.3.2. Hepatitis C Virus

Blood samples for HCV testing will be obtained at the screening visit. Participants with negative HCVAb are eligible. A positive HCVAb will trigger an HCV RNA test (reflex test). A participant will not be eligible and will be screen failed if test results indicate active hepatitis C (HCV RNA detectable in any participant with positive HCVAb). Participants who test positive for HCV but are successfully treated for HCV infection and have their screening visit at least 12 weeks after the last dose of HCV therapy may be eligible if HCV RNA is undetectable.



8.7. Unscheduled Visits

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

8.8. End of Treatment and/or Early Termination

The EOT1 coincides with the Week 12 visit and EOT2 with the Week 52 visit. A participant who completes the study through the Week 52/EOT2 visit will have reached the EOT with study cream.

If a decision is made that the participant will permanently discontinue study cream prior to the Week 12/EOT1 visit, then the ET1 visit should be conducted. If a participant completed the Week 12/EOT1 visit and permanently discontinues study cream prior to the Week 52/EOT2 visit, then the ET2 visit should be conducted. If the ET1 or ET2 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 ET1 or ET2 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.

8.9. Follow-Up

8.9.1. Safety Follow-Up

The safety follow-up period is the interval between the Week 52/EOT2 visit or ET visit and the scheduled follow-up visit, which should occur 30 (+ 7) days after the Week 52/EOT2 visit or ET visit, with the following 2 exceptions:

- If the Week 52/EOT2 visit or ET visit was not performed, the follow-up visit should occur 30 days after the last application of study cream.
- If the participant is in the OLE period and has been in an observation/no-treatment cycle with an IGA-CPG-S score of 0 and a WI-NRS score of 0 for at least 30 days prior to the Week 52/EOT2 visit, then the Week 52/EOT2 visit will also count as the safety follow-up visit.

During this period, new AEs and SAEs must be reported up to 30 days after the last application of study cream. All AEs and SAEs must be followed until resolution, return to baseline, stabilization, the event is otherwise explained, or the participant is lost to follow-up, whichever is longest. Reasonable efforts (eg, at least 2 documented attempts) should be made to have the participant return for the follow-up visit.

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 cream.
Additional Guidance for Events Meeting the Adverse Event Definition
• Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease) are to be reported as an AE. • Abnormal laboratory test results are to be reported as an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study cream. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal laboratory test result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition/disease, including either an increase in the frequency and/or intensity of the condition, is to be reported as an AE. • New conditions detected or diagnosed after the start of study cream application 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 application errors of a study cream (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. • A condition that leads to a medical or surgical procedure (eg, endoscopy, appendectomy) will be reported as an AE if it occurs after obtaining informed consent. If the condition is present before entering the study, then it should be captured as medical history. • Pre-existing diseases or conditions with expected fluctuations in signs or symptoms should be reported as an AE only if the investigator judges the fluctuation to have worsened more than expected during study participation.

9.2. Definition of Serious Adverse Event

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

A serious adverse event is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an adverse drug experience that places the participant, in the opinion of the initial reporter, at immediate risk of death from the adverse experience as it occurs. This does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (involving at least an overnight stay) at the hospital or emergency department for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment or planned surgery (eg, stent replacement, hip surgery) is not considered an SAE. Hospitalization for medical interventions in which no unfavorable medical occurrence occurred (ie, elective procedures or routine medical visits) is not considered an SAE.
d. Results in persistent or significant disability/incapacity The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is an important medical event An important medical event is an event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such events include new invasive or malignant cancers; intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; development of drug dependency or drug abuse; or suspected transmission of an infectious agent via a medicinal product.

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

Adverse Event and Serious Adverse Event Recording

- An AE/SAE that begins or worsens after informed consent is signed should be recorded on the Adverse Events Form in the eCRF. All AEs/SAEs should be reported for enrolled participants, but only SAEs need to be reported for screen failure participants. For enrolled participants, conditions that were present at the time informed consent was given should be recorded on the Medical History Form in the eCRF. For detailed information, refer to the eCRF guidelines.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator (or designee) will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completing the Adverse Events Form in the eCRF.
- There may be rare instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant 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 in the Study Reference Manual or as per SAE completing guidelines.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE/SAE.

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

- The severity grade (CTCAE v5.0 Grade 1 to 5). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study cream: 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 cream as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the Adverse Events Form and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Nondrug 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 cream 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 cream application, 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 cream, 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 (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]) 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 (or immediately as mandated per local country regulations).

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study cream or study procedure[s]), all SAEs occurring after the participant has signed the ICF through the last safety visit or at least 30 days after the last application of study cream 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. *Note: Immediate reporting of SAEs is required in certain countries as per local country regulations.

Investigators are not obligated to actively seek SAE information after the safety follow-up visit or more than 30 days after the last application of study cream. If the investigator learns of any SAE, including death, at any time and they consider the event to be reasonably related to the study cream or study participation, then the investigator must notify the sponsor (or designee) within 24 hours* of becoming aware of the event. *Note: Immediate reporting of SAEs is required in certain countries as per local country regulations.

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 for 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 for the study cream (new occurrence) and is thought to be related to the study cream, 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 cream that this SAE has been reported. Suspected unexpected serious adverse reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study 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. *Note: Immediate reporting of SAEs is required in select countries per local country regulations.
- 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 cream 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 investigator may unblind a participant in the event of a medical emergency. The IRT system has an option to select for "Emergency Code Break" action for a given participant. After entering the study cream 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 personnel performing assessments, or a participant is unblinded, then the participant must discontinue study cream 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 cream 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 cream, the following procedures should be followed in order to ensure safety:

- The study cream must be discontinued immediately (female participants only; see Section 6.5.1 for the maximum permitted duration of study cream interruption).
- 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 cream 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 or Study Reference Manual for further details.

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 cream, derived from safety information collected by the sponsor or its designee, are presented in the IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. Any important new safety information should be discussed with the participant during the study as necessary. If new significant risks are identified, they will be added to the ICF.

9.10. Product Complaints

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

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

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

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

9.11. Treatment of Overdose

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

10. STATISTICS

10.1. Sample Size Determination

Approximately 180 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, which is the proportion of participants with WI-NRS4 response at Week 12. The mechanism of stopping the itch-scratch cycle and reducing the pruritus are similar between PN and AD. Additionally, based on the results from a Phase 2 study in AD of nemolizumab (Silverberg et al 2020), and a Phase 2 study in PN (Galderma 2021) and a Phase 3 study in PN (Galderma 2022) of nemolizumab, the improvement in WI-NRS are not substantially different between AD and PN; therefore, the results from the 2 Phase 3 studies of ruxolitinib cream (INCB 18424-303 and -304) in the treatment of AD are used to build the assumptions of the proportion of participants with WI-NRS4 response, which are 50% for ruxolitinib 1.5% cream BID and 25% for vehicle cream BID. Using a 2-sided alpha of 0.05, the sample size based on the current assumption will have > 90% power to detect a difference between ruxolitinib cream and vehicle cream. In addition, the assumptions and powers for key secondary endpoints are provided in Table 12.

Table 12: Powering for Key Secondary Endpoints

Variables	Response Rates in Ruxolitinib 1.5% BID	Response Rates in Vehicle BID	Power: 1.5% BID vs Vehicle BID
WI-NRS4 response at Week 4	40%	15%	>90%
Overall-TS (WI-NRS4 response and IGA-CPG-S-TS) at Week 12	30%	10%	>90%
IGA-CPG-S-TS at Week 12	40%	20%	80%
WI-NRS4 response on Day 7	30%	10%	>90%

Note: Based on Fisher's exact test, 2-sided α= 0.05.

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 13.

Table 13: Populations for Analysis

Population	Description
ITT	The ITT population incudes all randomized participants.
PP	The PP population includes randomized participants who are considered to be sufficiently compliant with the Protocol.
Safety	The safety population includes all participants who applied at least 1 dose of study cream. Treatment groups for this population will be determined according to the actual treatment the participant received on Day 1.
PK evaluable	The PK evaluable population includes participants who applied ruxolitinib cream at least once and provided at least 1 postbaseline blood sample for PK analysis. The study pharmacokineticist will review data listings of participant application and sample records to identify participants to be excluded from the analysis.
PD evaluable	The PD evaluable population includes participants who applied study cream at least once and provided a baseline PD sample and at least 1 postbaseline PD sample for analysis. The study translational scientist will review data listings of participant application and sample records to identify participants to be excluded from the analysis.
PK/PD evaluable	The PK/PD evaluable population includes all participants who are in both PK evaluable and PD evaluable populations, as well as participants who are PD evaluable while receiving vehicle cream during the DBVC period.

10.3. Level of Significance

The gatekeeping testing strategy for the primary and key secondary analyses will be implemented to control the overall Type I error rate, 2-sided $\alpha = 0.05$. These endpoints will be tested in a fixed sequence at a 2-sided $\alpha = 0.05$ level in the following order:

- WI-NRS4 response at Week 12
- WI-NRS4 response at Week 4
- Overall-TS at Week 12, defined as achieving both WI-NRS4 response and IGA-CPG-S-TS
- IGA-CPG-S-TS at Week 12
- WI-NRS4 response on Day 7

10.4. Statistical Analyses

10.4.1. Primary Analysis

The primary analysis will be based on the ITT population. The baseline WI-NRS score will be determined by averaging the 7 daily NRS scores before Day 1 (Day −7 to Day −1). The by-visit WI-NRS score for postbaseline visits will be determined by averaging the 7 daily NRS scores before the visit day. If 4 or more daily scores are missing (out of the 7), the WI-NRS score at the visit will be set to missing. The proportion of participants with a WI-NRS4 response, defined as achieving a ≥ 4-point improvement in WI-NRS score from baseline to Week 12, will be

summarized by treatment groups. Table 14 presents the summary of the primary endpoint analysis.

Table 14: Summary of Primary Analysis

Parameter	Definition
Treatment	Ruxolitinib 1.5% cream compared with vehicle cream
Population	ITT population
Variable	WI-NRS4 response at Week 12
Population-level summary	WI-NRS4 response rate difference with 95% CI

The primary alternative hypothesis (superiority of active ruxolitinib group 1.5% BID compared with vehicle) will be tested at a 2-sided $\alpha = 0.05$ level using a CMH test stratified by stratification factors IGA-CPG-S score (2 or ≥ 3) and geographic region (North America or outside of North America). The p-value and stratum-adjusted WI-NRS4 response rate difference with 95% CI will be provided. Overall odds ratio will also be provided with 95% CI. Participants with missing Week 12 data for any reason and participants who develop AD lesions will be defined as nonresponders. No rescue therapy is allowed in this study.

Subgroup analysis by baseline characteristics such as geographic region and any underlying condition known to be associated with the clinical presentation of PN will be performed. In addition, the following sensitivity analyses may be performed, and details will be provided in the SAP.

- Longitudinal logistic regression with repeated measures:

  To adjust for the dependence underlying the hierarchical multilevel data structure (visit, participant, and site), a longitudinal logistic regression with repeated measures will be applied. In the model, visits are nested within participants, which are further nested within sites.

  The primary endpoint binary response of the participant at each of the postbaseline scheduled visits up to Week 12 will be included as the dependent variable. Treatment (ruxolitinib 1.5% cream BID and vehicle cream BID), randomization stratification factors, visit, and treatment by visit interaction will be included as fixed effects. Site-level intercept and participant nested in site-level intercept will be included as random effects. The within-participant and within-site errors will be modeled by an unstructured variance-covariance matrix. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom for this model.

- Last observation carried forward:

  For the participants who are missing postbaseline values, the last observed nonmissing postbaseline value will be used to fill in missing values at Week 12. Then a CMH test stratified by the randomization stratification factors will be performed using the imputed dataset.

- Multiple imputation:

  A fully conditional specification method (van Buuren 2007) that assumes the existence of a joint distribution for all variables will be used to impute missing 7-day average WI-NRS scores at each visit. A regression model, including treatment group, stratification factors, baseline WI-NRS score, and WI-NRS scores for each scheduled postbaseline visit, up to Week 12, will be specified for the fully conditional specification method. The imputation will be repeated a number of times to generate corresponding complete data sets, in order to reflect the uncertainty around the true values. After the missing values are imputed, the binary variables will be derived based on the definition. The CMH test similar to that for the primary analysis will be applied to each imputed dataset, and then the results will then be combined for the inference using Rubin's rule.

- Tipping point analysis:

  A tipping point analysis will be conducted to examine the potential effects of missing data. The missing binary response on the primary endpoint in each treatment group will be replaced by a range of values from the most conservative case to the most aggressive case. The most conservative case is that all the missing participants in the ruxolitinib cream group are nonresponders and all the missing participants in the vehicle cream group are responders, while the most aggressive case is the other way around. For each scenario, between-treatment comparisons will be performed using Fisher exact test.

10.4.2. Key Secondary Analysis

Key secondary efficacy analyses will be conducted on the ITT population. If the primary objective is achieved, the statistical comparisons for the key secondary endpoints will be tested in the order specified in Section 10.3.

The key secondary endpoints will be analyzed using the similar method as specified in the primary analysis. Participants with missing WI-NRS scores at Week 4 will be defined as nonresponders for the WI-NRS4 response for that week. Participants missing Week 12 data will be defined as nonresponders for the following endpoints: Overall-TS (both WI-NRS4 response and IGA-CPG-S-TS) at Week 12 and IGA-CPG-S-TS at Week 12.

For WI-NRS4 response on Day 7, missing daily WI-NRS scores from Day 1 to Day 7 will be imputed and analyzed using the similar multiple imputation method as specified in the sensitivity analysis for the primary endpoint.

The summary of key secondary endpoint analyses is provided in Table 15.

Table 15: Summary of Key Secondary Analyses

Parameter	Definition
Treatment	Ruxolitinib 1.5% cream compared with vehicle cream
Population	ITT population
Variable	WI-NRS4 response at Week 4 Overall-TS (WI-NRS4 response and IGA-CPG-S-TS at Week 12) IGA-CPG-S-TS at Week 12 WI-NRS4 response on Day 7
Population-level summary	Overall odds ration with 95% CI

10.4.3. Secondary Analyses

Secondary efficacy analyses will be conducted on the ITT population. For the time to achieve ≥ 2-point or ≥ 4-point improvement from baseline in WI-NRS, a log rank test stratified by randomization stratification factors 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 censoring 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).

All other secondary and exploratory efficacy variables will be summarized using descriptive statistics. For categorical measurements, summary statistics will include sample size, frequency, and percentages. Similar stratified CMH test as specified in the primary and key secondary analysis will be used if applicable. For continuous measurements, summary statistics will include sample size, mean, median, standard deviation, standard error of the mean, minimum, and maximum. Continuous efficacy endpoints, including the actual measurement, change from baseline, and percentage change from baseline, may also be analyzed by the mixed model for repeated measures.

10.4.4. 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 cream. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study cream application. 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 relationship to study cream will be considered treatment-related AEs. If the investigator does not specify the relationship of the AE to study cream, 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

No formal interim analysis is planned in this study. The primary analysis will occur after the primary database lock when all participants have completed the DBVC treatment period. The sponsor will be unblinded, but the investigators and participants will remain blinded to the study treatment after the primary database lock. The final analysis will occur when all participants have completed or withdrawn from the study.

If the p-value for the primary endpoint is deemed insignificant in the primary analysis outlined in Section 10.4.1, the study will be terminated due to a lack of demonstrable efficacy benefits for the participants.

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.
- The investigator will adhere to the Protocol as described in this document and agree 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, or biomarker plans, 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, biomarker data, photographs, eDiary data) or as otherwise specified in the Protocol.

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

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

- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and participant records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all participants.
  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.

11.3. Data Quality Assurance

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

Quality tolerance limits will be predefined in the Integrated Quality Risk 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 (Incyte), for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. Study results will be published in accordance with applicable local and national regulations. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

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

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

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

11.7. 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 or the IRB/IEC. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS AND DEFINITIONS

Definitions

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

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal with 1 of the following:[a]
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Female participants on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal, highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

For male participants of reproductive potential[b]

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

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

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

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

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

For female participants who are WOCBP

The following methods during the Protocol-defined timeframe in Section 5.1 that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods:

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

[a] Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
[b] If the male participant has a partner of childbearing potential, the partner should also use contraceptives.
[c] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.
[d] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method. In this case, 2 methods of contraception should be used.
[e] Contraception methods that in the context of this guidance are considered to have low user dependency.
[f] Vasectomized partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has received medical assessment of the surgical success.

Source: Clinical Trials Facilitation and Coordination Group 2020.

APPENDIX B. COVID-19 PANDEMIC MITIGATION STRATEGIES AND INSTRUCTIONS

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

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

Number of Study Participants

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

Study Visits

Remote Site Visit Guidelines:

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

- In order to minimize participant risk, study visits may be conducted via telemedicine modalities (phone or video calls). At a minimum, a review of AEs, concomitant medications, and study cream 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) may be allowed in 1 of 2 ways:
  - Use of home nursing services (if local acceptable per local regulations).
  - Instruction of the participant to undergo some laboratory tests at a local (nearby) hospital laboratory or facility closer to the participant's residence rather than at the investigational site. In this case, the study physician will provide the participant with the list of parameters to be checked. These tests should be performed at certified laboratories and copies of results provided to the site.

Mandatory On-Site Visits:

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

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

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

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

- Screening
- Day 1 (baseline)
- Week 4, 8, and 12 visits

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

- Week 52 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 cream via shipment to participants.

If the participant cannot attend a visit at the study site, adequate supplies of study cream 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 or 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 study site monitor will continue to employ off-site monitoring practices such as routine communication methods (eg, phone calls, e-mails, or video visits) with the sites to get information on trial progress, participant status, and information on issue resolution. The study monitor may remotely review data entered into the EDC for accuracy and completeness. If allowed by local regulations, remote source data verification may be implemented with agreement of the principal investigator and institution, as applicable.

If the study site monitor cannot be on-site to perform the final study cream 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 cream 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 or couriers).

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] or the costs of local [nearby] laboratory tests).

APPENDIX C. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1	14 NOV 2022
Amendment 2	01 DEC 2022
Amendment 3	14 JUN 2023
Amendment 4	21 FEB 2024

Amendment 4 (21 FEB 2024)

Overall Rationale for the Amendment

The primary purpose of this amendment is to address regulatory requests provided after review by the EU national health authorities.

1. **Section 10.5, Interim Analysis**

   Description of change: Included a provision that the study will be terminated if the primary analysis is deemed insignificant.

   Rationale for change: Health authority request.

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

Amendment 3 (14 JUN 2023)

Overall Rationale for the Amendment

The primary purpose of this amendment is to incorporate feedback from the FDA regarding the addition of hepatitis serology and washout periods for prohibited medications. Additional changes and clarifications are summarized below.

1. **Section 1, Protocol Summary (Table 4: Schedule of Activities for the Open-Label Extension Period); Section 7.1.2, Discontinuation Procedures; Section 8.9.1, Safety Follow-Up**

   Description of change: Clarified that if a participant has not applied study cream for at least 30 days during the OLE period due to a no-treatment cycle, then the Week 52/EOT2 visit will count as the safety follow-up visit.

   Rationale for change: To be consistent with the defined window for the safety follow-up period.

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities for the Double-Blind Vehicle-Controlled Period; Table 4: Schedule of Activities for the Open-Label Extension Period);** [redacted]

   Description of change: Added [redacted] and related endpoints.

   Rationale for change: To assess meaningful change in participant assessment of PN severity.

3. **Section 1, Protocol Summary (Table 3: Schedule of Activities for the Double-Blind Vehicle-Controlled Period); Section 5.2, Exclusion Criteria (Exclusion Criterion 6f); Section 8.4.5, Laboratory Assessments (Table 10: Required Laboratory Analytes); Section 8.4.5.3, Hepatitis Testing; Section 8.4.5.3.1, Hepatitis B Virus; Section 8.4.5.3.2, Hepatitis C Virus**

   Description of change: Added current hepatitis B or C virus infection and associated testing at screening and revised the related exclusion criterion.

   Rationale for change: Health Authority request.

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

   Description of change: Extended the window for exclusion of participants with active AD lesions to within 6 months of screening and baseline.

   Rationale for change: To minimize the potential for participants with active AD flares, which could confound the assessment of PN-related itch.

5. **Section 5.2, Exclusion Criteria (Exclusion Criterion 6g)**

   Description of change: Added exclusion of participants with an uncontrolled, underlying condition associated with PN.

   Rationale for change: Health Authority request.

6. **Section 5.2, Exclusion Criteria (Exclusion Criterion 8c)**

   Description of change: Revised the equation used for estimated glomerular filtration rate from Cockcroft-Gault to CKD-EPI 2021.

   Rationale for change: The CKD-EPI has a higher efficacy than Cockcroft-Gault.

7. **Section 5.2, Exclusion Criteria (Exclusion Criterion 9); Section 6.6.3, Prohibited Medications and Procedures**

   Description of change: Added the following prohibited medications with relevant washout periods: opioid antagonists, gabapentin, pregabalin, thalidomide, SSRIs, SNRIs, tricyclic antidepressants, cannabis, cannabinoids, and nonsedating antihistamines used for the treatment of PN.

   Rationale for change: Health Authority request and to minimize the potential for confounding efficacy assessments.

8. **Section 6.1, Study Treatments Administered; Section 7.1.1, Reasons for Discontinuation; Section 10.4.1, Primary Analysis**

   Description of change: Participants who develop AD lesions cannot treat AD with the study cream. A participant who develops AD lesions during the study must be discontinued from study treatment, will be considered a treatment failure, and will be defined as a nonresponder.

   Rationale for change: Health authority request due to AD possibly confounding efficacy assessments.

9. **Section 6.6.1, Permitted Medications and Procedures**

   Description of change: Clarified that participants may use nonsedating, over-the-counter antihistamines except for the treatment of PN.

   Rationale for change: To minimize the potential for confounding efficacy assessments.

10. **Section 6.6.1, Permitted Medications and Procedures**

    Description of change: Removed sedating antihistamines from the list of permitted medications.

    Rationale for change: Health authority request.

11. **Section 7.1.1, Reasons for Discontinuation**

    Description of change: Added worsening PN as a reason participants must be discontinued from study treatment if the total BSA treatment area exceeds 20%.

    Rationale for change: To be consistent with other sections of the Protocol.

12. **Section 8.1.5.1, Demographics and General Medical History**

    Description of change: Added history of atopy to the medical history collected.

    Rationale for change: To ensure atopic history is captured.

13. **Section 8.1.5.2, Disease Characteristics and Treatment History**

    Description of change: Added the acceptable documentation for prior prescription medications for PN.

    Rationale for change: Clarification of acceptable documentation.

14. [redacted]

15. **Section 10.4.1, Primary Analysis**

    Description of change: Added underlying conditions associated with PN to the subgroup analysis.

    Rationale for change: To minimize the potential for confounding efficacy assessments.

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

Amendment 2 (01 DEC 2022)

Overall Rationale for the Amendment

The primary purpose of this amendment is to remove the requirement for venous access in an untreated area. Additional changes and clarifications are summarized below.

1. **Section 1, Protocol Summary; Section 4.1, Overall Design**

   Description of change: Added pruriginous lesions to the areas for study cream application, and added PN affected areas only to the text for ruxolitinib 1.5% cream BID application during the OLE period.

   Rationale for change: To clarify partial or missing text for study cream application areas.

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities for the Double-Blind Vehicle-Controlled Period)**

   Description of change: Added a reminder card distribution at screening.

   Rationale for change: To inform sites that a reminder card should be issued at the screening visit.

3. **Section 1, Protocol Summary (Table 4: Schedule of Activities for the Open-Label Extension Period)**

   Description of change: Moved the WI-NRS to the efficacy assessments from the PRO assessments in the SoA.

   Rationale for change: To comply with Section 8.2.1.

4. **Section 3, Objectives and Endpoints (Table 5: Objectives and Endpoints)**

   Description of change: Revised the key secondary objective.

   Rationale for change: To be consistent with Table 1.

5. **Section 5.1, Inclusion Criteria (Criterion 7)**

   Description of change: Deleted inclusion criterion for drawing blood for PK from a treated area if no other venous access is available or acceptable.

   Rationale for change: To comply with instruction for blood draw in Protocol Amendment 1.

6. **Section 6.1, Study Treatments Administered**

   Description of change: Added the presence of PN-related itching to when study cream may be restarted, and replaced baseline visit with prior visit as the basis for determining when new lesions are more widespread.

   Rationale for change: To clarify missing text for itching and correct the visit for determination of more widespread new lesions.

7. **Section 6.3, Measures to Minimize Bias: Randomization and Blinding**

   Description of change: Added that during the OLE period, participants and investigators will remain blinded to the treatment assignment during the DBVC period.

   Rationale for change: To clarify that the treatment assignment during the DBVC period will not be unblinded to participants and investigators during the OLE period.

8. **Section 6.6.1, Permitted Medications and Procedures**

   Description of change: Added that mineral-based sunscreens are preferred and updated the timeframe for when participants may not change or introduce a new emollient to be within 4 weeks of the baseline visit through the end of the study.

   Rationale for change: To clarify that mineral-based sunscreens are preferred but not mandatory and that participants may not change an emollient use through the end of the study.

9. **Section 8.4, Pharmacokinetic Assessments**

   Description of change: Updated with IGA-CPG-S score and presence of PN-related itching to the reason for off-treatment participants to restart applying study drug. Clarified the timing details for blood samples that might need to be drawn from a treated area.

   Rationale for change: [redacted]

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

Amendment 1 (14 NOV 2022)

Overall Rationale for the Amendment

The primary purpose of this amendment is to incorporate feedback from the FDA and discussions with clinicians on the primary and key secondary endpoints. Additional changes and clarifications are summarized below.

1. **Title Page, Protocol Title; Section 1, Protocol Summary, Protocol Title; Section 1, Protocol Summary, Objectives and Endpoints, (Table 2: Key Study Design Elements); Section 2.2.1, Scientific Rationale for Study Design; Section 4.1, Overall Design; Section 10.1, Sample Size Determination**

   Description of change: Removed "Phase 2b" design.

   Rationale for change: Company decision to proceed to Phase 3.

2. **Section 1, Protocol Summary, (Table 1: Primary and Secondary Objectives and Endpoints); Section 3, Objectives and Endpoints, (Table 5: Objectives and Endpoints); Section 8.2.2.1: Investigator's Global Assessment for Stage of Chronic Prurigo; Section 10.3: Level of Significance**

   Description of change: Updated objectives and endpoints; updated the definition of IGA treatment success for IGA-CPG-S-TS.

   Rationale for change: Health authority feedback.

3. **Section 1, Protocol Summary, (Table 1: Primary and Key Secondary Objectives and Endpoints); Section 3, Objectives and Endpoints, (Table 5: Objectives and Endpoints); Section 10.1, Sample Size Determination; Section 10.3, Level of Significance; Section 10.4.1, Primary Analysis, (Table 13: Summary of Primary Analysis)**

   Description of change: Replaced ITCH4 terminology with WI-NRS4.

   Rationale for change: To be consistent with PN itch terminology.

4. **Section 1, Protocol Summary, (Table 1: Primary and Key Secondary Objectives and Endpoints), (Table 2: Key Study Design Elements), Treatment Groups and Duration, (Table 3: Schedule of Activities for Double-Blind Vehicle-Controlled Period), (Table 4: Schedule of Activities for the Open-Label Extension Period); Section 2.2.1, Scientific Rationale for Study Design; Section 3, Objectives and Endpoints, (Table 5: Objectives and Endpoints); Section 4.1, Overall Design; Section 5.1, Inclusion Criteria 5; Section 6.1, Study Treatments Administered; Section 6.3, Measures to Minimize Bias: Randomization and Blinding; Section 6.5, Dose Modifications; Section 8.2.2, Investigators Global Assessment; Section 8.2.2.1, Investigator Global Assessment (IGA) for Stage of Chronic Prurigo (CPG) (IGA-CPG-S), (Table 8: IGA-CPG-S); Section 10.1, Sample Size Determination, (Table 11: Powering for Key Secondary Endpoints); Section 10.4, Primary Analysis, (Table 13: Summary of Primary Analysis); Section 10.4.2, Key Secondary Analysis, (Table 14: Summary of Key Secondary Analyses)**

   Description of change: Replaced the IGA scale with the IGA-CPG-S, or added the IGA-CPG-S scale as warranted by updated text.

   Rationale for change: Health authority discussion and clinician feedback on IGA scale.

5. **Section 1, Protocol Summary, (Table 2: Key Study Design Elements); Section 2.2.1, Scientific Rationale for Study Design; Section 4.1, Overall Design; Section 5.1, Inclusion Criteria 5; Section 8.2.2.1, Investigator Global Assessment (IGA) for Stage of Chronic Prurigo (CPG) (IGA-CPG-S)**

   Description of change: Revised the IGA inclusion criteria from 2 or 3 to ≥ 2.

   Rationale for change: To allow inclusion of the participants with numerous lesions in a BSA treatment area of < 20%.

6. **Section 1, Protocol Summary, (Table 2: Key Study Design Elements), Treatment Groups and Duration, (Figure 1: Study Design Schema), (Table 3: Schedule of Activities for Double-Blind Vehicle-Controlled Period); Section 2.2.1, Scientific Rationale for Study Design; Section 3, Objectives and Endpoints, (Table 5: Objectives and Endpoints); Section 4.1, Overall Design; Section 5.1, Inclusion Criteria, 4; Section 5, Exclusion Criteria, 2 and 6; Section 6.1, Study Treatments Administered; Section 6.6.2, Restricted Medications and Procedures; Section 8.2.2.1, Investigator Global Assessment (IGA) for Stage of Chronic Prurigo (CPG) (IGA-CPG-S), (Table 8: IGA-CPG-S); Section 8.2.2.2, Investigator's Global Assessment Investigator Global Assessment (IGA) for Activity of Chronic Prurigo (CPG) (IGA-CPG-A), (Table 9: IGA-CPG-Activity); Section 8.2.3, Prurigo Activity Score; Section 8.2.4, Body Surface Area; Section 8.6, Unscheduled Visits**

   Description of change: Replaced the term "nodules" with pruriginous lesions throughout the Protocol, with the exception of Section 2.1.2. Added descriptor, pruriginous, to describe lesions in order to conform to IGA-CPG-S terminology.

   Rationale for change: Health authority discussion and clinician feedback on IGA scale. The term pruriginous lesion(s) is consistent with the terminology in the IGA-CPG-S. In Section 2.1.2, the term nodule remains as referenced in the applicable publications.

7. **Section 1, Protocol Summary, (Table 2: Key Study Design Elements), Treatment Groups and Duration; Section 2.2.1, Scientific Rationale for Study Design; Section 4.1, Overall Design; Section 5.1, Inclusion Criteria, 4**

   Description of change: Revised the number of nodules for inclusion to ≥ 6 pruriginous lesions with a BSA treatment area ≤ 20%.

   Rationale for change: Revised to be consistent with IGA-CPG-S and to clarify the allowable treatment area (≤ 20% BSA).

8. **Section 1, Protocol Summary, (Table 2: Key Study Design Elements); Section 2.2.1, Scientific Rationale for Study Design; Section 4.1, Overall Design; Section 5.1 Inclusion Criteria, 6**

   Description of change: Revised, or added, the WI-NRS inclusion criteria from ≥ 4 to ≥ 7.

   Rationale for change: Health authority request. The WI-NRS score ≥ 7 is reflective of the severe pruritus that characterizes active PN lesions.

9. **Section 1, Protocol Summary, (Table 2: Key Study Design Elements), Treatment Groups and Duration, (Table 3: Schedule of Activities for Double-Blind Vehicle-Controlled Period), (Table 4: Schedule of Activities for the Open-Label Extension Period); Section 2.2.1, Scientific Rationale for Study Design; Section 4.1, Overall Design; Section 6.1, Study Treatments Administered; Section 8.2.4, Body Surface Area**

   Description of change: Added a definition of total BSA treatment area.

   Rationale for change: To clarify for investigators how to estimate the total %BSA to be treated.

10. **Section 1, Protocol Summary, (Table 2: Key Study Design Elements), Treatment Groups and Duration; Section 10.1, Sample Size Determination**

    Description of change: Reduced the number of participants to 180.

    Rationale for change: Based on revised sample size estimation.

11. **Section 1, Protocol Summary, (Table 2: Key Study Design Elements); Section 2.2.1 Scientific Rationale for Study Design; Section 4.1, Overall Design; Section 5.6, Data Monitoring Committee; Section 10.3 Level of Significance; Section 10.4.1, Primary Analysis; Section 10.5, Interim Analysis**

    Description of change: Removed adaptive design with interim analysis from the study. Updated text with regard to DMC, and removed Section 10.5 text referring to interim analysis.

    Rationale for change: Company decision to move directly to Phase 3.

12. **Section 1, Protocol Summary, Treatment Groups and Duration; Section 2.2.3, Justification for Vehicle Control; Section 4.1, Overall Design; Section 6.1: Study Treatments Administered; Section 6.5: Dose Modifications**

    Description of change: To clarify when the participant requires continuation of therapy in the OLE.

    Rationale for change: To clarify that the continuation of therapy in the OLE is based on the IGA-CPG-S score ≥ 1 and/or the presence of PN-related itching and application instructions.

13. **Section 1, Protocol Summary, (Figure 1: Study Design Schema)**

    Description of change: Updated the study design schema.

    Rationale for change: To reflect the revisions to the inclusion criteria, removal of the interim analysis, and the enrollment number.

14. **Section 1, Protocol Summary, (Table 3: Schedule of Activities for the Double-Blind Vehicle-Controlled Period); Section 8.1.6, [redacted]**

    Description of change: [redacted] added.

    Rationale for change: Health authority request.

15. **Section 1, Protocol Summary, (Table 3: Schedule of Activities for the Double-Blind Vehicle-Controlled Period), (Table 4 Schedule of Activities for the Open-Label Extension Period)**

    Description of change: Removed the requirement for application of study drug under supervision at Week 2, Week 4, Week 8, and Weeks 14 through 52.

    Rationale for change: To ease participant burden during in office visits.

16. **Section 1, Protocol Summary, (Table 3: Schedule of Activities for the Double-Blind Vehicle-Controlled Period), (Table 4: Schedule of Activities for the Open-Label Extension Period); Section 8.2.1, Worse-Itch Numeric Rating Scale**

    Description of change: Added the assessment of eDiary PRO compliance to the SoA.

    Rationale for change: To reinforce compliance with the collection of data for the primary endpoint.

17. **Section 1, Protocol Summary, (Table 3; Schedule of Activities for the Double-Blind Vehicle-Controlled Period), (Table 4: Schedule of Activities for the Open-Label Extension Period); Section 8.2.1, Worse-Itch Numeric Rating Scale**

    Description of change: Added a participant contact 1 week prior to study visits to the SoA.

    Rationale for change: To reinforce compliance with the collection of WI-NRS data for the primary endpoint.

18. **Section 1, Protocol Summary, (Table 3: Schedule of Activities for the Double-Blind Vehicle-Controlled Period), (Table 4: Schedule of Activities for the Open-Label Extension Period); Section 3, Objectives and Endpoints, (Table 5: Objectives and Endpoints); Section 8.2.2.2, Investigator's Global Assessment Investigator Global Assessment (IGA) for Activity of Chronic Prurigo (CPG) (IGA-CPG-A)**

    Description of change: Added the IGA-CPG-A and related secondary endpoint.

    Rationale for change: To include an activity related IGA.

19. **Section 1, Protocol Summary, (Table 3: Schedule of Activities for the Double-Blind Vehicle-Controlled Period); Section 8.5.2, Skin Samples (Skin Tape Discs); Section 8.5.2.1, Target Nodule Identification and Skin Sampling**

    Description of change: Added skin tapes at selected sites.

    Rationale for change: To characterize the biomarkers associated with PN.

20. **Section 1, Protocol Summary, (Table 1: Primary and Key Secondary Objectives and Endpoints); Section 3, Objectives and Endpoints, (Table 5: Objectives and Endpoints); Section 8.2.2.1, Investigator Global Assessment (IGA) for Stage of Chronic Prurigo (CPG) (IGA-CPG-S); Section 8.2.2.2, Investigator's Global Assessment Investigator Global Assessment (IGA) for Activity of Chronic Prurigo (CPG) (IGA-CPG-A); Section 10.1, Sample Size Determination, (Table 11: Powering for Key Secondary Endpoints); Section 10.3, Level of Significance; Section 10.4.2, Key Secondary Analysis, (Table 14: Summary of Key Secondary Analyses)**

    Description of change: Updated the IGA secondary endpoints to include both the IGA-CPG-A and IGA-CPG-S.

    Rationale for change: Updated to reflect the revised IGAs.

21. **Section 1, Protocol Summary, (Table 2: Key Study Design Elements); Section 4.1, Overall Design; Section 5.6, Data Monitoring Committee; Section 10.5, Analysis Plan,**

    Description of change: Removed the external DMC from the study and provided rationale for removal and clarified the primary analysis will occur after DB lock.

    Rationale for change: Interim analysis will no longer be conducted. (The safety database from other ruxolitinib cream studies depict that the extent and duration of exposure is similar, as is the nature of the primary endpoint.)

22. **Section 2.2.1, Ruxolitinib Cream**

    Description of change: Added Opzelura™ FDA approval for the topical treatment of vitiligo.

    Rationale for change: New information following FDA approval for vitiligo.

23. **Section 3, Objectives and Endpoints, (Table 5: Objectives and Endpoints)**

    Description of change: Removed secondary endpoint "IGA score of 0 or 1 at each postbaseline visit."

    Rationale for change: To remove duplicate endpoint.

24. **Section 3, Objectives and Endpoints, (Table 5: Objectives and Endpoints)**

    Description of change: Moved DLQI and EQ-5D-5L from exploratory endpoints to secondary endpoints.

    Rationale for change: Health authority preference.

25. **Section 3, Objectives and Endpoints, (Table 5: Objectives and Endpoints)**

    Description of change: Revised PAS endpoint text to "achieving > 75% healed lesions at each postbaseline visit."

    Rationale for change: Clarification of PAS endpoint analysis.

26. **Section 5.2, Exclusion Criteria, 1**

    Description of change: Added exclusion criteria conditions, with regard to chronic pruritus, to criterion 1.

    Rationale for change: Health authority guidance recommends to exclude other conditions associated with PN clinical presentation to avoid confounding the assessment of the impact of ruxolitinib cream.

27. **Section 5.2, Exclusion Criteria, 5**

    Description of change: Thyroid function was revised to hypo and hyperthyroidism, as was the stable thyroid regimen requirement in criterion 5 (ie, from 3 months to 6 weeks).

    Rationale for change: Six week timeframe is sufficient.

28. **Section 5.2, Exclusion Criteria, 9c and 11**

    Description of change: Added a washout period for JAK or TYK inhibitors to criterion 9c. Clarified that any participant who experienced prior treatment failure (ie, systemic or topical treatment with a JAK inhibitor) for PN, or any inflammatory condition, will be excluded from the study (criterion 11).

    Rationale for change: To allow inclusion of participants with prior JAK or TYK inhibitor treatment, provided they have not failed a prior course of therapy for PN or another inflammatory condition.

29. **Section 5.2, Exclusion Criteria, 15**

    Description of change: Removed exclusion criterion 15 (inadequate venous access).

    Rationale for change: Adequate venous access is already addressed in inclusion criterion 7.

30. **Section 5.2, Exclusion Criteria, 20**

    Description of change: Added exclusion criterion 20 from the French Public Health Code for participants in France.

    Rationale for change: Per local country requirements.

31. **Section 6.3, Measures to Minimize Bias: Randomization and Blinding; Section 10.4.1, Primary Analysis; Section 10.4.3, Secondary Analyses**

    Description of change: Revised the stratification factors.

32. **Rationale for change:** To be consistent with the revised inclusion criteria based on the number of pruriginous lesions.

33. **Section 6.6.2, Restricted Study Medications and Procedures**

    Description of change: Clarified restriction related to use of topical anti-infectives for an infected pruriginous lesion.

    Rationale for change: Short-term (≤ 5 days) use of an anti-infective should not impact the overall efficacy.

34. **Section 8.1.5.1, Demographics and General Medical History**

    Description of change: Added Fitzpatrick Skin Type assessment to the demographic information collected at screening.

    Rationale for change: Fitzpatrick Skin Type may be important in the response to study medication or findings of hypo- or hyperpigmentation following resolution of pruriginous lesions.

35. **Section 8.2.1, Worst-Itch Numeric Rating Scale**

    Description of change: Moved the WI-NRS from Section 8.3, Patient-Reported Outcomes, to Section 8.2, Efficacy Assessments.

    Rationale for change: WI-NRS is the primary efficacy endpoint.

36. **Section 8.2.3, Prurigo Activity Score**

    Description of change: Provided additional information about the PAS assessment.

    Rationale for change: To clarify the information obtained via the PAS tool.

37. **Section 8.2.5,** [redacted]

    Description of change: Replaced [redacted] of arms and legs with upper and lower half of the participant's body.

    Rationale for change: To clarify the photographic images captured.

38. **Section 10.1, Sample Size Determination**

    Description of change: Updated the sample size determination.

    Rationale for change: Revised based on additional data from published studies.

39. **Section 10.4.1, Primary Analysis**

    Description of change: Clarified how the WI-NRS will be determined following the screening and baseline visits. In addition, added multiple imputation section.

    Rationale for change: Health authority request.

40. **Section 10.4.2, Key Secondary Analysis**

    Description of change: Updated the statistical analyses to include the revised and additional key secondary endpoints.

    Rationale for change: Based on additional key secondary endpoints.

41. **Appendix C, Statistical Considerations**

    Description of change: Removed Appendix C.

    Rationale for change: Removal of the interim analysis; decision to move to Phase 3 study.

42. **Section 11.4, Data Privacy and Confidentiality of Study Records**

    Description of change: Revised language with regard to data management and data privacy.

    Rationale for change: For consistency with Incyte's standard language for clinical protocols.

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

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Approval Task	[redacted] Approver [redacted] Inflammation & Autoimmunity 22-Feb-2024 10:04:37 GMT+0000

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