Official Title: An Open-Label, Single-Arm Study to Evaluate the Effect of Ruxolitinib 1.5% Cream **on Itch in Adult Participants With Atopic Dermatitis (SCRATCH-AD)**

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Clinical Study Protocol

INCB 18424-901

An Open-Label, Single-Arm Study to Evaluate the Effect of Ruxolitinib 1.5% Cream on Itch in Adult Participants With Atopic Dermatitis (SCRATCH-AD)

Product:	**Ruxolitinib cream**
IND Number:	[redacted]
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, Delaware, USA 19803**
Original Protocol:	**22 FEB 2021**
Amendment 1:	**30 MAR 2021**
Amendment 2:	**13 AUG 2021**
Amendment 3:	**09 MAY 2022**

INVESTIGATOR'S AGREEMENT

I have read the INCB 18424-901 Protocol Amendment 3 (dated 09 MAY 2022) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

(Printed Name of Investigator)

(Signature of Investigator) (Date)

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AD	atopic dermatitis
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
BID	twice daily
BSA	body surface area
CFR	Code of Federal Regulations
CI	confidence interval
COVID-19	Coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
EASI	Eczema Area and Severity Index
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GFR	glomerular filtration rate
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IGA	Investigator Global Assessment
IGA-TS	Investigator Global Assessment-Treatment Success (IGA score of 0 or 1 with ≥ 2-grade improvement from baseline)
IRB	institutional review board
ITT	intent-to-treat
JAK	Janus kinase
LMW	low molecular weight
MCID	minimal clinically important difference

Abbreviations and Special Terms	Definition
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
mPP-NRS	modified peak pruritus numerical rating scale (current itch intensity)
NRS	numerical rating scale
NSAID	nonsteroidal anti-inflammatory drug
PDE-4	phosphodiesterase-4
PP-NRS	peak pruritus numerical rating scale (24-hour recall period)
PUVA	psoralen plus ultraviolet A
QD	once daily
RNA	ribonucleic acid
[redacted]	[redacted]
RSI	Reference Safety Information
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SoA	schedule of activities
SOP	standard operating procedure
SRM	Study Reference Manual
study drug	Incyte medicinal investigational product used for this study
TEAE	treatment-emergent adverse event
TEWL	transepidermal water loss
TSQM-9	Abbreviated 9-Item Treatment Satisfaction Questionnaire for Medication
ULN	upper limit of normal
WBC	white blood cell
WOCBP	woman of childbearing potential

1. PROTOCOL SUMMARY

Protocol Title: An Open-Label, Single-Arm Study to Evaluate the Effect of Ruxolitinib 1.5% Cream on Itch in Adult Participants With Atopic Dermatitis (SCRATCH-AD)

Protocol Number: INCB 18424-901

Objectives and Endpoints:

Table 1 presents the primary and secondary objectives and endpoints.

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of ruxolitinib 1.5% cream on pruritus in participants with AD.	Change from baseline in PP-NRS at Day 2 (24-hour recall period after first application).
Secondary	
To evaluate the efficacy of ruxolitinib 1.5% cream in participants with AD.	• Change from baseline in mPP-NRS (current itch intensity) at 15 and 30 minutes and 1, 2, 4, 6, and 12 hours postdose on Day 1; and in PP-NRS from Day 3 through Day 29. • Proportion of participants achieving at least a 1-grade decrease from baseline in mPP-NRS at 15 and 30 minutes and 1, 2, 4, 6, and 12 hours postdose on Day 1; and in PP-NRS from Day 2 through Day 29. • Proportion of participants achieving at least a 2-grade decrease from baseline in mPP-NRS at 15 and 30 minutes and 1, 2, 4, 6, and 12 hours postdose on Day 1; and in PP-NRS from Day 2 through Day 29. • Time to MCID (≥ 2-grade reduction in PP-NRS and mPP-NRS from baseline). • Change from baseline in IGA at Day 8, Day 15, and Day 29. • Proportion of participants achieving the IGA-TS (score of 0 or 1 in IGA with at least a 2-grade reduction from baseline) at Day 8, Day 15, and Day 29.
To evaluate the local and systemic safety and tolerability of ruxolitinib 1.5% cream in participants with AD.	Incidence and severity of local and systemic AEs.

Note: For efficacy endpoints related to PP-NRS, baseline is defined as the average of all nonmissing PP-NRS (24-hour recall period) scores reported during the 7-day run-in period. For the other efficacy variables (including the mPP-NRS), baseline is defined as the last nonmissing value before or on Day 1 (prior to first application of study drug).

Overall Design:

Table 2 presents the key study design elements. Further study details are presented after the table.

Table 2: Key Study Design Elements

Study Phase	Phase 2
Clinical Indication	Relief of itch in patients with AD.
Population	Men or women, aged 18 to 65 years (inclusive) at screening, who have a history of AD (1% to 20% BSA involvement) for at least 6 months, have a history of chronic itch (≥ 3 months) prior to screening, and a baseline mean PP-NRS score ≥ 4.0 during the run-in period.
Number of Participants	Approximately 48 participants will be included in the study.
Study Design	This is an open-label, single-arm study evaluating the effect of ruxolitinib 1.5% cream on itch.
Estimated Duration of Study Participation	Up to 37 days for screening period (including 7 days for the run-in period), 28 (± 2) days for the treatment period, and 15 (± 2) days for safety follow-up. It is estimated that an individual will participate in the study for up to approximately 3 months (80 days).
Data Monitoring Committee	No
Coordinating Principal Investigator	Not applicable.

Treatment Groups and Duration:

Participants will apply ruxolitinib 1.5% cream BID as a thin film for approximately 28 days (last application on the evening prior to the Day 29 visit). The study drug will be applied on all AD lesions, with a maximum treated area ≤ 20% BSA. All original areas of involvement identified on Day 1 (even in the event of lesions clearing), and any new lesions (a maximum of ≤ 20% BSA can be treated) must be treated until the evening prior to the Day 29 visit. On Day 1, participants will remain at the study center until after the 6-hour mPP-NRS assessment (approximately an 8-hour stay at the site). The 12-hour mPP-NRS assessment will be done at home just prior to the evening study drug application. On Day 8 and Day 15, the morning application of the study drug will be at the study center under the supervision of study staff. Other study drug applications will be self-administered by the participants at home.

Study drug application will occur in the morning and evening, with approximately 12 hours between applications. The evening dose should be applied at least 1 hour before bedtime. On Day 1, the mPP-NRS assessments should occur as close as possible to the scheduled time relative to the first study drug application. In addition, the 12-hour mPP-NRS should be completed **before** the evening study drug application. On Day 2, the PP-NRS assessment should be completed approximately 24 hours after the first study drug application and **before** the Day 2 morning dose. Refer to Table 5 for the sequence and timing of these assessments and allowed

windows on Day 1 and Day 2. From Day 3 until the Day 29 visit, the PP-NRS should be completed once daily, at approximately the same time in the morning, and prior to the study drug application.

Efficacy will be evaluated using the PP-NRS (worst itch over a 24-hour period), the mPP-NRS (current itch at the time of assessment), and the 5-point IGA.

The BSA and EASI will be used to evaluate the participant's AD severity on Day 1 and will be characterized during the study.

Medical photographs of the target lesion(s) and application site AEs will be taken during the study.

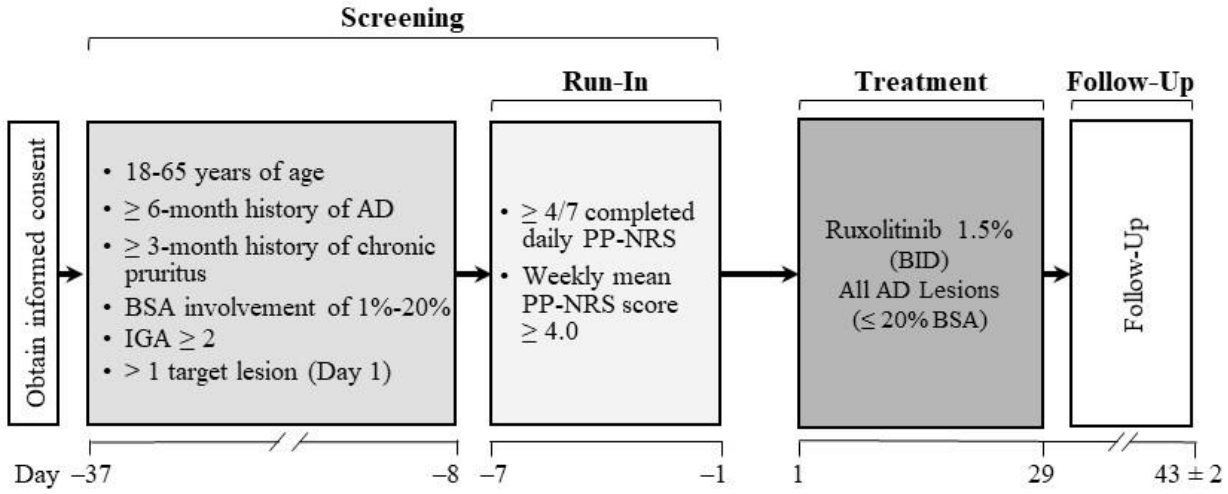
Participants will be asked to complete the TSQM-9 at the end of the treatment period (or at ET).

Safety will be assessed by collecting AEs, performing comprehensive and targeted physical examinations, and evaluating clinical laboratory assessments.

[redacted]

The study schema is shown in Figure 1.

Figure 1: Study Design Schema



Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. However, the Coronavirus Disease 2019 (COVID-19) pandemic may impact the ability to adhere to the study procedures described in the SoA (see Table 3) due to challenges that include but are not limited to participant preferences, site closures, travel restrictions, and quarantines. See Section 4.1.1 for more details on allowable, as necessary, modifications to the protocol due to COVID-19 restrictions.

Table 3: Schedule of Activities

Visit Day (Range) Visit Week	Screening Period Days −37 to −1 (Including a 7-Day Run-In Period)	Treatment Period Day 1[a]	Day 8 (± 2) Week 1	Day 15 (± 2) Week 2	Day 29 (± 2) Week 4	ET[b]	Safety Follow-Up Day 43 (15 ± 2 Days After Last Application) Week 6	Notes
Administrative procedures								
Informed consent	X							
Demographics	X							
Inclusion/exclusion criteria	X	X						
General and disease medical history	X	X						
Fitzpatrick skin type evaluation	X							
Prior/concomitant medications	X	X	X	X	X	X	X	
Identification of a target lesion	X	X						The target lesion should be representative of the participant's overall disease and should be treated with study drug. A target lesion that could accommodate all skin samples (tape strips, biopsies, skin microbiome, and TEWL) is the preferred scenario. However, a second target lesion could be selected, if needed.
BSA for eligibility (1-20% involvement excluding palms, soles, scalp, genitals, and folds)	X	X						
Identification of all lesions on a body diagram (BSA of treated area [up to 20%])		X						All body areas can be treated. If new lesions appear during the study, the BSA of treated area may need to be re-evaluated during the treatment period. Of note, BSA of treated area includes active, cleared, and new lesions. A maximum of ≤ 20% BSA can be treated during the study.

Table 3: Schedule of Activities (Continued)

Visit Day (Range) Visit Week	Screening Period Days −37 to −1 (Including a 7-Day Run-In Period)	Treatment Period Day 1[a] Week 1	Day 8 (± 2) Week 1	Day 15 (± 2) Week 2	Day 29 (± 2) Week 4	ET[b]	Safety Follow-Up Day 43 (15 ± 2 Days After Last Application) Week 6	Notes
Application of study drug BID		X----------X						The morning application will be on-site on Days 1, 8, and 15. Other study drug applications will be self-administered by the participants at home. Last application is on the evening prior to the Day 29 visit.
Give access to the participant's eDiary	X							eDiary for PP-NRS. Participants will be trained on eDiary at the screening visit.
Distribution of paper diary		X						Paper diary for study drug application. Participants will be trained on how to complete the paper diary at the Day 1 visit.
Review the participant's diaries		X	X	X	X	X		At each visit the participant will need to bring back both the paper diary and eDiary (tablet) for site review. The site will need to make copies of the paper diary before returning it to the participant.
Dispense study drug		X		X				
Study drug accountability			X	X	X	X		
Collect study drug				X	X	X		
Safety assessments								
AE assessments	X	X	X	X	X	X	X	
Comprehensive physical examination	X							
Targeted physical examination		X	X	X	X	X	X	
Vital signs	X							

Table 3: Schedule of Activities (Continued)

Visit Day (Range) Visit Week	Screening Period Days −37 to −1 (Including a 7-Day Run-In Period)	Treatment Period Day 1[a] Week 1	Day 8 (± 2) Week 1	Day 15 (± 2) Week 2	Day 29 (± 2) Week 4	ET[b]	Safety Follow-Up Day 43 (15 ± 2 Days After Last Application) Week 6	Notes
Efficacy assessments								
PP-NRS	X----------X							Completed at screening, immediately after signing consent, and then should be completed daily (in the morning) from screening to Day −1 and Day 2 to the Day 29 visit (ie, before morning study drug application from Day 2 until the day prior to the Day 29 visit). The PP-NRS should be performed before other efficacy assessments on visit days. See Table 5 for the sequence and timing of assessments on Day 1 and Day 2.
mPP-NRS		X						Evaluated onsite at the following intervals: predose, 15 minutes, 30 minutes, and 1, 2, 4, 6, and 12 hours after the morning study drug application. The 12-hour mPP-NRS evaluation will be done at home, prior to the second daily study drug application. See Table 5 for the sequence and timing of assessments on Day 1 and Day 2.
Medical photographs		X	X	X	X	X		Photograph of the target lesion(s) and any application site AEs.
IGA	X	X*	X*	X*	X	X	X	* Performed before morning application.
TEWL		X*			X			* Performed before morning application.
Total BSA% affected by AD		X*		X*	X	X	X	* Performed before morning application.
EASI		X*		X*	X	X	X	* Performed before morning application.
TSQM-9					X	X		
Laboratory assessments								
HIV	X							
Serum chemistries	X	X			X	X		
Hematology	X	X			X	X		

Table 3: Schedule of Activities (Continued)

Visit Day (Range) Visit Week	Screening Period Days −37 to −1 (Including a 7-Day Run-In Period)	Treatment Period Day 1[a]	Day 8 (± 2) Week 1	Day 15 (± 2) Week 2	Day 29 (± 2) Week 4	ET[b]	Safety Follow-Up Day 43 (15 ± 2 Days After Last Application) Week 6	Notes
Urinalysis	X	X			X	X		
Pregnancy testing	X	X			X	X	X	For WOCBP. Serum test at screening. Urine test at all other specified visits. A positive urine test must be confirmed by a serum test.
FSH	X							For female participants of nonchildbearing potential.
[redacted]								
Suture removal				X			X*	Within 11-14 days after biopsy collection, if applicable. *If skin biopsies are collected at ET, a follow-up visit for suture removal may be performed after 11-14 days, if applicable.

[a] On Day 1, participants will remain at the study center until after the 6-hour mPP-NRS assessment (approximately 8-hour stay at the site).

[b] Participants who withdraw from the study prematurely should complete an ET visit. Participants who are discontinued for safety reasons may be asked to come for additional follow-up visits, at the investigator's discretion, after the ET visit to ensure appropriate medical care and follow-up of AEs.

2. INTRODUCTION

2.1. Background

2.1.1. Ruxolitinib

Ruxolitinib cream is a topical formulation of INCB018424 phosphate, an investigational product that has been developed for the treatment of inflammatory diseases of the skin. Ruxolitinib phosphate is an inhibitor of the JAK family of protein tyrosine kinases, which play important roles in signal transduction downstream of cytokine and growth factor receptors. Ruxolitinib has shown preliminary efficacy in some chronic inflammatory conditions that present with an aberrant production of cytokines and growth factors, including psoriasis, vitiligo, and AD. In the US, OPZELURA™ (ruxolitinib) cream is FDA-approved for the topical short-term and noncontinuous chronic treatment of mild to moderate AD in nonimmunocompromised patients, aged 12 years and older, whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

2.1.2. Atopic Dermatitis and Itch

Atopic dermatitis is a chronic, recurring, and highly pruritic inflammatory skin condition characterized by erythematous lesions, xerosis, and frequent skin infections (Al-Shobaili et al 2016, Ong et al 2002). It typically begins early in infancy or childhood, although it can also develop in adulthood, and is more frequent among females than males (1.3 to 1.0 ratio; Eichenfield et al 2014, Wolff et al 2008). Several environmental factors, such as small family size and increased education, can heighten one's likelihood to develop AD; however, recent advancement in the molecular genetics of the disease indicate that AD may result from the inheritance of disease susceptibility variants of genes coding for constituents of the skin barrier and immune system (Al-Shobaili et al 2016, Wolff et al 2008). Evidence suggests that a complex interplay between these genes and environmental factors results in defective skin barrier integrity and altered immunologic/inflammatory responses and contributes to the development, progression, and chronicity of AD (Al-Shobaili et al 2016, National Eczema Association 2018, Rerknimitr et al 2017, Wolff et al 2008).

One of the most prominent and debilitating symptoms of AD is pruritus, also referred to as an "unpleasant sensation eliciting the urge to scratch" (Darsow et al 2011, Rerknimitr et al 2017, Wolff et al 2008, Yarbrough et al 2013). In most cases, this urge to scratch arises following exposure to triggering factors, such as irritants, allergens, infectious agents, and/or emotional stressors, which elicit a cutaneous hyper-reaction (Darsow et al 2011). The mechanical injury from scratching contributes to skin inflammation and exacerbates the scratch-itch cycle that perpetuates the disease (Wolff et al 2008). Pruritus affects the majority of patients with AD, and can be significantly bothersome and undermine the affected patient's quality of life and overall well-being (Farmer and Marathe 2017, Mochizuki et al 2017, Yosipovitch and Papoiu 2008). It can also disturb sleep and cause psychological problems such as depression and anxiety (Yarbrough et al 2013). Given the central role of pruritus in AD, it has become clear that the control of itch is critical to the management of the disease (Yarbrough et al 2013, Pavlis and Yosipovitch 2018).

Free nerve endings in the skin are involved in pruritus as itching receptors (Urashima and Mihara 1998). Histological examinations have revealed increased cutaneous nerve densities in patients with AD and animal models, suggesting that this higher density may be at least partly responsible for intense itching in the skin. The increased nerve fibers in the epidermis may be also activated by exogenous mechanical, chemical, and biological stimuli, resulting in itch responses. Previous observations suggest that an increase in nerve density in the epidermis may be caused by weakness or disruption of skin barrier function, allowing the invasion of exogenous substances into the skin. As itch is a biological sign, it is important for antipruritic therapy in AD to target cutaneous nerve fibers, their triggers, and barrier function (Tominaga and Takamori 2014).

Efforts have been made to find new and more appropriate treatment options to better meet the current and future medical needs of patients with AD. The results of recent trials indicated that oral JAK inhibitors may be effective in the treatment of AD and have elicited interest in the use of this drug class as a topical treatment for AD (Bissonnette et al 2019, Guttman-Yassky et al 2019, Levy et al 2015). Recent studies suggest that JAK inhibition may have antipruritic effects by acting directly on sensory nerve fibers (Hashimoto et al 2019). Ruxolitinib is a potent, selective inhibitor of JAK1 and JAK2, and its topical formulation may offer a novel therapeutic approach in AD with dual anti-inflammatory and antipruritic properties, providing a rationale for investigating the clinical utility of ruxolitinib cream for the treatment of this condition.

2.2. Study Rationale

Data from previous studies demonstrated that topical ruxolitinib cream is effective due to the dual anti-inflammatory and antipruritic properties. The purpose of this study is to further understand the short-term clinical and molecular benefits of ruxolitinib in the control of pruritus (primary outcome measure) and reduction of disease severity in participants with AD.

2.2.1. Scientific Rationale for Study Design

During the study, all participants will apply ruxolitinib 1.5% cream on all AD lesions for 28 (± 2) days. The proposed design is considered appropriate to evaluate the onset of itch reduction following application of ruxolitinib 1.5% cream, to assess the efficacy of ruxolitinib 1.5% cream in participants with AD, to understand the effect of ruxolitinib on the skin, and to provide further insight on the safety of ruxolitinib in participants with AD.

2.2.2. Justification for Dose

The clinical efficacy and safety of ruxolitinib cream was investigated in several studies, including 2 ongoing Phase 3 studies (INCB 18424-303 and INCB 18424-304) with more than 1235 participants with AD consisting of 1) a double-blind, vehicle-controlled period in which participants received ruxolitinib 0.75% or 1.5% or vehicle cream from Day 1 to Week 8, followed by 2) a double-blind, long-term safety extension (Week 8 to Week 52) in which participants initially randomized to vehicle were rerandomized to ruxolitinib 0.75% or 1.5% cream BID. As of 28 JUN 2020, no participant had a fatal TEAE. A few SAEs were reported, but all were considered by the investigator as unrelated to blinded study treatment.

In the INCB 18424-303 study, a total of 191 participants (30.3%) had at least 1 TEAE in the first part of the study. The most frequently reported TEAEs (≥ 1%) were nasopharyngitis

(n = 19 [3.0%]), upper respiratory tract infection (n = 18 [2.9%]), headache (n = 13 [2.1%]), dermatitis atopic (n = 12 [1.9%]), oropharyngeal pain and pruritus in 8 participants each (1.3%), and application site pain (n = 6 [1.0%]). Of the 542 participants continuing blinded study treatment after Week 8, a total of 265 participants (48.9%) had at least 1 TEAE. The most frequently reported TEAEs (≥ 2%) were upper respiratory tract infection (n = 49 [9.0%]); nasopharyngitis (n = 34 [6.3%]); headache (n = 20 [3.7%]); hypertension (n = 13 [2.4%]); bronchitis (n = 12 [2.2%]); and rhinitis (n = 11 [2.0%]).

In the INCB 18424-304 study, a total of 169 participants (27.3%) had at least 1 TEAE in the first part of the study. The most frequently reported TEAEs (≥ 1%) were nasopharyngitis (n = 13 [2.1%]), application site pain (n = 9 [1.5%]), application site pruritus (n = 8 [1.3%]), headache (n = 7 [1.1%]), and upper respiratory tract infection (n = 6 [1.0%]). Of the 529 participants continuing into the second part of the study, a total of 311 participants (58.8%) had at least 1 TEAE. The most frequently reported TEAEs (≥ 2%) were nasopharyngitis (n = 49 [9.3%]); upper respiratory tract infection (n = 41 [7.8%]); bronchitis (n = 16 [3.0%]); asthma, influenza, and rhinitis in 13 participants each (2.5%); and hypertension and pharyngitis in 11 participants each (2.1%).

In both studies, the majority of participants showed good local tolerability to study drug. Pooled analysis from both Phase 3 studies confirmed that the AE profile was similar to that in the vehicle group, with low rate of application site reactions and no serious AEs.

The efficacy data of these 2 Phase 3 studies revealed that either treatment regimen of ruxolitinib cream brought about rapid (within 12 hours of initiation of therapy), substantial, and sustained reduction in itch and showed superior efficacy versus vehicle in IGA-TS, ≥ 75% improvement in EASI score, and ≥ 4-point reduction in itch NRS score. Of note, numerically better results were observed in the ruxolitinib 1.5% BID group (Papp et al 2020). In addition, the Phase 2 study (INCB 18424-206) with 204 participants with AD randomized to treatment with ruxolitinib 0.15% cream QD (n = 51), ruxolitinib 0.5% cream QD (n = 51), ruxolitinib 1.5% cream QD (n = 52), or ruxolitinib 1.5% cream BID (n = 50) revealed that all ruxolitinib treatment groups were superior to the vehicle group for the percent change from baseline in EASI score at Week 4. Of note, the greatest change from baseline was measured in the ruxolitinib 1.5% cream BID group (−71.57% versus −11.90%; $p < 0.0001$).

Given the favorable safety and efficacy profile of ruxolitinib 1.5% cream BID in participants with AD, the 1.5% concentration of ruxolitinib cream applied BID was selected to evaluate the effect of ruxolitinib cream on itch in adult participants with AD in the present study.

2.3. Benefit/Risk Assessment

As of 28 JUN 2021, a total of 14 clinical studies with ruxolitinib cream had been completed (5 studies in healthy participants, 3 studies in participants with psoriasis, 1 study in participants with alopecia areata, and 5 studies in participants with AD) and 5 studies were ongoing (5 studies in participants with vitiligo). A total of 2613 unique participants had been exposed to ruxolitinib cream in completed studies.

An analysis of the clinical pharmacology of ruxolitinib cream applied in plaque psoriasis, alopecia areata, AD, and vitiligo uncovered that exposure to ruxolitinib is generally strength-dependent, and presents a moderate intersubject variability. In the psoriasis studies,

INCB 18424-201, INCB 18424-202, and INCB 18424-203, steady-state concentrations after application of ruxolitinib cream increased approximately proportional to the daily application strength. However, the bioavailability for ruxolitinib cream was independent of the strength of the cream formulation and percent BSA.

The most frequently reported (≥ 2%) TEAEs in participants with AD (n = 1595) were upper respiratory tract infection, nasopharyngitis, headache, atopic dermatitis, bronchitis, and rhinitis.

Based on earlier studies with ruxolitinib 1.5% cream, it is anticipated that participants will clinically benefit from their participation in the current study. Participation in this study may also help generate future benefit for larger groups of participants with inflammatory and pruritic skin conditions if ruxolitinib 1.5% cream proves to be efficient in prompt and maintained control of itch. Ultimately, this study may deepen the understanding of ruxolitinib 1.5% cream's mechanism of action and inform on possible future uses of ruxolitinib 1.5% cream.

All pharmacology and toxicology data and satisfactory safety and tolerability data demonstrated in nonclinical studies are considered sufficient to expect a positive benefit/risk ratio for the treatment of AD with ruxolitinib 1.5% cream and therefore to initiate this study.

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

2.3.1. COVID-19 Pandemic

As a consequence of the COVID-19 pandemic that has had a worldwide impact, including cases in North America, control measures in place in different regions may impact the ability to adhere to some of the study procedures described in this protocol. Due to challenges that include but are not limited to participant preferences, site closures, travel restrictions, and quarantines, some modifications to study conduct during the COVID-19 pandemic may be necessary to ensure study continuity. See Section 4.1.1 for more details on allowable, as necessary, modifications to the protocol due to COVID-19 restrictions.

3. OBJECTIVES AND ENDPOINTS

Table 4 presents the objectives and endpoints.

Table 4: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of ruxolitinib 1.5% cream on pruritus in participants with AD.	Change from baseline in PP-NRS at Day 2 (24-hour recall period after first application).
Secondary	
To evaluate the efficacy of ruxolitinib 1.5% cream in participants with AD.	• Change from baseline in mPP-NRS (current itch intensity) at 15 and 30 minutes and 1, 2, 4, 6, and 12 hours postdose on Day 1; and in PP-NRS from Day 3 through Day 29. • Proportion of participants achieving at least a 1-grade decrease from baseline in mPP-NRS at 15 and 30 minutes and 1, 2, 4, 6, and 12 hours postdose on Day 1; and in PP-NRS from Day 2 through Day 29. • Proportion of participants achieving at least a 2-grade decrease from baseline in mPP-NRS at 15 and 30 minutes and 1, 2, 4, 6, and 12 hours postdose on Day 1; and in PP-NRS from Day 2 through Day 29. • Time to MCID (≥ 2-grade reduction in PP-NRS and mPP-NRS from baseline). • Change from baseline in IGA at Day 8, Day 15, and Day 29. • Proportion of participants achieving the IGA-TS (score of 0 or 1 in IGA with at least a 2-grade reduction from baseline) at Day 8, Day 15, and Day 29.
To evaluate the local and systemic safety and tolerability of ruxolitinib 1.5% cream in participants with AD.	Incidence and severity of local and systemic AEs.

Table 4: Objectives and Endpoints (Continued)

Objectives	Endpoints
Exploratory	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Note: For efficacy endpoints related to PP-NRS, baseline is defined as the average of all nonmissing PP-NRS (24-hour recall period) scores reported during the 7-day run-in period. For the other efficacy variables (including the mPP-NRS), baseline is defined as the last nonmissing value before or on Day 1 (prior to first application of study drug).

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, open-label, single-arm study evaluating the effect of ruxolitinib 1.5% cream on itch. This study will include approximately 48 adult participants (18-65 years old, inclusively) who have at least a 6-month history of AD and at least a 3-month history of chronic itch.

All participants will read and sign an ICF prior to any study procedures being performed and then undergo screening for study eligibility. Participants who meet initial screening requirements will be given access to an eDiary to complete the PP-NRS each morning (24-hour recall period), from screening to Day −1 and from Day 2 to the Day 29 visit. Participants must be willing and able to complete the eDiary on a daily basis for the duration of the study. During the last 7 days prior to Day 1 (run-in period; Day −7 to Day −1), participants will be required to complete at least 4 of 7 PP-NRS assessments in their eDiary. Inclusion of participants completing fewer than 4 of 7 PP-NRS questionnaires during the last 7 days of the screening period (run-in period) must be approved by the sponsor.

After a screening period of no more than 37 days (from Day −37 to Day −1, including a 7-day run-in period), participants who fulfill all of the inclusion criteria, none of the exclusion criteria, and have a baseline mean PP-NRS score ≥ 4.0 during the run-in period will be eligible to start the treatment period. The baseline mean PP-NRS score is defined as the average of all nonmissing PP-NRS scores reported during the run-in period.

During the treatment period, participants will apply ruxolitinib 1.5% cream BID as a thin film for 28 (± 2) days (last application on the evening prior to the Day 29 visit). The study drug will be applied on all AD lesions, with a maximum treated area ≤ 20% BSA. All original areas of involvement on Day 1 (even in the event of lesions clearing), and any new lesions (a maximum of ≤ 20% BSA can be treated) must be treated until the evening prior to the Day 29 visit. On Day 1, participants will remain at the study center until after the 6-hour mPP-NRS assessment (approximately an 8-hour stay at the site). The 12-hour mPP-NRS assessment will be done at home just prior to the evening study drug application. On Day 8 and Day 15, the morning application of the study drug will be at the study center under the supervision of study staff. Other study drug applications will be self-administered by the participants at home. The study schema is shown in Figure 1.

Study drug application will occur in the morning and evening from Day 1 until the day prior to the Day 29 visit, with approximately 12 hours between applications. The evening dose should be applied at least 1 hour before bedtime. On Day 1, the mPP-NRS assessments should occur as close as possible to the scheduled time relative to the first study drug application. In addition, the 12-hour mPP-NRS should be completed **before** the evening study drug application. On Day 2, the PP-NRS assessment should be completed approximately 24 hours after the first study drug application and **before** the Day 2 morning dose. Refer to Table 5 for the sequence and timing of these assessments and allowed windows on Day 1 and Day 2. From Day 3 until the Day 29 visit, the PP-NRS should be completed once daily, at approximately the same time in the morning, and prior to the study drug application.

Table 5: Sequence and Timing of mPP-NRS, PP-NRS, and Study Drug Applications on Days 1 and 2

Study Day **Order of Assessments**	**Scheduled Time (Window)**
Day 1	
Preapplication mPP-NRS	Prior to first study drug application
Morning study drug application (first application)	—
15-minutes postapplication mPP-NRS	15 minutes (± 2 minutes) after first study drug application
30-minutes postapplication mPP-NRS	30 minutes (± 2 minutes) after first study drug application
1-hour postapplication mPP-NRS	1 hour (± 2 minutes) after first study drug application
2-hours postapplication mPP-NRS	2 hours (± 5 minutes) after first study drug application
4-hours postapplication mPP-NRS	4 hours (± 5 minutes) after first study drug application
6-hours postapplication mPP-NRS	6 hours (± 5 minutes) after first study drug application
12-hours postapplication mPP-NRS	12 hours (± 5 minutes) after first study drug application
Evening study drug application (second application)	Approximately 12 hours after first study drug application **– After the 12-hour mPP-NRS**
Day 2	
PP-NRS	24 hours (± 1 hour) after the first study drug application (ie, after Day 1 morning dose)
Morning study drug application (third application)	Approximately 12 hours after the Day 1 evening dose **– After Day 2 PP-NRS**
Evening study drug application (fourth application)	Approximately 12 hours after the Day 2 morning dose

Note: From Day 3 until the Day 29 visit, the PP-NRS should be completed once daily, at approximately the same time in the morning, and prior to the study drug application.

Efficacy will be evaluated using the PP-NRS (worst itch over a 24-hour period), the mPP-NRS (current itch at the time of assessment), and the 5-point IGA.

The BSA and EASI will be used to evaluate the participant's AD severity on Day 1 and will be characterized during the study.

Medical photographs of the target lesion(s) and application site AEs will be taken during the study.

Participants will be asked to complete the TSQM-9 at the end of the treatment period (or ET, if applicable).

Safety will be assessed by collecting AEs, performing comprehensive and targeted physical examinations, and evaluating clinical laboratory assessments.

[redacted]

4.1.1. Study Conduct During the COVID-19 Pandemic

As a consequence of the COVID-19 pandemic that has had a worldwide impact, including cases in North America, control measures in place in different regions may impact the ability to adhere to some of the study procedures described in this protocol. Due to challenges that include but are not limited to participant preferences, site closures, travel restrictions, and quarantines, some modifications to study conduct during the COVID-19 pandemic may be necessary to ensure study continuity. The following are allowable, as necessary, modifications to study conduct during the COVID-19 pandemic.

- Prior to a study visit at the site, the participant may be contacted and screened for potential exposure or infection to COVID-19 per site, local, or federal requirements. If the participant is suspected to have been exposed or infected with COVID-19, the on-site visit should either be rescheduled or a virtual visit may be performed instead, as applicable.
- In the event that a participant cannot attend their regularly scheduled study visits in-person due to COVID-19 necessitating a limit on in-person contact, the investigator may perform safety and efficacy assessments by phone or video, except for the screening and Day 1 visits. If the screening visit cannot be performed on-site, the participant should not be screened. If the Day 1 visit cannot be performed on-site, the participant should be considered to have failed screening. Participants who fail screening due to COVID-19 restrictions at screening or Day 1 may be rescreened at a later time, if feasible. Every effort should be made to perform the Day 8 and Day 29 visits on-site to allow for skin and/or blood sample collection. Protocol deviations due to missed study visits, missed applications, or missed study procedures as well as study discontinuations due to COVID-19 restrictions should be documented accordingly.
- Participants should continue answering the daily PP-NRS via eDiary (tablet) and record their BID application of study drug in the paper diary. Safety must be assessed during the virtual visit by collecting AEs and concomitant medications. Other safety or efficacy assessments may be performed as reasonably practicable.
- Clinical laboratory tests (eg, serum chemistries, hematology, urinalysis) and pregnancy tests may be performed by a local laboratory if these procedures cannot be performed at the study site due to COVID-19–related limitations, including but not limited to site closure. Clinically significant abnormal laboratory results should be promptly communicated to the medical monitor within 72 hours of receipt, as per investigator's judgment. Participant' anonymity must be maintained when communicating results to the medical monitor.
- Source documentation should note that the visit was performed virtually (not face-to-face) and note the name of the local laboratory where laboratory tests were performed.

A detailed assessment of COVID-19–related risk and mitigation measures will be documented in the appropriate study plans.

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 when all participants have completed the Day 43 visit or discontinued study drug (ET) and have completed all applicable follow-up assessments.

It is estimated that an individual will participate in the study for up to approximately 3 months (80 days); inclusive of a maximum of 37 days for the screening period (including 7 days for the run-in period), 28 (± 2) days for the treatment period, and 15 (± 2) days for safety follow-up.

A participant is considered to have completed the study if he/she has completed all parts of the study including the last visit or the last scheduled procedure shown in Table 3.

4.3. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator is to notify the IRB/IEC of the study's completion or early termination 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 or if required by regulatory decision. In the event of significant safety findings, the study will be terminated. 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 the Protocol is essential. Prospective approval of Protocol deviations to recruitment and enrollment criteria, also known as Protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

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

1. Male or female participant aged 18 to 65 years, inclusive, at screening.
2. Participant is able to comprehend and willing to sign a written ICF for this study.
   Note: Consent must be obtained prior to any study-related procedures.
3. Participant has clinically confirmed diagnosis of active AD according to Hanifin and Rajka (1980) criteria (see Appendix B).
4. Participant has at least a 6-month history of AD (information obtained from medical chart, participant's physician, or directly from the participant).
5. Participant has chronic pruritus related to AD for at least 3 months before the screening visit (information obtained from medical chart, participant's physician, or directly from the participant).
6. Participant has an overall BSA (excluding palms, soles, scalp, genitals, and folds) affected by AD of 1% to 20% on Day 1.
7. Participant has an IGA score of at least 2 on Day 1.
8. Participant has 1 target AD lesion on Day 1 that can allow for the collection of skin samples as per study requirement (excluding face, scalp, genitals, axillae, groin, folds, palms, and soles). The target lesion should be representative of the participant's overall disease and should be treated with study drug.

   Note: A target lesion that could accommodate all skin samples (tape strips, biopsies, and skin microbiome) and TEWL assessment is the preferred scenario. However, a second target lesion could be selected, if needed. If selecting 2 target lesions on Day 1, they should be of similar severity and preferably from the same anatomical region.
9. Participant has a single PP-NRS score ≥ 4 in the 24-hour period prior to the screening visit.
10. Participant must be willing to complete the once-daily PP-NRS (24-hour recall period) entries at approximately the same time each day during the study (from screening to Day −1 and from Day 2 to the Day 29 visit).

    Note: Inclusion of participants completing fewer than 4 of 7 daily PP-NRS questionnaires during the last 7 days of the screening period (run-in period) must be approved by the sponsor.

11. Prior to the first application of study drug, participant has a baseline mean PP-NRS (24-hour recall period) score ≥ 4.0 during the run-in period, defined as the average of all nonmissing scores reported during the 7-day run-in period.
12. Participant has been using an emollient for at least 2 weeks prior to Day 1 (ie, 1 week prior to run-in period), and agrees to continue using that same emollient daily at the same frequency, applied on nontreated areas, throughout the study. The chosen emollient should not contain urea, camphor, menthol, lactic acid, or pramoxine.
13. 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 the last application of study drug and must refrain from donating sperm during this period. Permitted methods in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    b. Female participants who are WOCBP must have a negative serum pregnancy test at screening and a negative urine pregnancy test before the first application on Day 1 and must agree to take appropriate precautions to avoid pregnancy from screening through the last application of study drug 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.
14. Participant must be willing to comply with all study procedures and restrictions including discontinuation of all current therapies for AD and pruritus (unless otherwise specified), and must be available for the duration of the study.

5.2. Exclusion Criteria

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

1. Participant is a female who is breastfeeding, pregnant, or planning to become pregnant during the study.
2. Participant had significant flares or unstable course in AD (ie, condition worsened significantly or required significant change in medications, as per medical judgment) in the previous 4 weeks before screening (information obtained from medical chart, participant's physician, or directly from the participant).
3. Participant has clinically infected AD or has used antibiotics (systemic or topical) for their infected AD within 2 weeks prior to the run-in period.
4. Participant has a history of skin disease or presence of skin condition that, in the opinion of the investigator, would interfere with the study assessments (eg, generalized erythroderma, Netherton syndrome, psoriasis, or any skin condition other than AD that may risk inducing a pruritus flare/worsening).
5. Participant has a presence of any tattoos, scratches, open sores, excessive hair, or skin damages that, in the opinion of the investigator, may interfere with study evaluations.

6. Participant has a clearly defined etiology for pruritus other than AD, including but not limited to urticaria, psoriasis, or other nonatopic dermatologic conditions; hepatic or renal disease; psychogenic pruritus; drug reaction; uncontrolled hyperthyroidism; and infection.
7. Participant is known to have immune deficiency or is immunocompromised (eg, lymphoma, acquired immunodeficiency syndrome, Wiskott-Aldrich syndrome).
8. Participant has a history of cancer or lymphoproliferative disease within 5 years prior to Day 1, with the exception of successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix.
9. Participant had a major surgery within 8 weeks prior to Day 1 or has a major surgery planned during the study.
10. Participant has any clinically significant medical condition or physical/laboratory/vital sign abnormality that would, in the opinion of the investigator, put the participant at undue risk or interfere with interpretation of study results, including but not limited to participants with renal disease requiring dialysis.
11. Participant has any of the following clinical laboratory test results at screening:
    a. Hemoglobin (< 10 g/dL) or absolute neutrophil count (ANC) of < 1000/uL or platelets count < 100,000/uL.
    b. Liver function tests:
        - AST or ALT ≥ 2.5 × ULN
        - Total bilirubin > 1.5 × ULN (isolated bilirubin > 1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin is < 35%).
    c. Estimated GFR < 30 mL/min/1.73 m^2 (using the Modification of Diet in Renal Disease equation).
    d. Positive serology test results at screening for HIV antibody.
    e. Any other clinically significant laboratory result which in the opinion of the investigator, pose a significant risk to the participant.
12. Removed during Protocol Amendment 2.
13. Participant has used any oral, sedative, H_1 antihistamine (including but not limited to diphenhydramine and hydroxyzine) within 2 weeks prior to the run-in period.

    Note: Oral, nonsedative, H_1 antihistamines to treat allergies will be permitted during the study only if the participant has been on a stable dose for at least 2 weeks prior to run-in and continues to use the same agent at the same frequency throughout the study.
14. Participant has used doxepin within 2 weeks prior to the run-in period.
15. Participant has used any topical medicated treatment that could affect AD and/or pruritus within 2 weeks prior to the run-in period, including but not limited to topical corticosteroids, crisaborole, calcineurin inhibitors, antihistamines, pramoxine, tars, antimicrobials, or stable doses of prescription or over-the-counter topical analgesics/moisturizers containing menthol, camphor, urea additives, or lactic acid.

16. Participant has used systemic corticosteroids (oral/injectable) within 4 weeks prior to the run-in period.

    Note: Intranasal and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.

17. Participant has used systemic treatments (other than biologics) that could affect AD and/or pruritus within 4 weeks prior to the run-in period (eg, retinoids, calcineurin inhibitors, PDE-4 inhibitors, methotrexate, cyclosporine, hydroxycarbamide [hydroxyurea], azathioprine, interferon-gamma, or opioids [agonist, partial agonist-mixed, or antagonist]).
18. Participant has received any ultraviolet B phototherapy (including tanning beds) or excimer laser within 4 weeks prior to the run-in period.
19. Participant has had PUVA treatment within 4 weeks prior to the run-in period.
20. Participant has had excessive sun exposure, is planning a trip to a sunny climate, or has used tanning booths within 4 weeks prior to the run-in period or is not willing to minimize natural and artificial sunlight exposure during the study.
21. Participant has received a nonbiological investigational product or device within 4 weeks prior to the run-in period, or is currently enrolled in another investigational drug study.
22. Participant has received any marketed or investigational biological agent that could interfere with the course or assessments of AD within 12 weeks or 5 half-lives (whichever is longer) prior to the run-in period.
23. Participant has used dupilumab within 26 weeks prior to the run-in period.
24. Participant has received a live-attenuated vaccine within 4 weeks prior to the run-in period or plans to receive a live-attenuated vaccine during the study and up to 4 weeks or 5 half-lives (of the study drug), whichever is longer, after the last application of study drug.
25. Participant has received treatment with JAK inhibitors (systemic or topical) within 4 weeks prior to the run-in period.
26. Participant had prior treatment with a JAK inhibitor that was discontinued for safety reasons or tolerance problems.
27. Participant has a known or suspected allergy to ruxolitinib or any component of the study drug.
28. Participant has a known history of clinically significant drug or alcohol abuse in the last year prior to Day 1.
29. Participant has a history of an allergic reaction or significant sensitivity to lidocaine or other local anesthetics.
30. Participant has a history of hypertrophic scarring or keloid formation in scars or suture sites.

31. Participant has taken anticoagulant medication, such as heparin, LMW-heparin, warfarin, or antiplatelets (except low-dose aspirin ≤ 81 mg, which will be allowed), within 2 weeks prior to Day 1, or has a contraindication to skin biopsies.

    Note: NSAIDs will not be considered antiplatelets and will be allowed.

32. Participant is unlikely, in the opinion of the investigator, to be compliant with study procedures and requirements.
33. Participant has a close affiliation (eg, a close relative) with the investigator, including any study staff of the sites or persons working at the contract research organization, or participant is an employee of the sponsor.
34. History of hepatitis B virus or hepatitis C virus infection.

5.3. Lifestyle Considerations

Participants should abstain from taking a bath/shower within 2 hours following study drug application.

Participants should abstain from physical activity that can cause significant sweating within 2 hours following study drug application.

Prolonged exposure to natural or artificial sources of ultraviolet radiation (eg, sun lamps, tanning booths) is prohibited within 4 weeks prior to the run-in period through the last study visit. Use of sunscreen products and protective apparel are recommended when sun exposure cannot be avoided. When outdoors, participants will be advised to wear loose-fitting clothing that protects the treated area from the sun.

Any sunscreen, makeup, or other cosmetics should be applied to the areas to be treated at least 4 hours before and 2 hours after application of study drug. If sunscreen, makeup, or other cosmetic has been applied to the areas to be treated, participants should wash the treatment areas with mild soap and water and pat dry before application of the study drug. However, on the days of a study visit, participants should refrain from washing or applying cosmetics (makeup, creams, etc) to the target lesion area(s) and adjacent area(s) for at least 5 hours prior to the visit.

Participants are to wash their hands thoroughly with soap and warm water prior to study drug application. Participants with AD lesions on their hands must avoid washing their hands for approximately 2 hours after drug application. Participants without AD lesions on their hands will be instructed to wash their hands thoroughly with soap and warm water after study drug application.

Use of swimming pools during the treatment period of the study is not recommended. If unavoidable, it is recommended that swimming should not take place within 2 hours before and after the planned study drug application.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the treatment period of the study.

Tests with results that fail eligibility requirements may be repeated once during screening if deemed acceptable by the investigator. Additionally, individuals who do not meet the criteria for

participation in this study (screen failure) may be rescreened once, if deemed acceptable by the investigator. However, participants who do not meet the criteria for the single PP-NRS score at screening or the baseline mean PP-NRS score of eligibility for the 7-day run-in period may not be rescreened. 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.

6. STUDY TREATMENT

6.1. Study Treatment Administered

Ruxolitinib 1.5% cream will be supplied in 60-g tubes. The study drug will be provided by the sponsor and dispensed at the study visits summarized in the SoA (see Table 3). On Day 1, study staff will instruct participants on proper application of study drug.

All participants will apply ruxolitinib 1.5% cream for 28 (± 2) days. The study drug will be applied as a thin film, BID, on all AD lesions with a maximum treated area ≤ 20% BSA. All original areas of involvement identified on Day 1 (even in the event of lesions clearing), and any new lesions (a maximum of ≤ 20% BSA can be treated) must be treated until the evening prior to the Day 29 visit. The last application will be on the evening prior to the Day 29 visit. On Day 1, participants will remain at the study center until after the 6-hour mPP-NRS assessment (approximately an 8-hour stay at the site). The 12-hour mPP-NRS assessment will be done at home just prior to the evening study drug application. On Day 8 and Day 15, the morning application of the study drug will be at the study center under the supervision of study staff. Other study drug applications will be self-administered by the participants at home.

Participants will be instructed to apply the study drug at approximately the same time of the day (once in the morning and once in the evening, approximately 12 hours apart). The evening dose should be applied at least 1 hour before bedtime. On Day 1, the mPP-NRS assessments should occur as close as possible to the scheduled time relative to the first study drug application. In addition, the 12-hour mPP-NRS should be completed **before** the evening study drug application. On Day 2, the PP-NRS assessment should be completed approximately 24 hours after the first study drug application and **before** the Day 2 morning dose. Refer to Table 5 for of the sequence and timing of these assessments and allowed windows on Day 1 and Day 2. From Day 3 until the Day 29 visit, the PP-NRS should be completed once daily, at approximately the same time in the morning, and prior to the study drug application.

Table 6 presents the study treatment information.

Table 6: Study Treatment Information

Study treatment name:	Ruxolitinib
Mechanism of action:	JAK1 and JAK2 inhibitor
Dosage formulation:	Cream
Unit dose strength(s)/ dosage level(s):	1.5% BID
Administration instructions:	Applied BID as a thin film, at an interval of approximately 12 hours, on all AD lesions (up to 20% BSA) for 28 (± 2) days.
Packaging and labeling:	Ruxolitinib will be provided in 60-g tubes. Tubes will include labeling in the local language, and each tube will be labeled as required per country requirement.
Storage:	Ambient (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 (ruxolitinib cream stored at ambient temperature between 15°C and 30°C [59°F-86°F]) have been maintained during transit for all study treatments received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply study treatment. Participants are to wash their hands thoroughly with soap and warm water before application of ruxolitinib cream. Participants with AD lesions on their hands must avoid washing their hands for approximately 2 hours after drug application. Participants without AD lesions on their hands will be instructed to wash their hands thoroughly with soap and warm water after study drug application. Refer to the SRM for participant instructions for handling of study drug.

All study treatment at the site must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. Participants should store study treatment at ambient temperature conditions (15°C-30°C [59°F-86°F]).

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

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

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the participants were provided the specified study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study participants. In case of missed visits related to the COVID-19 pandemic, alternative, secure delivery methods may be considered as well as changes in the dispensing schedule to ensure continued treatment with the study drug until the end of the treatment period. Accountability processes will be maintained during the COVID-19 pandemic and all efforts will be made to ensure that all medication is returned at the site (even when last study visit is virtual).

Completed accountability records will be archived by the site. Returned study drug should not be redispensed to the participants. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional SOPs. If local procedures mandate on-

site destruction of the investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study; no comparisons will be made between participants or against historical controls. Measurements of safety and efficacy are objective measurements, and only comparisons to pretreatment conditions will be made.

6.4. Study Treatment Compliance

Compliance with study-related treatment should be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study. To facilitate compliance assessment during the treatment period, participants will be supplied with a paper diary and instructed to record the time and date for each application of study drug.

Study treatment compliance will be monitored at each visit. Compliance will be assessed for frequency of application of study drug by reviewing the participant diary. Qualified clinical staff will review the entries for compliance. Participants will also be questioned regarding study drug application technique, missed applications, and use of any additional prescription or over-the-counter topical or systemic products. For participants who miss more than 3 consecutive study drug applications or have a compliance below 80%, the investigator should discuss with the medical monitor and/or sponsor for continued participation in the study.

Participants will be considered compliant with the treatment regimen if they apply at least 80% but no more than 120% of the prescribed number of applications during the treatment period of the study. Drug accountability will be assessed by documenting the quantities of drug used between study visits (tube counts and weighing). Participants will be instructed to bring all study drugs with them at the visits specified in Table 3 in order for site personnel to assess study drug accountability. The drug usage will be used by the sponsor to evaluate drug accountability.

6.5. Dose Modifications

During the 28 (± 2)-day treatment period, participants should treat all AD lesions identified for treatment on Day 1, even if lesions improve. Participants who have additional areas of AD developing after the initiation of treatment should also treat these additional areas (a maximum of ≤ 20% BSA can be treated) with approval from the investigator. Approval to treat additional areas may occur via telephone. The site should consider having the participant come in for an unscheduled visit to document the new %BSA if the additional areas of AD constitute a clinically meaningful increase in BSA. The change in %BSA treated should be documented in the eCRF. It is recommended that, in such situations, an increase in the overall BSA to be treated does not exceed approximately 10% over the baseline BSA affected by AD. If at any time during the study the participant's BSA exceeds 20%, the participant should be considered for termination.

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

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

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of AEs or laboratory abnormalities that may have an unclear relationship to study drug. Except in cases of emergency, it is recommended that the investigator consult with the sponsor's medical monitor (or other representative of the sponsor) immediately upon occurrence or awareness before temporarily interrupting study drug. Additionally, the investigator must obtain approval from the sponsor before restarting study drug that was temporarily interrupted because of an AE or laboratory abnormality.

Individual participants may have administration interrupted at the discretion of the investigator, in consultation with the sponsor, for AEs or laboratory abnormalities until these have resolved.

Instructions for application interruptions for ruxolitinib cream are outlined in Table 7. Individual decisions regarding interruptions should be made using clinical judgment in consultation with the medical monitor (whenever possible), taking into account relatedness of the AE to the study treatment and the participant's underlying condition.

Table 7: Guidelines for Interruption and Restarting of Treatment Applications if Adverse Event is Deemed Related to the Study Drug

Adverse Event Related to Study Drug[a]	Action Taken
ANC < 750/uL (without fever); < 1000/uL (with fever)	• Laboratory abnormalities should be confirmed with repeat testing within 48 hours whenever possible and immediate delivery of the laboratory results requested. • Study drug applications must be interrupted. At the discretion of the investigator, after consultation with the sponsor, study drug application may be restored once these have resolved.
Any other Grade 3 laboratory abnormality (eg, hemoglobin with the exception of asymptomatic elevations in triglyceride, cholesterol, or amylase)	• Laboratory abnormalities should be confirmed with repeat testing within 48 hours whenever possible and immediate delivery of the laboratory results requested. • Study drug applications must be interrupted. At the discretion of the investigator, after consultation with the sponsor, study drug application may be restored once these have resolved.
Any Grade 4 laboratory abnormality or AST or ALT (> 20 × ULN)	• Laboratory abnormalities should be confirmed with repeat testing within 48 hours whenever possible and immediate delivery of the laboratory results requested. • Discontinue study drug if laboratory abnormalities are confirmed.

Note: Grading using the CTCAE v5.0.
[a] In the opinion of the investigator.

6.5.2. Criteria for Permanent Discontinuation of Study Drug

The occurrence of unacceptable toxicity not caused by the underlying disease will require that the study drug be permanently discontinued. Unacceptable toxicity is defined as follows:

- The occurrence of an AE that is related to study treatment 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.
- A worsening of AD that requires treatment with a prohibited concomitant medication.
- A persistent AE requiring a delay of therapy for more than 2 weeks without resolution of the AE (unless a greater delay has been approved by the sponsor).

See Section 7.1.2 for discontinuation procedures.

6.6. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. All prior medications for AD and any medications received within 28 days before the screening visit, throughout the study, and up to the safety follow-up visit will be recorded in the eCRF. The medication record will be maintained after signing the ICF to document prior/concomitant medications, including any changes to the dose or regimen. Concomitant treatments and/or procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant medications administered within 15 (± 2) days after the last application of study treatment should be recorded for SAEs as defined in Section 9.4. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1. Permitted Medications and Procedures

6.6.1.1. Emollients

Participants must apply an emollient of their choice (except those containing urea, camphor, menthol, lactic acid, or pramixide) on their skin during the study. Emollients should be applied everywhere on the body, **including on AD lesions**, during the screening and the follow-up periods. Emollients should be applied everywhere on the body, **except on treated AD lesions**, during the treatment period. Participants should continue on their established emollient application scheme and **not initiate a new one at least 2 weeks prior to Day 1** (ie, 1 week prior to run-in period), and participants must continue using it at the same frequency (ideally QD or BID) throughout the study. However, on the day of scheduled visits, participants cannot apply emollient before their scheduled visit time.

Every effort should be made to keep the same emollient throughout the study for the same body region. However, the chosen emollient may differ depending on the body region (eg, body vs face emollient may be different). The commercial name of the selected emollient(s) will be recorded in the source document and the eCRF. No other products may be applied to the lesions during the study.

6.6.1.2. Other Permitted Therapies

The following medications and procedures are permitted:

- Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.
- Bathing during the study should be limited to once daily for no longer than 15 minutes. During baths, tepid (not hot) water and mild cleansing agents (eg, Basis® Bar or Dove®) should be used. Showers should be limited in time with warm water and mild cleansing agents used.
- Use of sunscreen products and protective apparel are recommended when sun exposure cannot be avoided. If sunscreen is needed, a mineral-based sunscreen (such as zinc oxide– or titanium oxide–based) may be used at least 4 hours before and 2 hours after study drug application.

6.6.2. Restricted Medications and Procedures

The following are permitted during the study under specified conditions:

- Oral, nonsedative, H_1 antihistamines to treat allergies are allowed during the study only if the participant has been on a stable dose for at least 2 weeks prior to the run-in period and continues to use the same agent at the same frequency throughout the study.
- Bleach baths are allowed as long as their frequency remains the same throughout the study.
- Participants should abstain from taking a bath/shower within 2 hours following study drug application.
- Use of swimming pools during the treatment period of the study is not recommended. If unavoidable, it is recommended that swimming should not take place within 2 hours before and after the planned study drug application.
- Participants should abstain from physical activity that can cause significant sweating within 2 hours following study drug application.

6.6.3. Prohibited Medications and Procedures

Table 8 lists prohibited medications that are not to be used from the defined washout periods prior to the run-in period through the last study visit.

Participants who start prohibited medications or therapies that have been demonstrated to be effective for treatment of AD/pruritus during the study will be withdrawn from the study. Participants who start prohibited medications or therapies for other reasons during the study may be withdrawn from the study if an impact on efficacy assessment or safety of the participants is expected. If in any doubt, investigators are advised to discuss medications with the medical monitor.

Participants who present with a worsening of AD that requires treatment with a prohibited concomitant medication will have the study drug permanently discontinued.

Table 8: Prohibited Therapies or Procedures

Prohibited Medications, Products, and Procedures	Washout Period Prior to:	
	Run-In Period	Day 1
Dupilumab	26 weeks	–
Any marketed or investigational biological agent that may impact the course of AD or its assessments	12 weeks or 5 half-lives (whichever is longer)	–
Major surgery	–	8 weeks
JAK inhibitor (systemic or topical)	4 weeks	–
Nonbiological investigational product or device	4 weeks	–
Live-attenuated vaccine	4 weeks or 5 half-lives (whichever is longer)	–
Systemic corticosteroid (oral/injectable)[a]	4 weeks	–
Systemic treatment (other than biologics) that could affect AD and/or pruritus[b]	4 weeks	–
PUVA treatment, UV-B phototherapy (including tanning beds) or excimer laser, excessive sun exposure	4 weeks	–
Topical medicated treatment that could affect AD and/or pruritus[c]	2 weeks	–
Doxepin	2 weeks	–
Oral, sedative, H_1 antihistamine[d]	2 weeks	–
Anticoagulant medication[e]	–	2 weeks
Antibiotics (systemic or topical) for infected AD	2 weeks	–

[a] Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.
[b] For example, retinoids, calcineurin inhibitors, PDE-4 inhibitors, methotrexate, cyclosporine, hydroxycarbamide (hydroxyurea), azathioprine, interferon-gamma, or opioids (agonist, partial agonist-mixed, or antagonist).
[c] Including but not limited to topical corticosteroids, crisaborole, calcineurin inhibitors, antihistamine, pramoxine, tars, antimicrobials, stable doses of prescription topical analgesics/moisturizers or over-the-counter topical analgesics/moisturizers containing menthol, camphor, urea additives, or lactic acid.
[d] Including, but not limited to, diphenhydramine and hydroxyzine. Note: Oral, nonsedative, H1 antihistamines to treat allergies will be permitted during the study only if the participant has been on a stable dose for at least 2 weeks prior to the run-in period and continues to use the same agent at the same frequency throughout the study.
[e] For example, heparin, LMW-heparin, warfarin, antiplatelets (except low-dose aspirin ≤ 81 mg, which will be allowed). Note: NSAIDs will not be considered antiplatelets and will be allowed.

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 he/she does not want to be followed any longer; in this case no further data, except data in public domain, may be solicited from or collected on the participant. Participants may choose to discontinue study treatment and remain in the study to be followed for safety.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
  - If this decision is made because of an SAE, the participant must discontinue study drug immediately, and appropriate measures are to be taken. The investigator will notify the sponsor immediately.
- If an application site reaction occurs, the investigator should use their best medical judgement as to whether to continue the participant's treatment.
- Unacceptable toxicity as noted in Section 6.5.2.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

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

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

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study drug, the ET visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit. These visits are described in Table 3. Participants who are discontinued for safety reasons may be asked to come for additional follow-up visits, at the investigator's discretion, after the ET visit to ensure appropriate medical care and AE follow-up. The last date of the last application of study drug and the reason for discontinuation of study drug will be recorded in the eCRF.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for discontinuation must be documented in the participant's medical record and the primary reason for discontinuation must be included in the eCRF.
- The ET visit should be performed and date recorded.
- The status of the participant should be updated to ET in the EDC system.
- Unless the participant is lost to follow-up, the participant must be followed for safety until the time of the follow-up visit or until study drug–related toxicities resolve, return to baseline, stabilize, or are deemed irreversible, whichever is longest.

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

7.2. Participant Withdrawal From the Study

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

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

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

7.3. Lost to Follow-Up

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

The following actions must be taken if a participant fails to return to the clinic for a required study visit (unless a virtual visit is scheduled due to COVID-19–related reasons):

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the participant. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF must contain all required elements and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the countries in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must provide consent to the most current version of the ICF during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and the day the participant receives the first application of study drug (Day 1). Informed consent must be obtained before performing any study-specific procedures. Screening may not exceed 37 days (including 7 days for the run-in period). Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process. Screening procedures are listed in Table 3.

Results from the screening visit evaluations will be reviewed to confirm eligibility before the first application of study drug. Tests with results that fail eligibility requirements may be repeated once during screening, if deemed acceptable by the investigator. For screening assessments that are repeated, the most recent available result before first application of study drug will be used to determine eligibility.

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 (eg, following recovery from an infection). Participants that do not meet the criteria for the single PP-NRS score at screening or for the baseline mean PP-NRS score of eligibility of the 7-day run-in period may not be rescreened and will be considered screen failures.

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

8.1.3. Participant Numbering and Treatment Assignment

All participant ID numbers will be 6 digits; the first 3 digits will be the site number, and the last 3 digits will be the participant's number. This participant number will be maintained throughout the study and will not be reassigned. Participants who withdraw consent or withdraw from the study after being assigned a participant number will retain their initial number. If a participant fails screening and is rescreened, a new participant number must be assigned.

The investigator or designee will select the appropriate number of kits from their stock that corresponds to the %BSA affected by AD at baseline and dispense an individually customized number of kits to the participant. All subsequent dispensing of study drug should follow this process (refer to the SRM).

8.1.4. Diaries

At the screening visit, participant email addresses will be collected and used for log-in access to an eDiary (tablet). Participants will be trained to complete the eDiary once daily, starting from screening and up to the Day 29 visit, and will receive daily email reminders for completion. The eDiary will capture the daily PP-NRS assessment starting at screening up to the Day 29 visit with the exception of Day 1.

A paper diary will also be provided to participants to capture the date and time of twice daily study drug applications starting at the Day 1 visit.

Participants may be contacted on Day 1 and Day 2 as a reminder to complete their dairies.

The completed diaries will be reviewed during each study visit, and data will be confirmed by the study staff. Qualified clinical staff will review the participants' entries for compliance.

Participants will be considered compliant with the treatment regimen if they apply at least 80% but no more than 120% of the expected number of applications during participation in the treatment period of the study. Participants who are noncompliant will have their administration instructions reinforced by the investigator or a qualified designee.

8.1.5. Demography and Medical History

8.1.5.1. Demographics and General Medical History

Demographic data, general medical history, and the Fitzpatrick score will be collected at screening by the investigator or qualified designee and will include age, race, ethnicity, medical and surgical history, and current illnesses. General medical history will be assessed on Day 1 for any changes from screening. Medical history will include relevant medical or surgical treatment within the last 2 years that are considered to be clinically significant by the investigator.

8.1.5.2. Disease Characteristics and Treatment History

A disease-targeted medical and treatment history for the past year will be collected at screening and assessed on Day 1 for any changes from screening by the investigator or qualified designee. Details regarding the participant's history of AD, including date of diagnosis, relevant disease characteristics, and prior treatments, including systemic treatments, radiation, and surgical procedures, will be recorded. The participant's history of chronic itch and the participant's medical history of other conditions related to AD will also be collected at this time.

8.2. Efficacy Assessments

Clinical evaluations of AD will be performed by an experienced and qualified dermatologist (board certified or equivalent) or other suitably qualified and experienced physician. To assure consistency and reduce variability, the same assessor should perform all assessments on a given participant whenever possible.

Unless specified otherwise, the efficacy assessments scheduled during the study visits, as specified in Table 3, will be performed before study drug application. In addition, assessments performed by participants (ie, PP-NRS, mPP-NRS, and TSQM-9 questionnaire) should be completed before the investigator assessments. In addition, refer to Table 5 for the sequence, timing, and allowed windows of mPP-NRS, PP-NRS, and study drug applications on Day 1 and Day 2.

8.2.1. Health Economics

Health Economics parameters are not evaluated in this study.

8.2.2. Assessed by Participant

8.2.2.1. Pruritus Numeric Rating Scale

8.2.2.1.1. Peak-Pruritus Numerical Rating Scale (24-Hour Recall Period)

As specified in Table 3, the intensity of pruritus (itch) will be recorded in the eDairy using an NRS (Phan et al 2012, Yosipovitch et al 2019). Intensity will be evaluated by asking participants

to assign a numerical score representing their itch at the worst moment during the previous 24 hours on a scale of 0 to 10, with 0 being no itch and 10 being the worst itch imaginable. This exercise will be completed daily, in the morning, from the screening visit until Day −1 and from Day 2 to the Day 29 visit. On Day 2, the PP-NRS should be completed approximately 24 (±1) hours after the Day 1 morning dose and before the Day 2 morning dose (refer to Table 5 for details). From Day 3 to the Day 29 visit, the PP-NRS should be completed at approximately the same time each morning and should be complete prior to each morning study drug application, per protocol. The PP-NRS (24-hour recall period) is presented in Appendix C. To be eligible for this study, participants must complete at least 4 daily PP-NRS questionnaires during the last 7 days of screening (the run-in period) and have a mean baseline PP-NRS score ≥ 4.0 during the run-in period, which is defined as the average of all nonmissing scores reported during the 7-day run-in period (Day −7 to Day −1). Inclusion of participants completing fewer than 4 of 7 daily PP-NRS questionnaires during the last 7 days of screening (the run-in period) must be approved by the sponsor.

8.2.2.1.2. Modified Peak-Pruritus Numerical Rating Scale (Current Itch Intensity)

On Day 1 only, participants will be asked to evaluate the current intensity of their itch at the time of assessment (ie, prior to the morning study drug application, as well as at 15 and 30 minutes and 1, 2, 4, 6, and 12 hours after the morning study drug application; the 12-hour evaluation will occur prior to the second daily study drug application [refer to Table 5 for details and allowed windows]) on a scale from 0 to 10, with 0 indicating no itch and 10 indicating the worst imaginable itch (Phan et al 2012, Verweyen et al 2019, Yosipovitch et al 2019). The mPP-NRS (current itch intensity) was modified from the PP-NRS and is presented in Appendix C.

8.2.2.2. Abbreviated 9-Item Treatment Satisfaction Questionnaire for Medication

On Day 29 (or ET as applicable), participants will be asked to complete the TSQM-9. The TSQM-9 is a 9-item measure that assesses the most common dimensions participants use to evaluate their medication (ie, global satisfaction, effectiveness, and convenience). The results for each scale are presented from 0 to 100, where higher scores represent better satisfaction. The questionnaire is provided separately from the protocol.

8.2.3. Assessed by Investigator

8.2.3.1. Investigator's Global Assessment

The IGA of the current state of the disease will be performed at the visits specified in Table 3. It is a 5-point morphological assessment of overall disease severity. The grades for the IGA are shown in Table 9. To be eligible for this study, participants must have an IGA score of at least 2 on Day 1.

Table 9: Investigator's Global Assessment

Grade	Severity	Status
0	Clear	No erythema or induration/papulation, no oozing/crusting; there may be minor residual discoloration.
1	Almost clear	There may be trace faint pink erythema with almost no induration/papulation and no oozing/crusting.
2	Mild	There may be faint pink erythema with mild induration/papulation and no oozing/crusting.
3	Moderate	There may be pink-red erythema with moderate induration/papulation, and there may be some oozing/crusting.
4	Severe	There may be deep or bright red erythema with severe induration/papulation and with oozing/crusting.

Source: www.homeforeczema.org.

The IGA-TS is defined as an IGA score of 0 or 1 with at least a 2-grade reduction from baseline.

8.2.3.2. Body Surface Area

The overall BSA affected by AD (total BSA%) will be evaluated (from 0% to 100%) at the visits specified in Table 3. The palmar surface of 1 hand (using the participant's hand and including the fingers and thumb) represents 1% of his or her total BSA (Thomas and Finlay 2007).

In addition, at the screening and Day 1 visits, the BSA will be evaluated to verify each participant's eligibility, but excluding palms, soles, scalp, genitals, and folds. To be eligible to enroll in this study, participants must have a BSA involvement between 1% and 20% (excluding palms, soles, scalp, genitals, and folds) on Day 1.

Furthermore, on Day 1, the lesions to be treated will be identified on a body diagram. All body areas can be treated. If new lesions appear during the study, the BSA of treated area may need to be re-evaluated. Of note, the BSA of treated area includes active, cleared, and new lesions and should not exceed 20% BSA.

8.2.3.3. Eczema Area and Severity Index

The EASI will be assessed at the visits specified in Table 3. It quantifies the severity of a participant's AD based on both lesion severity and the percentage of BSA affected (Hanifin et al 2001). The EASI is a composite score ranging from 0 to 72 that takes into account the degree of erythema, induration/infiltration (papules), excoriation, and lichenification (each scored from 0 to 3 separately) for each of 4 body regions, with adjustment for the percentage of BSA involved for each body region and for the proportion of the body region to the whole body. A detailed procedure of EASI score calculation is provided in Appendix D. There is no minimum requirement in EASI to be eligible to enter this study.

8.2.3.4. Medical Photography

Medical photographs of the target lesion(s) (even if the AD lesion has cleared or disappeared) will be performed at the visits specified in Table 3 via 2 views (close-up and regional). Medical photographs of application site AEs should also be taken.

Care will be taken to use the same camera, the same magnification, and the same settings for each photograph at each visit in order to obtain comparable pictures. Medical photographs will be taken using a blue background.

8.2.3.5. Transepidermial Water Loss

Transepidermial water loss will be evaluated at the visits specified in Table 3. This measurement quantifies the clinical severity of AD and the associated effect on skin barrier function.

Transepidermial water loss will be measured on the lesional (target lesion) and nonlesional skin on Day 1 and Day 29. The TEWL assessment should be performed after medical photographs but prior to skin sample collection and at least 3 centimeters away from sites of skin sample collection and previous scars (for Day 29). The location(s) of TEWL will be recorded. On Day 1, TEWL assessments should be performed prior to study drug application. On Day 29, TEWL should be performed on the same lesional and nonlesional skin identified on Day 1, even if the lesion has cleared. Three TEWL readings will be taken at each location. The readings should be taken in standard room ambient conditions (20°C to 22°C ± 1°C and < 60% relative humidity); the mean or median of the TEWL measurements will be used for analysis. More details can be found in the SRM and SAP.

8.3. Safety Assessments

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

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 15 (± 2) days after the last study drug application. Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study drug. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

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

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

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

8.3.2. Physical Examinations

Physical examinations must be performed by a medically qualified individual, such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, as local law permits. Abnormalities identified after the first application 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 drug. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2.1. Comprehensive Physical Examination

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

8.3.2.2. Targeted Physical Examination

Targeted physical examinations will be performed as needed at the visits specified in Table 3.

The targeted physical examination will be a symptom-directed evaluation and will include assessment of the body systems or organs as indicated by participant symptoms, AEs, or other findings and documented on the AE eCRF.

8.3.3. Vital Signs

Vital signs will be collected at the screening visit. Vital sign measurements (to be taken before blood collection for laboratory tests) include systolic and diastolic blood pressure (mmHg), pulse (bpm), body temperature (°C), and respiratory rate (breaths/min). If vital signs cannot be taken before blood collection for laboratory tests, there must be a minimum of 30 minutes from the completion of the blood collection procedures to the beginning of the vital signs collection. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after 5 minutes of rest.

If deemed appropriate by the investigator, clinically significant findings in the vital signs assessment will exclude a participant from study participation. Any abnormal finding related to vital signs that the investigator considers to be clinically significant must be recorded as an AE.

8.3.4. Laboratory Assessments

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

Additional testing may be required by the sponsor based on emerging safety data. All Protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual and Table 3. Information regarding collection, processing, and shipping of samples for laboratory assessment is provided in the Laboratory Manual.

Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 15 (± 2) days after the last application of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

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

Table 10: Required Laboratory Analytes

Serum Chemistries	Hematology	Urinalysis	Serology
Albumin Alkaline phosphatase ALT AST Blood urea nitrogen or urea Chloride Creatinine Gamma-glutamyl transferase Glucose random Lactate dehydrogenase Potassium Sodium Total bilirubin Direct bilirubin (if total bilirubin is elevated above ULN) Lipid panel Uric acid	Complete blood count, including: • Hemoglobin • Mean corpuscular hemoglobin • Hematocrit • Platelet count • Mean platelet volume • Red blood cell count • Mean corpuscular volume • WBC count Differential count, including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils Absolute values must be provided for: • WBC differential laboratory results	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein Urobilinogen Microscopic analysis (as required)	HIV **Pregnancy Testing** hCG (WOCBP only; serum and urine) **Other** FSH (only for female participants of nonchildbearing potential who had a cessation of menses for at least 12 months without an alternative medical cause)

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.

8.3.4.1. Chemistry, Serology, Hematology, and Urinalysis

A panel of standard serum chemistries, hematology, and urinalysis tests will be analyzed at times shown in Table 3. A list of required analytes is provided in Table 10. All serum chemistries will be performed from blood samples collected without respect to food intake (ie, nonfasting).

Assessments will be performed at the screening visit to rule out HIV infection. Serology tests should be performed early in the screening process due to the length of time needed to obtain the results. Additional tests may be performed if clinically needed.

8.3.4.2. Pregnancy Testing

A serum pregnancy test will be required for all WOCBP during screening. Urine pregnancy tests will be performed at other specified visits outlined in Table 3. If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test.

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

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

[redacted]

[redacted]

8.6. Unscheduled Visits

Unscheduled study visits may occur at any time as medically warranted. Any assessments performed at those visits should be recorded in the eCRF.

If the participant develops new areas of AD, documentation of the new BSA may occur at an unscheduled visit if appropriate.

8.7. End of Treatment and/or Early Termination

If a decision is made that the participant will permanently discontinue study drug, then the ET visit should be conducted. If the ET visit coincides with a regular study visit, the ET evaluations will supersede those of that scheduled visit, and the data should be entered in the ET visit 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 have the ET procedures completed. The participant should be encouraged to return for the follow-up visit.

8.8. Follow-Up

8.8.1. Safety Follow-Up

The safety follow-up period is the interval between the Day 29 visit and the scheduled follow-up visit and should occur 15 (± 2) days after the last application of study drug. Adverse events and SAEs must be reported up until 1) within 15 (± 2) days after the last application of study drug or 2) until toxicities resolve, return to baseline, stabilize, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant return for the follow-up visit and report any AEs that may occur during this period.

9. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

9.1. Definition of Adverse Event

Adverse Event Definition
• An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug-related. • An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.
Additional Guidance for Events Meeting the Adverse Event Definition
• Any safety assessments (eg, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease) are to be reported as an AE. • Abnormal laboratory test results are to be reported as an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal laboratory test result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition/disease, including either an increase in the frequency and/or intensity of the condition, is to be reported as an AE. • New conditions detected or diagnosed after the start of study drug administration are to be reported as an AE. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction are to be reported as an AE. • Signs and/or symptoms from dosing errors of a study drug (eg, overdose) or a concomitant medication are to be reported as an AE. • "Lack of efficacy," "disease progression," or "failure of expected pharmacological action" will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. • 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 ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment 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) are not considered SAEs.
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, or development of drug dependency or drug abuse.

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

Adverse Event and Serious Adverse Event Recording

- An AE/SAE (including local and systemic reactions) that begins or worsens after informed consent is signed should be recorded on the Adverse Event Form in the eCRF. 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 delegate) will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completing the Adverse Event 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 SRM.
- 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 severity.
- Whether there is at least a reasonable possibility that the AE is related to the study drug: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at the final safety follow-up visit.
- The action taken with regard to study drug as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the Adverse Event Form and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Non-Drug Therapy).

Assessment of Intensity

The severity of AEs/SAEs 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. For grading of AEs related to laboratory values; the CTCAE grading of the laboratory result should generally be followed (eg, for an AE of thrombocytopenia, the CTCAE grading of platelet count decreased should be followed).

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

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
- **Grade 2:** Moderate; minimal, local, or noninvasive treatment indicated; limiting age-appropriate activities of daily living.
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- **Grade 4:** Life-threatening consequences; urgent treatment indicated.
- **Grade 5:** Fatal.

Assessment of Causality

- The investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are medical facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the possibility of a relationship.
- The investigator will also consult the RSI in the IB in making his/her assessment.
- Alternative causes, such as underlying or concurrent disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, the causality assessment is one of the criteria used when determining regulatory reporting requirements. **Therefore, it is very important that the investigator always make an assessment of causality based on the available information for every event before the initial transmission of the SAE.**
  - The investigator may change his/her opinion of causality in light of follow-up information and 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 AE eCRFs until it has resolved, has stabilized, or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome. • When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings, including histopathology. • Updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance 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.

In the event a participant experiences a skin reaction and that an allergic contact dermatitis is suspected, the event should be documented as an AE, and patch testing may be performed to confirm the diagnosis.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study drug or study procedures), all SAEs occurring after the participant has signed the ICF through the last safety visit or within 15 (± 2) days after the last application of study drug must be reported to the sponsor (or designee) immediately, without undue delay but not later than within **24 hours** of obtaining knowledge of its occurrence unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) immediately, without undue delay but not later than within 24 hours of it being available.

Investigators are not obligated to actively seek SAE information after the safety follow-up visit or 15 (± 2) days after the last application of study drug. However, if the investigator learns of any SAE, including death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must notify the sponsor (or designee) within 24 hours of becoming aware of the event.

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

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

If the SAE is not documented in the RSI of the IB for the study drug (new occurrence) and is thought to be related to the study drug, the sponsor or its designee may urgently require further information from the investigator for expedited reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected unexpected serious adverse reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or 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 Event Form in the eCRF. • The investigator must report within 24 hours of learning of its occurrence any SAE by completing the Serious Adverse Event Report Form in English. • Follow-up information is also recorded and transmitted to Incyte Pharmacovigilance on an amended or new Serious Adverse Event Report Form, with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous Serious Adverse Event Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as a follow-up to that event, regardless of when it occurs. • Contacts for SAE reporting can be found in SRM.

9.5. Events of Clinical Interest

Not applicable.

9.5.1. Adverse Events of Special Interest

Not applicable.

9.6. Emergency Unblinding of Treatment Assignment

Not applicable.

9.7. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a participant during maternal or paternal exposure to study drug, the following procedures should be followed in order to ensure safety:

- The study drug must be discontinued immediately (female participants only).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy Form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

Data on fetal outcome are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form or SRM.

Any SAE occurring during pregnancy of a study participant must be recorded on the Serious Adverse Event Report Form and submitted to the sponsor or its designee.

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

9.8. Warnings and Precautions

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

9.9. Product Complaints

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

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

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

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

9.10. Treatment of Overdose

Overdose is not an SAE unless it meets the criteria of an SAE (see Section 9.2).

For this study, an overdose may consist of accidental or intentional ingestion of the study cream or excessive application onto the skin (eg, exposure to a meaningfully larger BSA than identified at baseline, using a greater quantity of cream versus the initial amount established at baseline, or applying more frequently than instructed).

In the event of overdose, the investigator or treating physician should contact the medical monitor to discuss the event and proceed with the following as appropriate for the circumstances:

- In case of excessive topical application, instruct the participant to wash ruxolitinib cream off of the skin and monitor for application site AEs.
- Obtain a blood sample within 2 days from the date of the last application of study treatment or date of ingestion of cream to determine possible systemic exposure to ruxolitinib (if requested by the medical monitor; determined on a case-by-case basis).
- Monitor the participant for systemic AEs/SAEs and laboratory abnormalities until ruxolitinib can no longer be detected systemically (at least 7 days).
- In the event of ingestion of ruxolitinib cream, general symptomatic treatment should be given as necessary.
- Document the quantity of ruxolitinib cream applied or ingested (eg, by weighing the tube of cream), as well as the duration of excessive application or exposure, in the CRF.

10. STATISTICS

10.1. Sample Size Determination

Approximately 36 participants were planned to be enrolled into the study to receive ruxolitinib 1.5% cream. The sample size calculation was based on the CI for 1-sample mean. With an approximate 10% missing assessment rate at 24 hours, a sample size of 36 is required to produce a 2-sided 95% CI for the expected change from baseline in PP-NRS (24-hour recall period), with a precision of 0.57. The SD of 1.64 is estimated from 2 Phase 3, double-blind, randomized studies (INCB 18424-303 and INCB 18424-304). To ensure data quality and support study interpretation after deviations from protocol related to the timing of efficacy assessments were observed in the first participants enrolled, it was decided to enroll an additional 12 participants for a total of approximately 48 participants to be included.

10.2. Populations for Analysis

The populations for analysis are provided in Table 12.

Table 12: Populations for Analysis

Population	Description
Enrolled	All participants who sign the ICF.
ITT	All enrolled participants who complete the run-in period and meet the inclusion and exclusion criteria. The ITT population will be used for the summary of demographics, baseline characteristics, and participants disposition.
mITT	The mITT population is a subset of the ITT population, including participants who have both baseline and at least 1 postbaseline PP-NRS or mPP-NRS assessment within the treatment period. The mITT population will be used for all efficacy analyses.
Per protocol	The per protocol population is a subset of the mITT population, excluding participants with major protocol deviations that could potentially affect the efficacy evaluations. The per protocol population will be used as supportive information for all efficacy analyses.
Safety	The safety population will include all enrolled participants who received at least 1 application of ruxolitinib 1.5% cream. All safety analyses will be conducted using the safety population.
[redacted]	[redacted]

10.3. Level of Significance

No formal statistical comparisons will be performed. All CIs will be 95%.

10.4. Statistical Analyses

10.4.1. General Considerations

The baseline value for a variable will be defined as the last nonmissing value before or on Day 1 (prior to the first application of study drug), unless otherwise specified. For PP-NRS, the baseline is defined as the average of all nonmissing PP-NRS scores reported during the 7-day run-in period (Day −7 to Day −1).

For continuous measurements, summary statistics will include sample size, mean, median, SD, standard error of the mean, minimum, and maximum. Summary statistics for continuous measures will be provided for baseline, the actual measurements at each visit, and the change and percentage change from baseline at each visit, if applicable. For categorical measurements, summary statistics will include sample size, frequency, and percentages.

Any deviation(s) from the SAP will be described and justified in the final report, as appropriate.

10.4.2. Primary Analysis

The primary endpoint, change in PP-NRS from baseline at Day 2 (24-hour recall period after first application), will be analyzed descriptively. The 95% CI will be provided for the mean change. The baseline for this analysis will be the average of all nonmissing PP-NRS scores reported during the 7-day run-in period (Day −7 to Day −1); at least 4 completed PP-NRS worksheets will be required prior to Day 1 (unless otherwise approved by the sponsor).

10.4.3. Secondary Analysis

All secondary efficacy endpoints will be analyzed descriptively, with summary statistics for continuous endpoints and frequency distribution for binary endpoints. The onset of action will be analyzed using a change from baseline in mPP-NRS (current itch intensity) on Day 1, in which baseline is defined as the current itch (mPP-NRS) prior to the first application of study drug on Day 1. The 95% CIs will also be provided. The change in PP-NRS over time from baseline will be presented graphically. The log-rank test with the Kaplan-Meier curves will be applied to the time-to-event endpoints.

10.4.4. Safety Analyses

Safety analyses will be conducted for the safety population.

Adverse events (local and systemic) will be coded by the MedDRA dictionary, and TEAEs (ie, AEs reported for the first time or worsening of a pre-existing event after first application of study drug) will be tabulated by preferred term and system organ class for all events, related events, and events of Grade 3 or higher. Quantitative safety variables (eg, laboratory assessments, vital signs) and their changes from baseline will be summarized with descriptive statistics. Clinically notable abnormal values will be flagged and tabulated based on predefined criteria.

The clinical laboratory data will be analyzed using summary statistics. Descriptive statistics will be determined for vital signs. Vital sign results will be reviewed for clinically notable abnormalities.

Measures of exposure (eg, days of exposure, number of applications) to study drug will be summarized by means of summary statistics.

[redacted]

10.4.6. Other Analysis

TSQM-9 data will be summarized using descriptive statistics.

10.5. Interim Analysis

No formal interim analysis is planned in this study.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol Amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require approval from both Health Authorities and IRB/IEC before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB/IEC requirements, institutional requirements, and applicable laws and country-specific regulations.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling participants who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
  - All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

11.2. 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 (or delegate) 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 [redacted], or data transfer specifications or agreements, as applicable.

The sponsor (or designee) will be responsible for:

- Managing the integrity of the data and the quality of the conduct of the study, such as ensuring that study monitors perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved Protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Managing and reconciling the data generated, and/or collected including documents and results such as laboratory or imaging data analyzed centrally by a designated vendor of the sponsor.

The investigator will be responsible for:

- Recording, or ensuring the recording of, all relevant data relating to the study in the eCRF.
- Delivering, or ensuring the delivery of, all other results, documents, data, know-how, or formulas relating to the study to the sponsor or designee electronically and/or centrally (eg, laboratory data, imaging data, [redacted], photographs, diary data), or as otherwise specified in the Protocol.
- Maintaining adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source data are in general all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
- Verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

- Maintaining accurate documentation (source data) that supports the information entered in the eCRF, or sent to a central vendor designated by the sponsor, or as described in other study and data flow manuals.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed 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, or copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and participant records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all participants.
  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.

11.3. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that sensitive personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable. Appropriate consent for collection, use and disclosure and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws.

Participant names will not be supplied to the sponsor or its designee. Only the participant number will be recorded in the eCRF; if the participant's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with appropriate technical and organizational measures as required by local data protection laws.

11.4. Financial Disclosure

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

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

11.5. Publication Policy

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

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

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

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

11.6. Study and Site Closure

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS 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
  - Female participant who has had a cessation of menses for at least 12 months prior to the screening visit without an alternative medical cause, and an FSH test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory levels).

For male participants of reproductive potential[b]

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

- Barrier method (use of a male condom or partner use of a female condom, cervical cap, diaphragm, or contraceptive sponge) in conjuction with spermicide
- Vasectomy (performed ≥ 4 months prior to screening)
- Partner use of hormonal contraceptives (eg, combined oral contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices, or intrauterine systems
- Partner has had a tubal ligation
- Sexual abstinence[c]
  - Abstinence from penile-vaginal intercourse

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

- Periodic abstinence (calendar, symptothermal, post ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method
- Male 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 are considered effective:

- Barrier method (use of a male condom or partner use of a female condom, cervical cap, diaphragm, or contraceptive sponge) in conjuction with spermicide
- Hormonal contraception (eg, combined oral contraceptive, patch, vaginal ring, injectable, or implant)
- Intrauterine device
- Intrauterine hormone-releasing system
- Tubal ligation
- Vasectomized partner (provided vasectomy was performed ≥ 4 months prior to screening)
- 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 (excluding vasectomized participants) has a partner with 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 treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.

Source: Clinical Trials Facilitation and Coordination Group (2020).

APPENDIX B. DIAGNOSTIC CRITERIA FOR ATOPIC DERMATITIS

A participant is to have a clinical diagnosis of AD according to the criteria of Hanifin and Rajka (1980). The criteria are as follows:

Major Criteria (must have at least 3)

- Pruritus
- Typical morphology and distribution:
  - Adults: flexural lichenification or linearity
  - Children and infants: involvement of facial and extensor surfaces
- Chronic or chronically relapsing dermatitis
- Personal or family history of atopy (asthma, allergic rhinitis, AD)

Minor Criteria (must have at least 3)

- Xerosis
- Ichthyosis/keratosis pilaris/palmar hyperlinearity
- Immediate (Type 1) skin test reactivity
- Elevated serum IgE
- Early age at onset
- Tendency to skin infections (*Staphylococcus aureus*, herpes simplex)/impaired cellular immunity
- Tendency to nonspecific hand/foot dermatitis
- Nipple eczema
- Cheilitis
- Recurrent conjunctivitis
- Dennie-Morgan infraorbital fold
- Keratoconus
- Anterior subcapsular cataracts
- Orbital darkening
- Facial pallor/erythema
- Pityriasis alba
- Anterior neck folds
- Itch when sweating
- Intolerance to wool and lipid solvents
- Perifollicular accentuation
- Food intolerance
- Course influenced by environmental/emotional factors
- White dermographism/delayed blanch

APPENDIX C. PRURITUS NUMERIC RATING SCALE

Peak Pruritus NRS (24-hour recall period)

On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?

Numeric Rating Scale

0	1	2	3	4	5	6	7	8	9	10

No itch — Worst itch imaginable

Modified Peak Pruritus NRS (current itch intensity)

On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your current itch?

Numeric Rating Scale

0	1	2	3	4	5	6	7	8	9	10

No itch — Worst itch imaginable

Note: This scale is a modified version of the PP-NRS (Phan et al 2012, Verweyen et al 2019).

APPENDIX D. ECZEMA AREA AND SEVERITY INDEX

Four anatomic sites (head, upper extremities, trunk, and lower extremities) are assessed for erythema, induration/infiltration (papules), excoriation, and lichenification as seen on the day of the examination. The severity of each sign is assessed using the following 4-point scale (half steps **are** allowed; eg, 0.5, 1.5, and 2.5):

- 0 = none
- 1 = mild
- 2 = moderate
- 3 = severe

The area affected by AD within a given anatomic site is estimated as a percentage of the total area of that anatomic site and assigned a numerical value according to the degree of AD involvement as follows:

- 0 = no involvement
- 1 = < 10%
- 2 = 10% to < 30%
- 3 = 30% to < 50%
- 4 = 50% to < 70%
- 5 = 70% to < 90%
- 6 = 90% to 100%

The EASI score is obtained by using the following formula:

$$EASI = 0.1 (E_h + I_h + Ex_h + L_h) A_h + 0.2 (E_u + I_u + Ex_u + L_u) A_u + 0.3 (E_t + I_t + Ex_t + L_t) A_t + 0.4 (E_l + I_l + Ex_l + L_l) A_l.$$

Where E, I, Ex, L, and A denote erythema, induration, excoriation, lichenification, and area, respectively, and h, u, t, and l denote head, upper extremities, trunk, and lower extremities, respectively.

APPENDIX E. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1	30 MAR 2021
Amendment 2	13 AUG 2021
Amendment 3	09 MAY 2022

Amendment 3 (09 MAY 2022)

The primary purpose of this amendment is two-fold: to clarify the sequence and timing of events on Day 1 and Day 2 for the mPP-NRS, PP-NRS, and study drug applications, and to increase the number of participants to be included in the study.

1. **Section 1, Protocol Summary (Treatment Groups and Duration; Table 3: Schedule of Activities); Section 4.1, Overall Design; Section 6.1, Study Treatment Administered (Table 6: Study Treatment Information); Section 8.2, Efficacy Assessments; Section 8.2.2.1.1, Peak-Pruritus Numerical Rating Scale (24-Hour Recall Period); Section 8.2.2.1.2, Modified Peak-Pruritus Numerical Rating Scale (Current Itch Intensity)**

   Description of change: Updated with additional text and added new table (ie, Table 5) to clarify mPP-NRS and PP-NRS timing, and to allow windows of mPP-NRS, PP-NRS, and study drug applications on Day 1 and Day 2.

   Rationale for change: Timing of mPP-NRS and PP-NRS are critical, and should take precedence on Day 1 and Day 2.

2. **Section 1, Protocol Summary (Table 2: Key Study Design Elements); Section 4.1, Overall Design; Section 10.1, Sample Size Determination**

   Description of change: Increased the number of participants from 36 to 48.

   Rationale for change: To ensure data quality and support study interpretation after deviations from protocol related to the timing of efficacy assessments were observed in the first participants enrolled.

3. **Section 1, Protocol Summary (Treatment Groups and Duration); Section 4.1, Overall Design; Section 6.1, Study Treatment Administered**

   Description of change: Removed the ± 2 hours window for the every 12 hours (BID) study drug application.

   Rationale for change: To avoid confusion and potential error regarding the sequence of NRS completion and IP application.

4. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 4.1.1, Study Conduct During the COVID-19 Pandemic; Section 6.4, Study Treatment Compliance; Section 8.1.4, Diaries**

   Description of change: Clarified that the twice daily study drug application will be captured in a paper diary, and only the daily PP-NRS assessment will be captured in the eDiary.

Rationale for change: The eDiary does not collect time of study drug applications as indicated in Protocol Section 6.4.

5. **Section 1, Protocol Summary (Treatment Groups and Duration; Table 3: Schedule of Activities); Section 4.1.1, Overall Design; Section 5.1, Inclusion Criteria (Criterion #10); Section 6.1, Study Treatment Administered; Section 8.2.2.1.1, PP-NRS**

   Description of change: Clarified that the PP-NRS should be completed from screening to Day −1 and from Day 2 to the Day 29 visit (before morning study drug application).

   Rationale for change: As the PP-NRS efficacy endpoints are up to Day 29, the PP-NRS needs to be collected up to the Day 29 visit.

6. **Section 2.1.1, Ruxolitinib**

   Description of change: Updated to acknowledge the recent FDA approval of ruxolitinib 1.5% cream for treatment of atopic dermatitis.

   Rationale for change: Ruxolitinib 1.5% cream received FDA approval on 21 SEP 2021 for the atopic dermatitis indication.

7. **Section 2.3, Benefit/Risk Assessment**

   Description of change: Updated to be aligned with the latest version of the IB.

   Rationale for change: A new IB dated 16 AUG 2021 is now available.

8. **Section 5.3, Lifestyle Considerations**

   Description of change: Addition of text for participants to refrain from washing or applying cosmetics to the targeted lesions(s) and adjacent areas.

   Rationale for change: To align with current microbiome skin swab kit recommendations and with the laboratory manual.

9. **Section 10.2, Populations for Analysis (Table 13: Populations for Analysis)**

   Description of change: Added a per protocol population as supportive information for the efficacy analyses.

   Rationale for change: To exclude participants with major protocol deviations that could potentially affect the efficacy evaluations.

10. **Section 10.4.4, Safety Analyses**

    Description of change: Removed the distributions of key laboratory parameters over time and the change from baseline in vital signs.

    Rationale for change: As laboratory values are only measured at baseline and Week 4/ET, laboratory values will not be plotted over time. Similarly, as vital signs are only collected at screening, no change from baseline will be reported.

11. **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 2 (13 AUG 2021)

The primary purpose of this amendment is to revise exclusion criteria, translational assessments and analyses, as well as provide other general clarifications.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Table 3: Schedule of Activities); Section 2.2.1, Scientific Rationale for Study Design; Section 4.1, Overall Design; Section 4.2, Overall Study Duration; Section 6.1, Study Treatment Administered (Table 5: Study Treatment Information); Section 6.5, Dose Modifications; Section 8.1.4, Electronic Diaries**

   Description of change:

   - Added ± 2 days to the treatment period to be 28 (± 2) days, and updated the estimated time an individual will participate in the study to 80 days.
   - Updated that treatment will be approximately 28 days, and the last application to occur the evening prior to the Day 29 visit.
   - Clarified that any new lesions must be treated until the evening prior to the Day 29 visit.

   Rationale for change: The intent is for participants to continue to apply the study drug up until the evening prior to the Day 29 visit. With the allowed visit window of ± 2 days, there may be situations where a participant does not have their Day 29 visit until Day 31, but would have stopped application of study drug on the evening of Day 28. This allows the participant to continue treatment up to their Day 29 visit.

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 8.2.2.1.2, Modified Peak-Pruritis Numerical Rating Scale (Current Itch Intensity)**

   Description of change: Removed the mPP-NRS assessment from the participant's eDiary notes of the SoA, and updated the mPP-NRS 0.25 and 0.5 hour time points to 15 and 30 minutes in the PP-NRS and mPP-NRS notes of the SoA and in Section 8.2.2.1.2.

   Rationale for change: The mPP-NRS is completed on paper, and therefore, not linked to the eDiary. The time points for the mPP-NRS assessments were updated to align with the objectives and endpoints and improve clarity.

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

   Description of change: [redacted]

   Rationale for change: Analyses was no longer logistically feasible given the study timelines and was removed.

4. **Section 5.2, Exclusion Criteria (Criteria #10, #11, #12, and #34)**

Description of change: Updated criterion #10 to include renal disease requiring dialysis as one of the limiting medical conditions. Revised the list of clinical lab test results at screening in criterion #11. Removed criterion #12 regarding the positive result for HIV as it was moved into criterion #11. Added new criterion #34 for a history of hepatitis B virus or hepatitis C virus infection.

Rational for change: The criterion #10 addition of renal disease was to add more clarification for the limiting medical conditions. Criterion #11 was determined to be overly restrictive and could potentially limit enrollment. This revision also ensures consistency across the ruxolitinib cream AD program and does not impose additional risks to participants. The estimated GFR criterion was also updated to a more conservative value to ensure participant safety. Criterion #12 removal was due to it being moved into a screening exclusion in criterion #11. Criterion #34 was added to capture the history of hepatitis B or hepatitis C viruses since it was previously omitted.

5. **Section 6.5, Dose Modifications**

   Description of change: Added that at any time during the study the participant's BSA exceeds 20%, the participant should be considered for termination.

   Rational for change: In response to agency feedback as well as to ensure consistency across the ruxolitinib AD program.

6. **Section 6.5.1, Criteria and Procedures for Application Interruptions and Adjustments of Study Drug (Table 6: Guidelines for Interruption and Restarting of Treatment Applications if Adverse Event is Deemed Related to the Study Drug)**

   Description of change: Replaced the AE related to study drug list in the table.

   Rationale for change: The changes were implemented to better align with the revised exclusion criterion.

7. **Section 8.1.4, Electronic Diaries**

   Description of change: Revised text to include collection of each participant's email address for log-in access to an eDiary, receipt of twice daily email reminders, and that the eDiary will capture twice daily study drug applications.

   Rationale for change: To clarify procedures related to use and programming of the eDiary.

[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 (30 MAR 2021)

The primary purpose of this amendment is to incorporate Health Authority comments.

1. **Section 5.2, Exclusion Criteria**

   Description of change: Exclusion Criterion 11b was revised to include any participant who is on maintenance dialysis or has an estimated GFR ≤ 15 mL/min/1.73 m^2.

   Rationale for the change: To incorporate Health Authority comments.

2. **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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