Official Title: A Phase 3, Double-Blind, Randomized, Vehicle-Controlled, Efficacy and Safety Study of Ruxolitinib Cream Followed by a Long-Term Safety Extension Period in Children (Ages ≥ 2 Years to < 12 Years) With Atopic Dermatitis

NCT Number: NCT04921969

Document Date: Protocol Amendment 6: 23-February-2023

Clinical Study Protocol

INCB 18424-305

Topical **Ru**xolitinib **E**valuation in **A**topic **D**ermatitis Study **3**
(TRuE-AD3)

A Phase 3, Double-Blind, Randomized, Vehicle-Controlled, Efficacy and Safety Study of Ruxolitinib Cream Followed by a Long-Term Safety Extension Period in Children (Ages ≥ 2 Years to < 12 Years) With Atopic Dermatitis

Product:	**Ruxolitinib Cream**
IND Number:	[redacted]
EudraCT number:	**2021-000489-14**
Phase of Study:	**3**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, Delaware, USA 19803**
Original Protocol:	**25 MAR 2021**
Protocol Amendment 1:	**06 MAY 2021**
Protocol Amendment 2:	**02 AUG 2021**
Protocol Amendment 3:	**19 AUG 2021**
Protocol Amendment 4:	**06 APR 2022**
Protocol Amendment 5:	**29 JUL 2022**
Protocol Amendment 6:	**22 FEB 2023**

INVESTIGATOR'S AGREEMENT

I have read the INCB 18424-305 Protocol (Amendment 6 dated 22 FEB 2023) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

(Printed Name of Investigator)

(Signature of Investigator) (Date)

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BID	twice daily
BSA	body surface area
[redacted]	[redacted]
CFR	Code of Federal Regulations
COVID-19	coronavirus disease 2019
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
EASI	Eczema Area and Severity Index
EASI50/75/90	≥ 50%/75%/90% improvement in Eczema Area and Severity Index score
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GFR	glomerular filtration rate
HCV	hepatitis C virus
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
[redacted]	[redacted]
IEC	independent ethics committee
IGA	Investigator's Global Assessment
IGA-TS	Investigator's Global Assessment Treatment Success

Abbreviations and Special Terms	Definition
IL	interleukin
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
JAK	Janus kinase
LLN	lower limit of normal
LTS	long-term safety
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numerical Rating Scale
P1NP	procollagen type 1 N-terminal propeptide
PD	pharmacodynamic
PDE4	phosphodiesterase 4
[redacted]	[redacted]
PK	pharmacokinetics
[redacted]	[redacted]
PP	per protocol
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
SOP	standard operating procedure
SPF	sun protection factor
Study cream	This term refers to Incyte medicinal investigational product(s) or matching placebo(s) used for this study.
Study treatment	This term refers to all medications that the participant is required to receive as part of this study.
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UV	ultraviolet
[redacted]	[redacted]
VC	vehicle-controlled

1. PROTOCOL SUMMARY

Protocol Title:

Topical **Ru**xolitinib **E**valuation in **A**topic **D**ermatitis Study **3** (TRuE-AD3)

A Phase 3, Double-Blind, Randomized, Vehicle-Controlled, Efficacy and Safety Study of Ruxolitinib Cream Followed by a Long-Term Safety Extension Period in Children (Ages ≥ 2 Years to < 12 Years) With Atopic Dermatitis

Protocol Number: INCB 18424-305

Objectives and Endpoints:

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

Table 1: Primary and Key Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To establish the efficacy of ruxolitinib cream in participants with AD.	Proportion of participants who achieve IGA-TS at Week 8.
Key Secondary	
To further assess the treatment effects of ruxolitinib cream.	Proportion of participants with a ≥ 4-point improvement in Itch NRS score from baseline to Week 8. Proportion of participants with a ≥ 4-point improvement in Itch NRS score from baseline to Day 7 (Week 1). Proportion of participants with a ≥ 4-point improvement in Itch NRS score from baseline to Day 3.

Overall Design:

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

Table 2: Key Study Design Elements

Study Phase	Phase 3
Clinical Indication	Atopic dermatitis
Population	Children aged ≥ 2 years to < 12 years (with at least 40% of participants ages ≥ 2 years to 6 years) who have been diagnosed with AD for at least 3 months, have an IGA score of 2 to 3, and have %BSA involvement (excluding the scalp) of 3% to 20%.
Number of Participants	Approximately 315 participants will be randomized 2:2:1 to 1 of 3 treatment groups (ruxolitinib cream 0.75% BID [n = 126], ruxolitinib cream 1.5% BID [n = 126], or vehicle cream BID [n = 63]). The study will be conducted at approximately 60 sites in the United States and Canada.
Study Design	Randomized (2:2:1), double-blind, VC period (8 weeks) followed by an LTS period (44 weeks) and a 30-day safety follow-up period after the last application of study cream. In the LTS period, participants initially randomized to vehicle cream will be rerandomized (1:1) in a blinded manner to ruxolitinib cream 0.75% or 1.5%, and participants initially randomized to an active treatment group will continue in the same treatment group.
Estimated Duration of Study Participation	Screening period: up to 28 (+ 7) days VC period: approximately 8 weeks LTS period: approximately 44 weeks Safety follow-up period: 30 days after the last application of study treatment or last study visit Total: up to approximately 61 weeks
Data Safety Monitoring Board/Data Monitoring Committee	No
Coordinating Principal Investigator	[redacted], MD

Treatment Groups and Duration:

Male and female children aged ≥ 2 years to < 12 years who have been diagnosed with AD for at least 3 months and have an IGA score of 2 to 3 and %BSA involvement (excluding the scalp) of 3% to 20% will be eligible to participate in the study. Participants who have met all of the inclusion criteria during the screening period (up to 28 days or up to 35 days for participants taking prior medications that require a 4-week washout period [see Section 5.2, Exclusion Criterion 6b]) will be enrolled (randomized 2:2:1) and receive blinded treatment with ruxolitinib 0.75% cream BID, ruxolitinib 1.5% cream BID, or vehicle cream for a total treatment duration of 8 weeks during the VC period of the study.

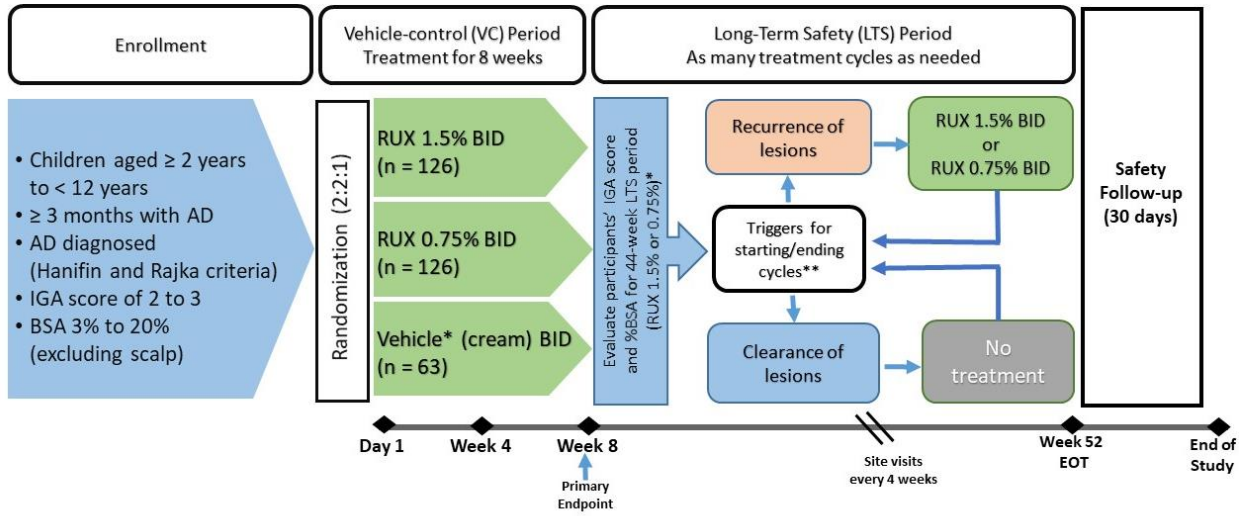
Participants who complete the Week 8 assessments with no additional safety concerns will continue into the 44-week LTS period with the same treatment regimen, except those initially treated with vehicle cream will be rerandomized (1:1) in a blinded manner to 1 of the 2 active

treatment groups (ruxolitinib cream 0.75% or 1.5% BID). The IGA score required for participants to enter the LTS period is 0 to 4, and participants must have a %BSA in the range of 0% to 20% (excluding the scalp).

Following the end of treatment (Week 52/EOT or ET), all participants will have a safety follow-up visit 30 days later (or 30 days after the last application of study treatment if the Week 52/EOT or ET visit was not performed).

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

Figure 1: Study Design Schema



* *At Week 8 (LTS baseline), participants initially on vehicle during the VC period will be rerandomized to either ruxolitinib 1.5% or 0.75% cream BID. Participants initially randomized to either ruxolitinib 0.75% or 1.5% BID will continue their treatment through the LTS period.*

** *Treatment is ceased 3 days after clearing of AD lesions. Treatment is restarted if AD lesions recur. There is no limit on the number of treatment cycles during the 44-week LTS.*

Table 3: Schedule of Activities: Vehicle-Controlled Period

Visit Day (Range)	Screening	VC Period				Notes and Protocol Section
	Days −28 (+ 7[a]) to −1	Day 1/ Baseline	Wk 2 (± 3 d)	Wk 4 (± 3 d)	Wk 8[b]/ET (± 3 d)	
Administrative procedures						
Informed consent/assent	X					Section 8.1.1.
Contact IRT	X	X	X	X	X	Section 8.1.3.
Inclusion/exclusion criteria	X	X				Section 5.
Demography and general medical history	X*					Section 8.1.5.1. *Height and weight of both parents, if available, should be obtained and entered into the EDC.
Relevant AD medical and treatment history	X					Section 8.1.5.2.
Collect/obtain growth measurements for the year prior to study entry	X*	X*				Section 8.4.3. *Collected at either screening or baseline. A reasonable effort must be made to collect and document measurements prior to baseline. If unable to obtain, the reason should be documented.
Prior/concomitant medications and procedures	X	X	X	X	X	Section 6.6.
Apply study cream at site		X	X	X	X*	Section 6.1; at each visit (except for the Week 8 visit if IGA is 0), starting at Day 1, the participant should apply the first (morning) application under direct site staff supervision to all areas identified at Day 1, even if the AD lesion is cleared or disappeared. *Not applicable to the ET visit.
Weigh and dispense study cream; dispense diary cards		X	X	X	X*	Section 6.1 and Section 8.1.4. * Not applicable to the Week 8 visit if IGA score = 0 or to the ET visit.
Collect and weigh study cream; collect diary cards			X	X	X	Section 6.1.
Assess compliance			X	X	X	Section 6.4.
Safety assessments						
AE assessment	X	X	X	X	X	Section 8.4.1.
Comprehensive physical examination	X				X*	Section 8.4.2.1. *For the ET visit only.

Table 3: Schedule of Activities: Vehicle-Controlled Period (Continued)

Visit Day (Range)	Screening	VC Period				Notes and Protocol Section
	Days −28 (+ 7[a]) to −1	Day 1/ Baseline	Wk 2 (± 3 d)	Wk 4 (± 3 d)	Wk 8[b]/ET (± 3 d)	
Safety assessments (continued)						
Targeted physical examination*		X	X	X	X†	Section 8.4.2.2. *Conducted only when indicated by symptoms reported by participant (ie, AEs or other findings); clinically significant abnormalities (in the investigator's judgment) are to be reported as AEs. †Not done for the ET visit.
Height and weight		X			X	Section 8.4.3; height should be measured with a stadiometer.
Vital signs	X	X	X	X	X	Section 8.4.3; vital signs are taken before blood sampling and other procedures.
Efficacy assessments						
Evaluate %BSA affected by AD (excluding skin dryness)	X	X	X	X	X*	Section 8.2.2; evaluate %BSA (excluding the scalp) affected by active AD lesions using the handprint method. *At Week 8, the %BSA range is 0% to ≤ 20% for the LTS period.
Target lesion identification	X	X*				Section 8.2.3; the longest diameter and the span perpendicular to the longest diameter will be measured in centimeters. *For photography participants, a lesion of ≥ 5 cm^2 (target lesion) is to be identified at screening and confirmed at the baseline visit (excluding the hands, feet, and genitalia).
Photography (target lesion and regional body area)*		X	X	X	X	Section 8.2.4; photography of the target lesion area identified at Day 1/baseline even if the lesion has cleared. *Performed only for photography participants at selected sites.
IGA	X	X	X	X	X*	Section 8.2.5. *At Week 8, the IGA range is 0 to 4 for the LTS period.
EASI	X	X	X	X	X	Section 8.2.6; evaluate EASI in 4 regions (head/neck, upper limbs, trunk, and lower limbs) and overall.
Itch NRS	eDiary is completed each evening from screening through the last application of study cream during the VC period (night prior to Week 8 visit).					Section 8.2.7; baseline itch (defined as the average of at least 4 of the 7 days directly before Day 1) must be NRS ≥ 4. Note: Itch is collected from participants ≥ 6 years of age.
[redacted]						

Table 3: Schedule of Activities: Vehicle-Controlled Period (Continued)

Visit Day (Range)	Screening	VC Period				Notes and Protocol Section
	Days −28 (+ 7[a]) to −1	Day 1/ Baseline	Wk 2 (± 3 d)	Wk 4 (± 3 d)	Wk 8[b]/ET (± 3 d)	
[redacted]						
Laboratory assessments						Blood draws for clinical laboratory tests must be performed before the in-clinic study cream application. Use of a topical anesthetic prior to blood draw is recommended.
Serum chemistries	X	X*	X		X	Section 8.4.4. *Day 1 testing will be performed only if the interval between this visit and the screening visit is > 2 weeks.
Hematology	X	X*	X		X	Section 8.4.4. *Day 1 testing will be performed only if the interval between this visit and the screening visit is > 2 weeks.
Serology	X*					Section 8.4.4.3. *HIV antibody.
Pregnancy testing	X	X*			X	Section 8.4.4.2; at the indicated visits, only female participants who have reached menarche will undergo a urine pregnancy test. A positive urine test must be confirmed by a serum test. *Day 1 testing will be performed only if the interval between this visit and screening is > 2 weeks.

Table 3: Schedule of Activities: Vehicle-Controlled Period (Continued)

Visit Day (Range)	Screening	VC Period				Notes and Protocol Section
	Days −28 (+ 7[a]) to −1	Day 1/ Baseline	Wk 2 (± 3 d)	Wk 4 (± 3 d)	Wk 8[b]/ET (± 3 d)	
[redacted]						

Note: Unscheduled visits may occur at any time at the investigator's discretion, and appropriate clinical and laboratory tests may be performed as clinically indicated.

[a] For prior medications that require a 4-week washout period (see Section 5.2, Exclusion Criterion 6b), a 35-day screening period is allowed.

[b] Week 8 is the baseline for participants eligible to continue in the LTS period (IGA score = 0-4 and BSA = 0%-20%).

Table 4: Schedule of Activities: Long-Term Safety Period

Visit Day (Range)	LTS Period					Unscheduled Visit	Safety Follow-Up	Notes and Protocol Section
	Wk 12 (± 7 d)	Wk 16, 20, and 24 (± 7 d)	Wk 28, 32, and 36 (± 7 d)	Wk 40, 44, and 48 (± 7 d)	Wk 52/ EOT/ET (± 7 d)		30 (+ 7) Days After Last Study Cream Application[a]	
Administrative procedures								
Contact IRT	X	X	X	X	X	X	X	Section 8.1.3.
Prior/concomitant medications and procedures	X	X	X	X	X	X	X	Section 6.6.
Apply study cream at site	X	X	X	X				Section 6.1; only for participants with active AD lesions at time of visit; apply the first (morning) application under direct site staff supervision.
Weigh and dispense study cream; dispense diary cards	X	X	X	X				Section 6.1 and Section 8.1.4.
Collect and weigh study cream; collect diary cards	X	X	X	X	X			Section 6.1.
Record start and end dates of treatment cycle(s)	X	X	X	X	X			Section 6.1; the start/end date will have been recorded by the participant. The end date should be 3 days after lesions clear; however, if this 3-day window is during a study visit and IGA score = 0, stop treatment and record the date of the study visit as the treatment cycle end date.
Assess compliance	X	X	X	X	X			Section 6.4.
Safety assessments								
AE assessments	X	X	X	X	X	X	X	Section 8.4.1.
Comprehensive physical examination					X			Section 8.4.2.1.
Targeted physical examination	X	X	X	X		X	X	Section 8.4.2.2; conducted only when indicated by symptoms reported by participant (AEs or other findings); clinically significant abnormalities (in the investigator's judgment) are to be reported as AEs.

Table 4: Schedule of Activities: Long-Term Safety Period (Continued)

Visit Day (Range)	LTS Period					Unscheduled Visit	Safety Follow-Up	Notes and Protocol Section
	Wk 12 (± 7 d)	Wk 16, 20, and 24 (± 7 d)	Wk 28, 32, and 36 (± 7 d)	Wk 40, 44, and 48 (± 7 d)	Wk 52/ EOT/ET (± 7 d)		30 (+ 7) Days After Last Study Cream Application[a]	
Safety assessments (continued)								
Height and weight		X*			X			Section 8.4.3; height should be measured with a stadiometer. *Only at Week 24.
Vital signs	X	X	X	X	X	X	X	Section 8.4.3; vital signs are taken before blood sampling and other procedures.
Disease severity assessments								
Evaluate %BSA affected by active AD lesions	X	X	X	X	X	X	X	Section 8.2.2; evaluate %BSA (excluding the scalp) affected by active AD lesions using the handprint method.
IGA	X	X	X	X	X	X	X	Section 8.2.5.
[redacted]								

Table 4: Schedule of Activities: Long-Term Safety Period (Continued)

Visit Day (Range)	LTS Period					Unscheduled Visit	Safety Follow-Up	Notes and Protocol Section
	Wk 12 (± 7 d)	Wk 16, 20, and 24 (± 7 d)	Wk 28, 32, and 36 (± 7 d)	Wk 40, 44, and 48 (± 7 d)	Wk 52/ EOT/ET (± 7 d)		30 (+ 7) Days After Last Study Cream Application[a]	
Laboratory assessments								Blood draws for clinical laboratory tests must be performed before the in-clinic study cream application.
Serum chemistries	X	X*	X*	X*	X	X	X	Section 8.4.4. *Only at Weeks 16, 24, 32, 40, and 48.
Hematology	X	X*	X*	X*	X	X	X	Section 8.4.4. *Only at Weeks 16, 24, 32, 40, and 48.
Pregnancy testing		X*	X*	X*			X	Section 8.4.4.2; at the indicated visits, only female participants who have reached menarche will have urine pregnancy test. A positive urine test must be confirmed by a serum test. *Only at Weeks 16, 24, 32, 40, and 48.
[redacted]								

Note: Unscheduled visits may occur at any time at the investigator's discretion, and appropriate clinical and laboratory tests may be performed as clinically indicated.

[a] Except for participants who have been in an observation/no treatment cycle with a total IGA score of 0 (clear) from Week 48 or earlier until Week 52; such participants should complete the safety follow-up and Week 52/EOT visits together. In practice, this would mean conducting all Week 52/EOT visit assessments plus the pregnancy test at the Week 52/EOT visit.

2. INTRODUCTION

2.1. Background

Ruxolitinib cream is a topical formulation of ruxolitinib phosphate under development for the treatment of patients with AD and vitiligo and was investigated earlier in alopecia areata and plaque psoriasis. Ruxolitinib phosphate is an inhibitor of the JAK family of protein tyrosine kinases. Inflammatory cytokines are strongly implicated in the pathogenesis of several dermatologic diseases. Because JAKs serve to translate extracellular signals from a number of relevant cytokines and growth factors upregulated in inflammatory diseases such as AD, alopecia areata, plaque psoriasis, and vitiligo, JAK inhibitors represent potential therapeutic agents for these disease states (Howell et al 2019).

Atopic dermatitis is a chronic, recurring, inflammatory, and highly pruritic skin condition that affects up to 25% of children and up to 12% of adults worldwide (Eichenfield et al 2014, Hanifin et al 2007, Harrop et al 2007, Rönmark et al 2012, Vinding et al 2014) and is one of the most common dermatoses encountered by pediatric health care providers. Although not life-threatening, patients with AD are at a higher risk for the development of other potentially life-threatening disorders such as asthma and/or food allergy (Spergel 2010). According to the recent Global Burden of Disease project, AD is one of the 50 most prevalent diseases worldwide and has the second highest disability ranking of all nonmalignant skin diseases (Hay et al 2014).

The clinical pattern of AD varies with age and generally develops during the first 5 years of life in 90% of patients (but not in the first weeks of life, as seen in the autosomal dominant hyper-immunoglobulin E syndrome; Lyons et al 2015). Infants usually show acute erythematous and often exudative papules on the face or scalp, which are often intensely pruritic. The childhood phase (2 years of age to puberty) and adult phase of AD tend to have less acute or exudative lesions but instead typically present with more lichenified and localized lesions (flexural folds, the face and neck, the upper arms and back, and the dorsa of the hands, feet, fingers, and toes), which represent a more chronic stage of the condition (Akdis et al 2006). The unifying and cardinal feature of all presentations of AD is the pronounced and often unbearable itching.

In addition to the allergy-related sequelae of AD affecting the skin, recent reports have shown that children with AD, compared to those without AD, are at a higher risk of developing psychosocial comorbidities such as attention-deficit/hyperactivity disorder and depression (de la O-Escamilla and Sidbury 2020, Hong et al 2019, van der Schans et al 2017, Yaghmaie et al 2013). Sleep disturbance, both in pediatric patients and their parents/caregivers, is also common and can significantly impair quality of life (Chang and Chiang 2018, Ramirez et al 2019, Yang et al 2019).

Despite the availability of a number of treatment options, there is still a significant medical need for safe topical therapies that provide rapid and effective control of the signs and symptoms of AD and that are also both effective and safe, particularly in children. Moderate to potent topical corticosteroids and calcineurin inhibitors have well-known safety restrictions limiting their use to 4 and 8 weeks, respectively. In addition, a PDE4 inhibitor, 2% crisaborole (Eucrisa®) ointment, was recently approved in the United States for patients aged 3 months and older with mild to

moderate AD and has no such safety limitations but was shown to have modest efficacy (Eucrisa 2020).

For patients with more severe AD, the most recent addition to the systemic drug armamentarium is dupilumab (Dupixent® 2020). Dupilumab is a monoclonal humanized antibody against IL-4Rα that blocks the action of IL-4 and IL-13 and was approved for adult patients with moderate to severe AD in 2017 and most recently in children aged 6 years and older in the United States (Dupixent 2020).

Studies with oral JAK inhibitors (tofacitinib and baricitinib) indicated that these drugs may be effective in the treatment of patients with AD (Levy et al 2015, Napolitano et al 2020) and have triggered further interest in their use as topical agents for this skin condition. A clinical study with topical tofacitinib confirmed that JAK inhibitors can be effective in AD also when used topically (Bissonnette et al 2016). Consequently, efforts have been made to find new treatment possibilities that would more appropriately address the medical needs of patients with AD.

Janus kinases are intracellular signaling enzymes that act downstream of key proinflammatory cytokines known to promote the pathogenesis of AD. Ruxolitinib (INCB018424) is a potent and selective JAK1 and JAK2 inhibitor that is currently approved for use in tablet form for the treatment of patients with myelofibrosis and polycythemia vera in multiple countries and acute graft-versus-host disease in the United States. Recent studies suggest that JAK inhibition may have antipruritic effects by acting directly on sensory nerve fibers and may offer a novel therapeutic approach with dual anti-inflammatory and antipruritic properties.

Nonclinical pharmacology, PK/PD, and toxicology data for ruxolitinib cream from in vitro and in vivo model systems support the use of topically applied ruxolitinib cream for the treatment of patients with AD, psoriasis, vitiligo, and other inflammatory diseases of the skin. Refer to the ruxolitinib cream IB for a summary of findings from the nonclinical studies.

2.2. Pivotal Phase 3 Studies and Pilot Pediatric Study

2.2.1. INCB 18424-303 and INCB 18424-304: Phase 3 Adolescent/Adult Studies

The ruxolitinib cream Phase 3 studies (INCB 18424-303 and INCB 18424-304) confirmed that 1.5% ruxolitinib cream applied BID for 8 weeks is a highly effective treatment for participants with AD and is not associated with safety concerns. A lower strength of ruxolitinib cream (0.75% BID for 8 weeks) was also investigated in these trials. While its safety profile was not different from that of 1.5% cream, it was less efficacious than the higher strength.

2.2.1.1. Safety

The primary analysis of the safety of ruxolitinib cream is based on pooled data from the VC period of the 2 confirmatory Phase 3 studies, INCB 18424-303 and INCB 18424-304 (ie, the Phase 3 AD VC population), in 1249 adolescents and adults with AD. Participants were randomized 2:2:1 to ruxolitinib 0.75% cream BID (500 participants), ruxolitinib 1.5% cream BID (499 participants), or vehicle cream BID (250 participants).

The most frequently reported TEAEs during the VC period are summarized in Table 5 and were consistent with the types of events that are common in patients with AD. The overall rate of

TEAEs in both studies after 8 weeks of treatment was comparable between the ruxolitinib cream regimens (0.75% BID, 29.0%; 1.5% BID, 26.5%) and vehicle cream (33.2%).

Table 5: Summary of Treatment-Emergent Adverse Events Occurring in ≥ 1% of Participants in Any Treatment Group (Phase 3 Atopic Dermatitis Vehicle-Controlled Population)

MedDRA Preferred Term, n (%)	Vehicle Cream BID (N = 250)	Ruxolitinib Cream Regimen		Ruxolitinib Cream Total (N = 999)
		0.75% BID (N = 500)	1.5% BID (N = 499)	
Participants with any TEAE	83 (33.2)	145 (29.0)	132 (26.5)	277 (27.7)
Nasopharyngitis	2 (0.8)	15 (3.0)	13 (2.6)	28 (2.8)
Upper respiratory tract infection	5 (2.0)	7 (1.4)	12 (2.4)	19 (1.9)
Headache	5 (2.0)	4 (0.8)	11 (2.2)	15 (1.5)
Oropharyngeal pain	3 (1.2)	3 (0.6)	5 (1.0)	8 (0.8)
Application site pain[a]	12 (4.8)	3 (0.6)	4 (0.8)	7 (0.7)
Application site pruritus	7 (2.8)	5 (1.0)	1 (0.2)	6 (0.6)
Pruritus	4 (1.6)	2 (0.4)	4 (0.8)	6 (0.6)
Dermatitis atopic[b]	11 (4.4)	1 (0.2)	2 (0.4)	3 (0.3)

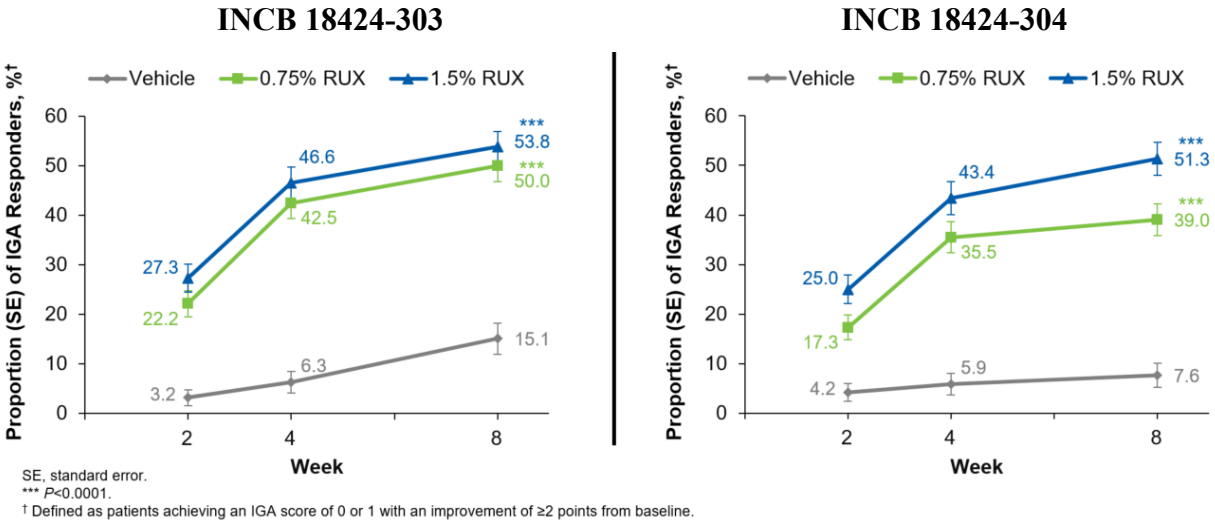
[a] Event lowest level terms included application site burning, application site stinging, and pain after application.
[b] Reported terms of atopic dermatitis flare, atopic dermatitis exacerbation, exacerbation of atopic dermatitis, intensification of atopic dermatitis, worsening of atopic dermatitis, flare of atopic dermatitis.

The frequency of application site reactions was low (1.6% and 1.0% in participants who applied ruxolitinib 0.75% and 1.5% cream BID, respectively, and 7.6% in participants who applied vehicle cream BID); no clinically significant application site reactions were observed, including areas of sensitive skin (eg, the face). The rate of SAEs was comparable among all treatment groups (0.75% ruxolitinib BID, 0.8%; 1.5% ruxolitinib BID, 0.6%; vehicle cream BID, 0.8%). Long-term safety data (44-week extension period of both studies) did not identify any safety concerns with prolonged intermittent use of ruxolitinib cream.

2.2.1.2. Efficacy

In Study INCB 18424-303 and Study INCB 18424-304, significantly more participants achieved IGA-TS with application of ruxolitinib cream 0.75% BID (50.0% and 39.0%) and 1.5% BID (53.8% and 51.3%) versus vehicle cream (15.1% and 7.6%; all $p < 0.0001$; see Figure 2), respectively.

Figure 2: Study INCB 18424-303 and Study INCB 18424-304: Proportions of Participants Who Achieved IGA-TS



SE, standard error.
*** $P<0.0001$.
† Defined as patients achieving an IGA score of 0 or 1 with an improvement of ≥2 points from baseline.

In Study INCB 18424-303 and Study INCB 18424-304, EASI75 was achieved by 56.0% and 51.5% of participants applying ruxolitinib cream 0.75% BID, 62.1% and 61.8% of participants applying ruxolitinib cream 1.5% BID, and 24.6% and 14.4% of participants applying vehicle cream (all $p < 0.0001$), respectively. A summary of the primary and select key secondary endpoints of responders at Week 8 is shown in Table 6.

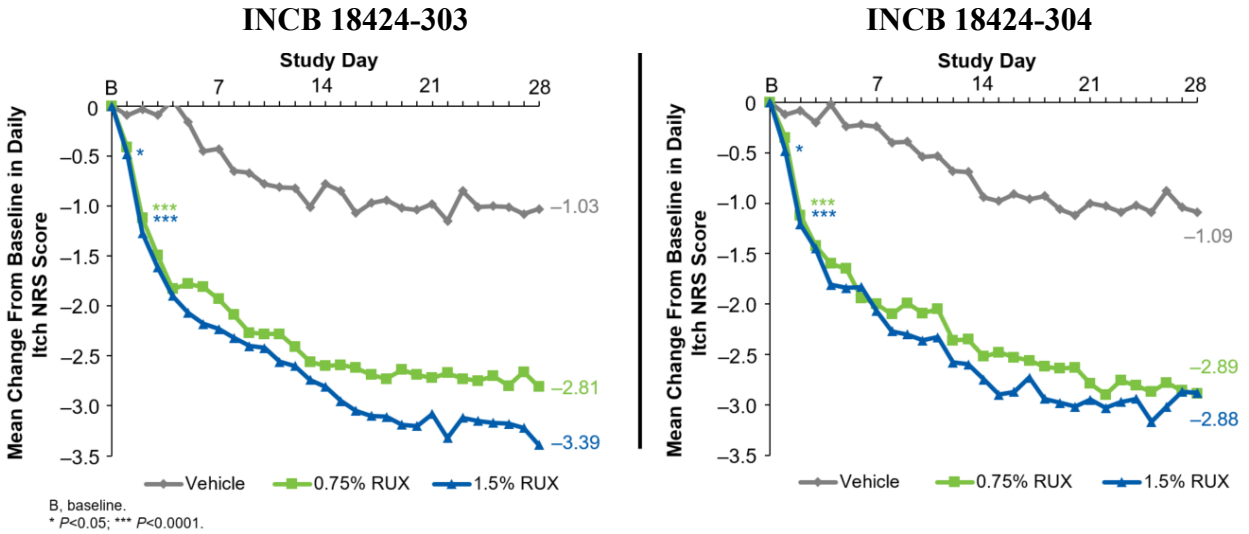
Table 6: Study INCB 18424-303 and Study INCB 18424-304: Primary and Key Secondary Endpoints – Responders at Week 8

	INCB 18424-303			INCB 18424-304		
	Vehicle Cream BID (N = 126)	Ruxolitinib 0.75% Cream BID (N = 252)	Ruxolitinib 1.5% Cream BID (N = 253)	Vehicle Cream BID (N = 118)	Ruxolitinib 0.75% Cream BID (N = 231)	Ruxolitinib 1.5% Cream BID (N = 228)
IGA-TS[a]	15.1%	50.0%[b]	53.8%[b]	7.6%	39.0%[b]	51.3%[b]
EASI75[c]	24.6%	56.0%[b]	62.1%[b]	14.4%	51.5%[b]	61.8%[b]
Itch NRS (≥ 4-point reduction)[d]	15.4%	40.4%[e]	52.2%[b]	16.3%	42.7%[b]	50.7%[b]

[a] IGA-TS was defined as an IGA score of 0 or 1 with a ≥ 2-grade improvement from baseline.
[b] $p < 0.0001$, ruxolitinib cream versus vehicle.
[c] An EASI75 responder was defined as a participant achieving ≥ 75% improvement from baseline in EASI score.
[d] An Itch 4 NRS responder was defined as a participant achieving a ≥ 4-point improvement from baseline in Itch NRS score. The denominator includes participants in the ITT population with baseline Itch NRS score ≥ 4.
[e] $p < 0.001$, ruxolitinib cream versus vehicle cream.

In both studies, significantly greater itch reduction was observed within 12 hours of the first application of ruxolitinib cream 1.5% BID versus vehicle cream ($p < 0.05$; see Figure 3). At Week 8, clinically meaningful reduction (≥ 4-point improvement in Itch NRS score) was achieved by more participants who applied ruxolitinib cream (0.75% BID, 40.4% and 42.7%; 1.5% BID, 52.2% and 50.7%) versus vehicle cream (15.4% and 16.3%, respectively; all $p < 0.0001$).

Figure 3: Study INCB 18424-303 and Study INCB 18424-304: Change From Baseline in Daily Itch NRS Score



Overall, ruxolitinib cream demonstrated superior efficacy versus vehicle cream for endpoints including IGA-TS, EASI75, and ≥ 4-point improvement in Itch NRS score. The safety profile was similar to that of vehicle cream and consistent between the 2 studies, and the rate of application site reactions was low.

2.2.2. INCB 18424-102: Pharmacokinetic Pediatric Study

The pilot pediatric study (INCB 18424-102), an open-label, descending age (≥ 12 to 17 years, ≥ 7 to < 12 years, and ≥ 2 to < 7 years), and increasing treatment strength (0.5%, 0.75%, or 1.5%) trial, was conducted to explore primarily the safety of several treatment regimens with ruxolitinib cream. Although not a dose range–finding study, it showed that the efficacy and safety of ruxolitinib cream 0.75% and 1.5% BID were similar in this pediatric age population to that in adolescents and adults with AD.

The results of Study INCB 18424-102 indicate that ruxolitinib cream at the 0.5%, 0.75%, and 1.5% strengths was safe and well-tolerated when administered BID for 4 weeks to pediatric participants with AD (aged ≥ 2 to 17 years). A summary of the results is listed below:

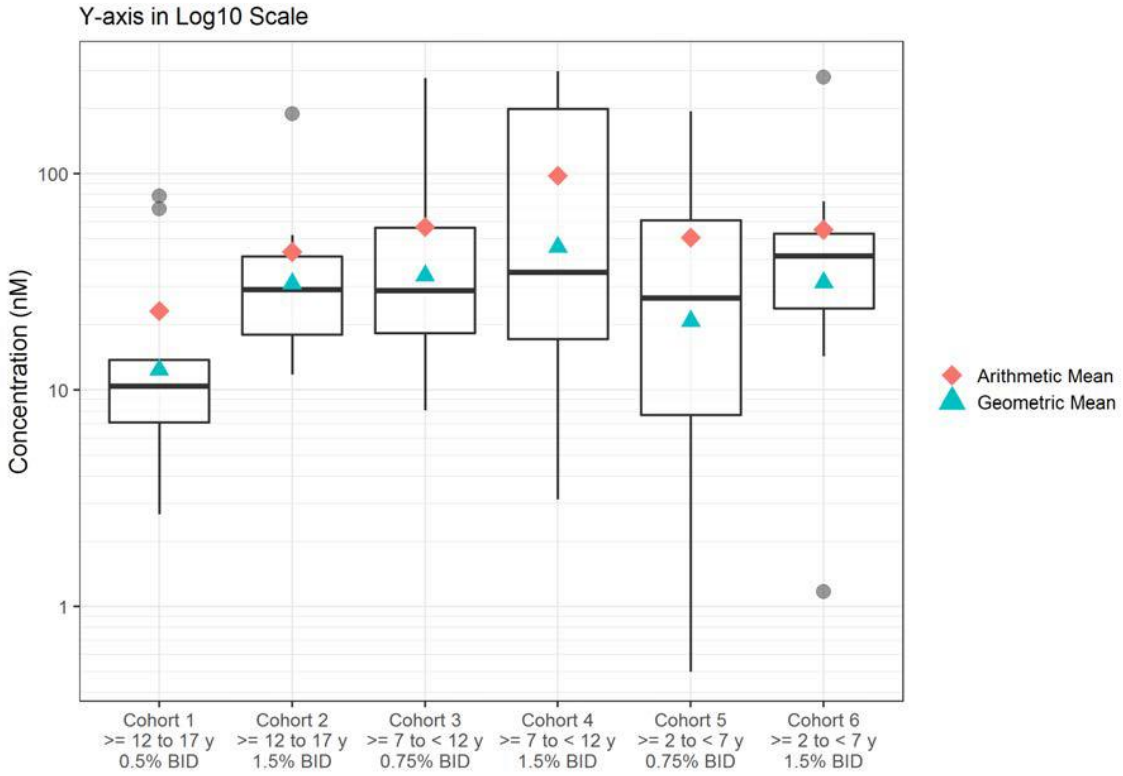
- There were no serious TEAEs or TEAEs with a fatal outcome. One participant (7.1%) in Cohort 6 (≥ 2 to < 7 years; ruxolitinib 1.5% cream BID) had a treatment-related TEAE of decreased neutrophil count with onset on Day 9 that led to study cream discontinuation. The event was Grade 1 in severity and resolved after 49 days.
- The overall incidences of TEAEs were highest among participants ≥ 12 to 17 years old (50.0% and 45.5% for Cohorts 1 and 2, respectively) and did not vary according to ruxolitinib cream strength. Treatment-emergent AEs were Grade 1 or 2 in severity with the exception of 2 Grade 3 events, tooth fracture and lip injury, in a participant in Cohort 3 (≥ 7 to < 12 years; ruxolitinib 0.75% cream BID).

- The most frequently reported TEAEs overall were headache (5.6%), atopic dermatitis (reported as worsening, flares, or exacerbations of atopic dermatitis; 4.2%), and otitis media and upper respiratory tract infection (2.8% each).
- The incidence of application site reaction TEAEs was low: 1 participant (10.0%) in Cohort 1 (≥ 12 to 17 years; ruxolitinib 0.5% cream BID) had an event of application site urticaria, and 1 participant (7.1%) in Cohort 4 (≥ 7 to < 12 years; ruxolitinib 1.5% cream BID) had 2 events of application site pain (reported term: stinging sensation). All application site reaction TEAEs were Grade 1 in severity and resolved on the same day as the event onset.
- There were no clinically meaningful changes in mean chemistry or hematology parameters over time, and no clinically meaningful changes were noted for vital signs or height.

2.2.2.1. Pharmacology Results

Plasma concentrations of ruxolitinib were in general low and showed substantial interindividual variability in all cohorts. The steady-state plasma concentrations of ruxolitinib increased in a less than proportional manner as the formulation strength increased. Mean steady-state plasma concentrations of ruxolitinib are shown in Figure 4.

Figure 4: Box Plots of Steady-State Plasma Concentrations Overlaid With Mean Values (Log_{10} Scale)



Note: Gray circles represent outliers (> 1.5 × interquartile range).

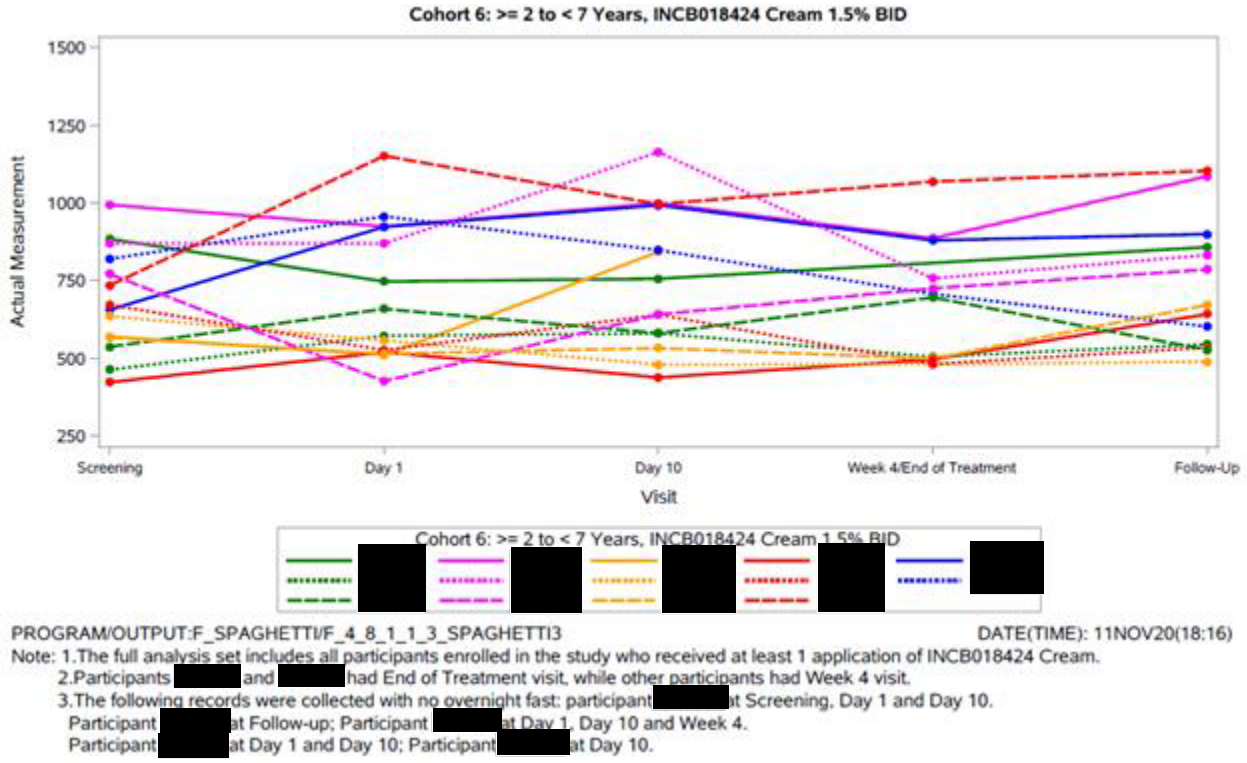
Overall, plasma PK of ruxolitinib in adolescent participants aged ≥ 12 to 17 years who applied ruxolitinib cream were similar to those previously observed in adult patients with AD.

Evaluation of serum bone markers related to bone development was included in the safety assessments for Cohorts 3 to 6 to provide safety monitoring for early detection of possible bone effects on P1NP and BSAP (bone formation markers) and CTx (a bone resorption marker).

A percentage decrease from the pretreatment levels (average of screening and baseline values) was used to monitor bone biomarker fluctuations in each participant.

Bone biomarker values were variable between participants. The normal ranges of serum bone biomarkers in children typically show high intraparticipant and interparticipant levels. Spaghetti plots of BSAP, CTx, and P1NP serum concentrations were used to illustrate the changes in these bone markers. A spaghetti plot from the youngest age group treated with 1.5% ruxolitinib cream (Cohort 6; ≥ 2 to < 7 years) is shown in Figure 5. This was the youngest age group treated with the highest strength of ruxolitinib cream and thus the most vulnerable from a safety point of view. This plot was also representative of the other cohorts in which bone markers were evaluated (Cohorts 3-5).

Figure 5: Study 18424-102: P1NP Concentrations for Individual Participants in Cohort 6 by Visit



These analyses did not reveal any pattern of change that would indicate any effect of ruxolitinib cream on bone growth.

[redacted]

2.3. Study Rationale

Ruxolitinib cream is a potent inhibitor of JAK1 and JAK2 with dual anti-inflammatory and antipruritic properties and has been recently shown to be an effective and safe therapy for AD in patients ≥ 12 years of age (Kim et al 2020a, Kim et al 2020b, Papp et al 2020). Given its topical application, treatment of AD with ruxolitinib cream selectively targets the diseased skin and minimizes the chance of safety concerns associated with the systemic administration of JAK inhibitors.

Five studies have been conducted to date evaluating the safety and efficacy of ruxolitinib cream in patients with AD (see Section 2.2): a Phase 1 maximum use trial (INCB 18424-103), a Phase 2 study (INCB 18424-206), 2 Phase 3 studies (INCB 18424-303 and -304; TRuE-AD1 and TRuE-AD2), and a Phase 1 pediatric PK study (INCB 18424-102). The results consistently demonstrated that ruxolitinib 1.5% cream is a safe and efficacious treatment of AD in adolescent participants and are in line with similar outcomes in adult participants.

This Phase 3 pediatric trial is a part of the pediatric clinical program with the objective to evaluate the efficacy and safety of ruxolitinib cream in children with AD ≥ 2 years to < 12 years of age.

2.3.1. Scientific Rationale for Study Design

Two identical Phase 3 studies (TRuE AD-1 and TRuE AD-2) were conducted to evaluate the efficacy of ruxolitinib cream in adolescents and adults ≥ 12 years of age with AD. The present study is intended to investigate and eventually confirm the findings of the above studies in a pediatric population ≥ 2 years to < 12 years of age. Owing to the prevalence of AD in patients < 12 years of age and the unmet need for novel topical therapies with improved efficacy/safety

ratios in this age group, this study will evaluate the safety and efficacy profile of ruxolitinib cream in younger children.

This Phase 3 pediatric trial (INCB 18424-305) is a double-blind study composed of sequential VC and LTS periods lasting 8 and 44 weeks, respectively, and replicates the design of the earlier pivotal studies in adolescent and adults with AD.

The VC period of the study will provide efficacy and safety data, and the LTS period will provide safety information when ruxolitinib cream is used intermittently for a longer period. It will also provide data about the duration of treatment effect after stopping therapy following lesion clearance and the nature and number of new disease exacerbation (flare) episodes. Additionally, this treat/re-treat manner of administration may reflect the likely use of the product in the post-approval, real-world setting. Other measures included in this study are Itch [redacted]

2.3.2. Justification for the Selected Treatment Regimen

The ruxolitinib cream Phase 2 dose range–finding study (INCB 18424-206) in adult participants with AD was the basis for the treatment strength selection for the Phase 3 studies. There were no meaningful differences in safety between all treatment regimens, and all treatment arms demonstrated unremarkable safety profiles with good tolerability on application sites.

The 1.5% BID regimen was found to be the most efficacious, with the near-maximal treatment effect obtained within 8 weeks of therapy and the leveling of response thereafter. In addition, a prompt and pronounced decrease in itch was observed relative to the other active treatment groups. Given that the 1.5% strength (BID, for up to 8 weeks) demonstrated the highest efficacy/safety ratio, this particular regimen was selected for the consecutive clinical studies.

Although ruxolitinib 0.75% BID was not tested in the earlier phase 2 dose range–finding study, the distinctive dose responses seen allowed the projection of its efficacy level to be intermediate between the 0.5% once daily and 1.5% BID strengths. It was also anticipated that reducing the ruxolitinib cream strength would lead to reduced systemic exposure.

While the efficacy of 1.5% ruxolitinib cream in the Phase 3 studies in adults and adolescents with AD was superior to that of 0.75% ruxolitinib cream, there were no meaningful differences in the safety profiles of these 2 regimens. However, there is a possibility that plasma levels of ruxolitinib may be relatively higher, especially in younger children (with a higher BSA/body mass ratio), than those observed in adolescent and adult participants. Therefore, both regimens will be evaluated in subsequent studies.

2.4. Benefit/Risk Assessment

See Appendix C for COVID-19–related guidance.

Despite available treatment options, there is still a significant medical need for topical therapies for AD that are both effective and safe, particularly in children. The overall benefit/risk assessment of ruxolitinib cream favors its use in adolescent and adult patients with AD, including those with involvement of sensitive skin areas (eg, the face). Ruxolitinib cream

rapidly and effectively treats both signs (erythema, induration/papulation, and oozing/crusting) and symptoms, most importantly pruritus, of AD.

All clinical studies with ruxolitinib cream in AD conducted to date confirm that both the 0.75% and 1.5% BID treatment regimens are most efficacious, compared with lower strengths of ruxolitinib cream evaluated, and are not associated with any concerning safety findings. Treatment with ruxolitinib cream 1.5% BID for 8 weeks demonstrated better efficacy and similar safety to the 0.75% BID treatment regimen, resulting in a better benefit/risk ratio in adolescents and adults.

A pilot pediatric study (INCB 18424-102) demonstrated a similar risk/benefit ratio for each treatment strength in pediatric participants (aged ≥ 2 to 17 years, inclusive). See Section 2.2.2.

The Phase 3 pivotal studies of ruxolitinib cream (INCB 18424-303 and INCB 18424-304) in adolescents and adults with AD are ongoing. However, the preliminary data are in line with the findings from other studies in terms of the efficacy and safety of this drug. See Section 2.2.

Based on the above information, ruxolitinib cream up to 1.5% BID can be safely used as a topical medication for AD and represents the treatment regimen with the best benefit/risk ratio from among those investigated.

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

3. OBJECTIVES AND ENDPOINTS

Table 7 presents the objectives and endpoints.

Table 7: Objectives and Endpoints

Objectives	Endpoints
Primary	
To establish the efficacy of ruxolitinib cream in participants with AD.	Proportion of participants who achieve IGA-TS at Week 8.
Key Secondary	
To further assess the treatment effects of ruxolitinib cream.	• Proportion of participants with a ≥ 4-point improvement in Itch NRS score from baseline to Week 8. • Proportion of participants with a ≥ 4-point improvement in Itch NRS score from baseline to Day 7 (Week 1). • Proportion of participants with a ≥ 4-point improvement in Itch NRS score from baseline to Day 3.
Secondary	
To evaluate the safety and tolerability of ruxolitinib cream.	The type, frequency, and severity of AEs and changes from baseline in physical examinations, vital signs, height, weight, and laboratory data for hematology and serum chemistry.
To further evaluate the efficacy of ruxolitinib cream.	• Proportion of participants who achieve IGA-TS at Weeks 2 and 4. • Proportion of participants with a ≥ 4-point improvement in Itch NRS score from baseline to Weeks 2 and 4. • Proportion of participants who achieve EASI75 at Weeks 2, 4, and 8. • Time to achieve Itch NRS score improvement of at least 2 or 4 points.
[redacted]	[redacted]

Table 7: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, VC study with an LTS period in pediatric participants with AD eligible for topical therapy, to be conducted at approximately 60 sites in the United States and Canada. For participants who meet all study inclusion criteria and none of the exclusion criteria, study cream will be assigned at the Day 1/baseline visit. Participants will be randomized 2:2:1 to blinded treatment with ruxolitinib cream 0.75% BID, ruxolitinib cream 1.5% BID, or vehicle cream BID, with stratification by baseline IGA score and age. Enrollment will be capped such that no more than approximately 25% of randomized participants have a baseline IGA score of 2. At least 40% of the overall study population will consist of children aged ≥ 2 years to 6 years.

During the 8-week VC period, participants will apply study treatment BID to all areas identified for treatment at the Day 1/baseline visit even if the AD begins to improve and lesions decrease in size. Note: Throughout this protocol, the term "participant" refers either to the participants themselves or, in the case of younger children, their parent or legal guardian.

At Week 8, efficacy (the primary endpoint of the study) will be evaluated as the proportion of participants achieving treatment success (IGA score of 0 or 1 with ≥ 2-grade improvement from baseline).

Participants who complete Week 8 assessments with no additional safety concerns will continue into the 44-week LTS period with the same treatment regimen, except those initially randomized to vehicle cream will be rerandomized (1:1) in a blinded manner to 1 of the 2 active treatment groups (ruxolitinib cream 0.75% or 1.5% BID). The IGA score required for participants to enter the LTS period is 0 to 4, and participants must have a %BSA in the range of 0% to 20% (excluding the scalp).

During the LTS period, participants will have study visits every 4 weeks until the end of the study (52 weeks total). At each of these visits, including Week 8 (baseline visit for the LTS period), the participant's AD lesions will be evaluated by the investigator to determine whether the participant requires continuation of treatment or should (re)enter an observation/no treatment cycle. If the IGA score is ≥ 1, the participant will start or continue active treatment with ruxolitinib cream (0.75% or 1.5%) BID. If the IGA score is 0 (clear), the participant will (re)enter an observation/no treatment cycle.

During the LTS period (ie, starting at the Week 8 visit), participants will self-evaluate the recurrence of AD and will treat areas of the skin with active AD changes only (not to exceed 20% BSA). If AD lesions clear between study visits, participants will stop treatment applications 3 days after the lesions have disappeared and record the dates of these events in their diaries. Similarly, those participants whose AD lesions recurred and who were previously in an observation/no treatment cycle will restart treatment at home at the first sign of recurrence and record the date of the new treatment cycle. All cycles of treatment will be captured in the study database with their beginning and end dates.

Throughout the study (VC period or LTS period), participants who develop new or expanded areas of AD may treat these additional areas with approval by the investigator as long as the total treated BSA does not exceed 20% and there are no safety concerns regarding the additional

application of study cream. Approval to treat additional areas may occur via telephone, although the investigator, at his/her discretion, may ask the participant to return for an unscheduled visit. This is a close reflection of the clinical practice of managing AD in the outpatient setting.

If the participant does not have a response during the LTS period (defined as no change/improvement in either %BSA or IGA score when treated continuously for 8 weeks during the LTS period), the participant must be discontinued from study treatment and an ET visit performed.

Throughout the study, participants will be assessed for safety and tolerability by monitoring the type, frequency, and severity of AEs; performing physical examinations; measuring vital signs, height, and weight; and conducting clinical and laboratory assessments as outlined in the SoA (see Table 3 [VC period] and Table 4 [LTS period]). Additional disease severity assessments, including PROs, will be conducted as outlined in the SoA (see Table 3 and Table 4).

[redacted]

Following the end of treatment (Week 52/EOT or ET), all participants will have a safety follow-up visit 30 days later to evaluate safety and duration of response. One exception to this would be for participants who have been in an observation/no treatment cycle with an IGA score of 0 (clear) from Week 48 or earlier until Week 52; such participants could complete the safety follow-up and Week 52/EOT visits together. In practice, this would mean conducting all Week 52/EOT visit assessments plus the pregnancy test at the Week 52/EOT visit.

Figure 1 presents the study design schema, and Table 3 (VC period) and Table 4 (LTS period) present the SoA.

4.2. Overall Study Duration

Participants will participate in the study for a duration of up to approximately 61 weeks: 28 (+ 7) days in the screening period, 8 weeks in the VC period, 44 weeks in the LTS period, and 30 days in the safety follow-up period (see Figure 1).

The study will begin when the first participant (or parent or guardian) signs the ICF (and, if needed, an assent form). The end of the study is defined as the date of the last visit of the last participant in the study or the date that the last participant has discontinued study cream and has completed applicable safety follow-up assessments or is lost to follow-up.

A participant is considered to have completed the study if he/she has completed all study visits, including the safety follow-up visit.

The investigator will be expected to monitor for and report any SAEs and pregnancies, as detailed in Section 9. The remaining participants are considered to be on study until a discontinuation criterion is met and written notification is provided to the sponsor.

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 agency. 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 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 and female children aged ≥ 2 years to < 12 years (at the screening visit).
2. Diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria.
3. AD duration of at least 3 months (participant/parent/guardian may verbally report signs and symptoms of AD with onset at least 3 months prior).
4. IGA score of 2 to 3 at the screening and baseline visits.
5. %BSA (excluding the scalp) with AD involvement of 3% to 20% at the screening and baseline visits.
6. For children aged 6 years to < 12 years, baseline itch NRS score ≥ 4 (see Section 8.2.7). Note: Participants who are aged 6 years to < 12 years must record Itch NRS scores for at least 4 of the 7 days immediately prior to the Day 1/baseline visit.
7. Participants/guardians who agree to discontinue all agents used by the participant to treat AD from the screening visit through the final safety follow-up visit.
8. For participants who sign photography consent, at least 1 target lesion that measures at least 5 cm^2 at the screening and baseline visits. The target lesion must be representative of the participant's disease state but not located on the hands, feet, or genitalia.

9. For sexually active participants, willingness to take appropriate contraceptive measures (see Appendix A) to avoid pregnancy or fathering a child for the duration of study participation with the exception of male and female participants who are prepubescent.

   Note: Female participants who have reached menarche must have a negative urine pregnancy test at the screening and baseline visits before the first application of study cream on Day 1. They must also take appropriate precautions to avoid pregnancy from the screening visit through the safety follow-up visit.

10. Ability to comprehend and willingness to sign an ICF or written informed consent of the parent(s) or legal guardian and a verbal or written assent from the participant when possible.

5.2. Exclusion Criteria

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

1. An unstable course of AD (spontaneously improving or rapidly deteriorating) as determined by the investigator over the previous 4 weeks before the baseline visit.
2. Concurrent conditions and history of other diseases as follows:
   a. Immunocompromised (eg, lymphoma, acquired immunodeficiency syndrome, Wiskott-Aldrich syndrome) or a history of malignant disease within 5 years before the baseline visit.
   b. Chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the baseline visit.
   c. Active acute bacterial, fungal, or viral skin infection (eg, herpes simplex, herpes zoster, chicken pox, clinically infected AD, impetigo) within 1 week before the baseline visit.
   d. Any other concomitant skin disorder (eg, generalized erythroderma such as Netherton syndrome), pigmentation, or extensive scarring that in the opinion of the investigator may interfere with the evaluation of AD lesions or compromise participant safety.
   e. Presence of AD lesions only on the hands or feet without prior history of involvement of other classic areas of involvement such as the face or the flexural folds.
   f. Other types of eczema.
   g. Chronic asthma requiring more than 880 µg/day of inhaled budesonide or equivalent high dose of other inhaled corticosteroids.
   h. Any participant on maintenance dialysis.
   i. A medical history of hepatitis B virus or hepatitis C virus infection.
3. Any of the following clinical laboratory test results at screening:
   a. Removed during Protocol Amendment 2.
   b. Removed (modified and moved to Exclusion Criterion 3d) during Protocol Amendment 2.
   c. Cytopenias at screening, defined as follows:
      - Hemoglobin < 10 g/dL
      - ANC < 1000/µL
      - Platelet count < 100,000/µL

d. 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%)
e. Estimated GFR < 30 mL/min/1.73 m^2 (using the Modification of Diet in Renal Disease equation).
f. Positive serology test results at screening for HIV antibody.
g. Any other clinically significant laboratory result that, in the opinion of the investigator, poses a significant risk to the participant.

4. Removed (moved to Exclusion Criterion 2i) during Protocol Amendment 2.
5. Any serious illness or medical, physical, or psychiatric condition(s) that, in the investigator's opinion, would interfere with full participation in the study, including administration of study cream and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.
6. Use of any of the following treatments within the indicated washout period before the baseline visit:
   a. 5 half-lives or 12 weeks, whichever is longer – biologic agents (eg, dupilumab).
   b. 4 weeks – systemic corticosteroids or adrenocorticotropic hormone analogues, cyclosporin, methotrexate, azathioprine, or other systemic immunosuppressive or immunomodulating agents (eg, mycophenolate or tacrolimus).
   c. 2 weeks – immunizations with live-attenuated vaccines; sedating antihistamines unless on a long-term stable regimen (nonsedating antihistamines are permitted).
      Note: Live-attenuated vaccines are not recommended during the VC period.
      Note: COVID-19 vaccination is allowed.
   d. 1 week – use of topical treatments for AD (other than bland emollients, eg, Aveeno® creams, ointments, sprays, soap substitutes), such as topical antipruritics (eg, doxepin cream), corticosteroids, calcineurin inhibitors, PDE4 inhibitors, coal tar (shampoo), topical antibiotics, or antibacterial cleansing body wash/soap.
      Note: Diluted sodium hypochlorite "bleach" baths are allowed as long as they do not exceed 2 baths per week and their frequency remains the same throughout the study.
7. Previous treatment with systemic or topical JAK inhibitors (eg, ruxolitinib, tofacitinib, baricitinib, filgotinib, lestaurtinib, pacritinib).
8. Ultraviolet light therapy or prolonged exposure to natural or artificial sources of UV radiation (eg, sunlight or tanning booth) within 2 weeks prior to the baseline visit and/or intention to have such exposure during the study, which is thought by the investigator to potentially impact the participant's AD.
9. Removed (moved to Exclusion Criterion 3f) during Protocol Amendment 2.
10. Current treatment or treatment within 30 days or 5 half-lives (whichever is longer) before the baseline visit with another investigational medication or current enrollment in another investigational drug protocol.
11. Removed during Protocol Amendment 4.

12. In the opinion of the investigator, unable or unlikely to comply with the administration schedule and study evaluations.
13. Employees of the sponsor or investigator or otherwise dependents of them.

5.3. Lifestyle Considerations

Prolonged exposure to natural or artificial sources of UV radiation (including sun lamps, tanning booths, etc) is prohibited from 2 weeks prior to the baseline visit through the last study visit. When outdoors, participants will be advised to wear loose-fitting clothing that protects the treated areas from the sun.

If sunscreen, makeup, or other cosmetics have 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 study cream. See Section 6.6.1 for additional guidance.

Participants should abstain from physical activity that can cause significant sweating for approximately 2 hours following study cream application.

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

5.4. Screen Failures

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

Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the result to be in error. Additionally, a participant who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status. Participants who rescreen must reconsent (if rescreened ≥ 28 days after the initial screening or ≥ 35 days after the initial screening for those participants on prior medications requiring a 4-week washout period, as described in Section 5.2, Exclusion Criterion 6b) and be assigned a new screening number.

5.5. Replacement of Participants

Participants are not anticipated to be replaced during the study. However, as noted in Appendix C (COVID-19–related guidance), due to the evolving situation of the COVID-19 pandemic, the sponsor may decide to recruit additional participants in the study beyond the expected number (eg, if a substantial number of participants withdraw early from the study).

6. STUDY TREATMENTS

See Appendix C for COVID-19–related guidance.

6.1. Study Treatments Administered

Table 8 presents the study treatment information.

Table 8: Study Treatment Information

	Study Treatment 1	Study Treatment 2	Study Treatment 3
Study treatment name:	Ruxolitinib cream 1.5%	Ruxolitinib cream 0.75%	Vehicle
Treatment strength:	1.5%	0.75%	Not applicable
Mechanism of action:	Inhibitor of the JAK family of protein tyrosine kinases	Inhibitor of the JAK family of protein tyrosine kinases	Not applicable
Dosage formulation:	Cream		
Route of administration:	Topical		
Administration instructions:	VC period: BID (morning and evening applications at least 1 hour before bedtime); a thin film is applied to affected areas.		
	LTS period: BID (morning and evening applications at least 1 hour before bedtime); a thin film is applied to affected areas.		LTS period: Not applicable.
Packaging and labeling:	Ruxolitinib cream and vehicle cream will be provided in 60-g tubes. Each tube will be labeled as required per country requirements.		
Storage:	Ambient (15°C-30°C/59°F-86°F)		
Status of treatment in participating countries:	Investigational	Investigational	Not applicable

Study treatments (ruxolitinib cream 1.5%, ruxolitinib cream 0.75%, and matching vehicle cream formulation that does not contain active drug) will be supplied in 60-g tubes and applied topically as a thin film BID (optimally at equal intervals, eg, ideally 12 hours apart but with at least 8 hours between applications) to the affected areas in the morning and in the evening, with the evening application at least 1 hour before bedtime.

At the baseline visit, an estimate of the %BSA to be treated will be used by the IRT system to calculate the number of tubes of study cream to be dispensed. All areas identified at the baseline visit should continue to be treated through the end of the VC period (at Week 8), even if the area begins to improve or the AD resolves completely, unless the participant meets criteria for stopping study cream.

If there are new areas to be treated, including expansion of existing areas or development of new areas, after consultation with the investigator, study cream should be applied to these areas in addition to the areas identified at the baseline visit (up to 20% BSA) for the remainder of the VC period, and the percentage of BSA to be treated will be recalculated and increased. This new estimate will be entered into the IRT system to calculate the number of tubes of study cream to be dispensed. Approval to treat these additional areas may occur via telephone, although the investigator, at their discretion, may ask the participant to return for an unscheduled visit. This is a close reflection of the clinical practice of managing AD in the outpatient setting. Participants

whose additional new areas to be treated in addition to the areas identified at the baseline visit exceed 20% BSA should be discontinued from study treatment and complete the EOT assessments.

During the LTS period starting at the Week 8 visit, participants will have study visits every 4 weeks until the end of the study (44 weeks total). At those visits, AD lesions will be evaluated by the investigator to confirm whether the participant still requires continuation of therapy (IGA score ≥ 1) or can otherwise (re)enter the observation/no treatment cycle (IGA score = 0). During this period, only areas with active disease need to be treated. Participants who develop new or expanded areas of AD may treat these additional areas with approval by the investigator as long as the total treated BSA does not exceed 20% and there are no safety concerns regarding the additional application of study cream. At Week 8, each participant will receive a prespecified number of tubes of study cream corresponding to a lower %BSA affected (up to 5%) or higher number of tubes corresponding to their affected %BSA (> 5%). This new estimate will be entered into the IRT system to calculate the number of tubes of study cream to be dispensed.

The start and end dates of treatment applications will be captured by the participant. Once the lesions clear, participants should continue to apply study cream for an additional 3 days to the areas of the body where lesions were last present before discontinuing treatment. If this 3-day window is during a study visit and the IGA score is 0, as assessed by the investigator, treatment is to be stopped. The date of the study visit will be recorded as the treatment cycle end date. If a lesion recurs, then treatment should be resumed at the first sign of recurrence.

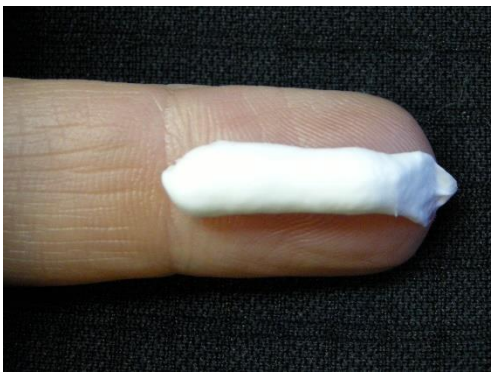
At any time during the LTS period, if a participant's new areas to be treated in addition to the areas identified at the previous visit exceed 20% BSA, then the participant should be discontinued from study treatment and complete the EOT assessments.

No study treatment adjustments are allowed except for temporary drug discontinuation, if needed (eg, for management of an AE; see Section 6.5).

6.1.1. Study Treatment Application Guidance

Participants should remove Study Cream from the tube and apply the Study Cream with their fingertip in small amounts until all of the areas to be treated are covered by a thin, even film (see Figure 8).

Figure 8: Study Cream Application Using a Fingertip



Source: DermNet New Zealand (www.dermnetnz.org).

In the clinic, the amount of study cream used will be determined by weighing a tube(s) before and after the participant or guardian applies a thin film of study cream to the affected areas.

On the day of a visit, the participant should not apply their morning application of study cream at home; instead, study cream will be applied in the clinic during the visit, under direct supervision of the site staff. The tube will be weighed before and after application to determine the participant's usage.

Application instructions will be provided by the site study staff, and the participants will record their daily applications via a diary card provided at each study visit. Participants must not apply study cream more often than BID. Refer to the Study Reference Manual for participant instructions for handling study cream.

6.2. Preparation, Handling, and Accountability

The investigator or designee must confirm appropriate temperature conditions (both ruxolitinib cream and vehicle cream are to be stored between 15°C and 30°C [59°F-86°F]) have been maintained during transit for all study treatments received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study cream, and only authorized site staff may distribute study cream. The cream will be applied by the participant or her/his parent/legal guardian. Immediately after application of study cream, the hands should be thoroughly washed with soap and water. Note that the study cream is for exclusive use on the skin. In case of accidental exposure to the eyes or mucous membranes, the cream should be immediately removed from that area and necessary supportive measures taken. Refer to the Study Reference Manual for participant instructions for handling of study cream.

All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. Participants should store study cream at ambient temperature conditions.

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

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

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the participants were provided the specified study cream. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study participants.

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study cream until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study cream 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 cream is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to study treatment using an IRT system. The system will assign in a 2:2:1 ratio, stratified by baseline IGA score (2 or 3) and age, assign the participant study number, track participant visits, randomize according to the defined parameters, maintain the blinding, and manage study cream inventory. Full details will be provided in the IRT Manual. Study treatment will be dispensed at the study visits summarized in the SoA (see Table 3 and Table 4).

6.4. Study Treatment Compliance

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

Qualified clinical staff will review the diary entries for compliance. Participants will be considered compliant with the treatment regimen if they apply at least 80% but no more than 120% of the prescribed number of applications during participation in the VC period of the study. Participants who are noncompliant during the VC period and LTS period (if on a treatment cycle) will be reinstructed by the investigator (or designee), and the sponsor should be consulted by the investigator for instruction on the proper handling of the participant.

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

6.5. Dose Modifications

Application adjustments/modifications (decrease or increase in study cream strength or frequency of application) are not allowed except for study cream interruption or permanent discontinuation if needed (eg, for management of an AE).

Temporary study cream interruption could be due to an AE during the VC or LTS periods or due to clearance of the AD lesions during the LTS period, as described in Section 6.1.

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

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

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of AEs or laboratory abnormalities that may have an unclear relationship to study cream. In the event of an AE is present at a specific site of application, treatment may be temporarily withheld only at that lesional site and continued elsewhere. This should be recorded as a dose interruption on the AE eCRF page. Except in cases of emergency, it is recommended that any findings of concern (eg, AE) be confirmed and that the investigator consult with the sponsor medical monitor (or other representative of the sponsor) before interrupting study cream applications. Additionally, the investigator must obtain approval from the sponsor before restarting study cream. Participants who experience a recurrence of the initial AEs upon restarting the study cream may need to permanently discontinue treatment with the study cream.

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

Instructions for application interruptions of study cream are outlined in Table 9. 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 cream and the participant's underlying condition.

Table 9: Guidelines for Interruption and Restarting of Treatment Applications if Adverse Event Is Deemed Related to the Study Cream

Adverse Event Related to Study Cream[a]	Action Taken
ANC < 750/µL (without fever); < 1000/µL (with fever)	• Laboratory abnormalities should be confirmed with repeat testing within 48 hours whenever possible and immediate delivery of the laboratory results requested. • Study cream applications must be interrupted. At the discretion of the investigator, after consultation with the sponsor, study cream application may be restored once these have resolved.
Any other Grade 3 or higher 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 cream applications must be interrupted. At the discretion of the investigator, after consultation with the sponsor, study cream 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 cream if laboratory abnormalities are confirmed.

[a] In the opinion of the investigator.

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

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

- Occurrence of an AE that is related to treatment with the study cream that, in the judgment of the investigator or the sponsor's medical monitor, compromised the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.
- Participant presents with a worsening of AD that requires treatment with a prohibited concomitant medication.
- Persistent AE requiring a delay of therapy for more than 2 weeks without resolution of the AE.
- Any Grade 4 laboratory abnormality related to the study cream (see Table 9).

See Section 7 for discontinuation procedures.

6.6. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. Any prior medication received up to 28 days before the first application of study treatment and any new or ongoing medication used during the study through 30 days after the last application of study treatment will be recorded in the eCRF.

Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant medications administered after 30 days after the last application of study treatment should be recorded for SAEs as defined in Section 9.3. Concomitant treatments/procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1. Permitted Medications and Procedures

The following are permitted during the study:

- Participants may use bland emollients (except those containing urea, salicylic acid, or lactic acid) such as Eucerin® cream. Participants should continue to use the bland emollient/moisturizer in the same manner they did before entering the study and throughout the course of the study.

  Note: Emollients should not be used within 4 hours before and 2 hours after application of study cream.
- Bathing during the study should be limited to once daily for no longer than 15 minutes and not within 2 hours following study cream application. During baths, tepid (not hot) water and mild cleansing agents (eg, Basis® bar or Dove®) should be used. (See Section 5.3 for swimming guidance.) Showers should be limited in time with warm water and mild cleansing agents used.
- If sunscreen is needed, a mineral-based sunscreen (such as zinc oxide– or titanium oxide–based) with SPF of at least 30 may be used not less than 4 hours before and at least 2 hours after study cream application.
- Participants may use nonsedating, over-the-counter antihistamines.

6.6.2. Restricted Medications and Procedures

The following are permitted during the study under specified conditions:

- Short-term use of systemic corticosteroids may be permitted to treat acute AEs (eg, asthma, croup) during the LTS period, and the decision to keep the participant in the study (or to permanently discontinue study cream) will be made in consultation with the medical monitor.
- Participants may continue using sedating antihistaminic drugs as long as their use is part of a preexisting and well-established regimen. There are no restrictions for use of nonsedating antihistamines.

- Use of any over-the-counter, nonprescription preparations deemed acceptable by the investigator is permitted under an established and stable treatment regimen.
- Use of any prescription medication (including phytotherapeutic, herbal, or plant-derived preparations) within 7 days before the baseline visit through the safety follow-up visit, unless deemed acceptable by the investigator.
- Immunizations with a live-attenuated vaccine are not recommended during the VC period (first 8 weeks) unless deemed necessary by the investigator.
- Allergen immunotherapy (desensitization) that is ongoing at a stable dose at the time of study entry may be continued while on study but only at the same dose.
- Bleach baths are allowed as long as they do not exceed 2 baths per week and their frequency remains the same throughout the study.
- Participants should not take baths or showers within 2 hours after study cream application.
- Topical anti-infectives or other topical treatments applied to active AD lesions should not be used for at least 4 hours before and 2 hours after application of study cream.

6.6.3. Prohibited Medications and Procedures

The following are not permitted during the study:

- Any investigational medication other than the study cream.
- Topical corticosteroids, tacrolimus, pimecrolimus, and PDE4-inhibitors (Eucrisa).
- Other topical agents for AD (except bland emollients as noted in Section 6.6.1).
- Treatment known to affect the course of AD.
- Systemic corticosteroids (except the example stated in Section 6.6.2), methotrexate, cyclosporin A, azathioprine and biologic therapies, or other immunosuppressant agents.
- Phototherapy or tanning beds.

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:

- Lack of efficacy response during the LTS period (defined as no change/improvement in either %BSA or IGA when treated continuously for 8 weeks).
- AD worsens during either the VC period or the LTS period, to the point where the extent of AD to be treated (ie. all areas excluding the scalp) exceeds 20% BSA.
- 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 the public domain, may be solicited from or collected on the participant. Participants may choose to discontinue study treatment and remain in the study to be followed for safety monitoring.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Any AE of unacceptable severity 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, after 2 consecutive study visits and reinforcement of study cream application by site staff, a participant's drug usage exceeds one 60-g tube every 4 days, a participant who again fails to meet compliance benchmarks at a subsequent visit may be considered for withdrawal from the study. The medical monitor should be consulted for instruction on handling the participant.
- If, 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 cream administration in the investigator's opinion, the medical monitor should be consulted for instruction on handling the participant.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment prior to the Week 52/EOT study visit, the ET visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit. The date of the last application of study cream and the reason for discontinuation of study cream will be recorded in the eCRF.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the participant's medical record and the primary reason for withdrawal must be included in the eCRF.
- The ET visit should be performed.
- The date of the ET visit should be recorded in the eCRF.
- Participants must be followed for safety until the time of the follow-up visit or until study treatment–related AEs resolve, return to baseline, or are deemed irreversible, whichever is longest.

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

7.2. Participant Withdrawal From the Study

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

Data to be collected at the time of study discontinuation and follow-up and for any further evaluations should conform to the requirements of the ET/EOT visit (see Table 3 and Table 4).

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make a reasonable effort to regain contact with the participant (where possible, 3 telephone calls and, if unsuccessful, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

See Appendix C for COVID-19–related guidance.

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/assent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent/assent 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/assent 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/assent 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/assent 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/assent.
- Participants must provide consent to the most current version of the ICF(s)/assent(s) during their participation in the study.
- A copy of the signed ICF(s)/assent(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/assent (if rescreened > 28 days after the initial screening [or > 35 days for participants on prior medications requiring a 4-week washout period as described in Section 5.2, Exclusion Criterion 6b]) and must be assigned a new participant number.

8.1.2. Screening Procedures

Screening is the interval between signing the ICF/assent and the day the participant is enrolled in the study (Day 1). Informed consent (or assent) must be obtained before performing any study-specific procedures. Screening assessments for determination of eligibility may be performed over a period of up to 28 days, or up to 35 days for participants on prior medications requiring a 4-week washout period as described in Section 5.2 (Exclusion Criterion 6b). Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

Results from the screening visit evaluations will be reviewed to confirm eligibility before enrollment or the administration of study cream. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available laboratory results before randomization/treatment assignment 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, after recovery from an infection). The participant is not required to sign another ICF if the rescreening occurs within 28 days (or 35 days for participants on prior medications requiring a 4-week washout period) of the previous ICF signature date (screening period).

See Section 5.4 for information regarding screen failures and the rescreening procedure for participants.

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of the site ID and participant number. Site staff should contact the IRT system to obtain the participant ID number during screening. Upon determining that the participant is eligible for study entry, the IRT system will be contacted to obtain the study medication kit assignment. Additionally, the IRT system will be contacted at each regular study visit during both the VC period and the LTS period as indicated in Table 3 and Table 4 to update the study cream supply. The IRT system will also be used during the study visits to recalculate the amount of study cream to be dispensed if the participant's %BSA of AD lesions to be treated has

increased (during the VC period) or has either increased or decreased (during the LTS period). Additional details are provided in the IRT Manual.

8.1.4. Distribution of Reminder Cards and Diaries

Starting at Day 1 visit and each visit thereafter, a study cream–specific diary will be given to each participant in order to record use of the study cream. The completed diary will be reviewed during each of the participant's study visits and data uploaded will be confirmed by the study staff.

Qualified clinical study staff will review the participants' entries for compliance. Participants who are noncompliant with their study cream schedule (defined as < 80% or > 120% of the expected number of applications between study visits) will have their administration instructions reinforced by the investigator or a qualified designee. Participants will be considered compliant with the treatment regimen if they apply at least 80% but no more than 120% of the expected applications during participation in the VC period of the study.

Participants will be provided with a reminder card starting on Day 1 and at all VC and all LTS visits through Week 48. The reminder card will indicate the date and time of the next visit and will also remind the participant that their morning application of study cream will be take place at the clinic under site supervision [redacted] safety evaluations have been completed.

8.1.5. Demography and Medical History

8.1.5.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening by the investigator or qualified designee and will include year of birth/age, race, ethnicity, medical and surgical history, and current illnesses. Medical history will include relevant medical or surgical treatment within the past 2 years that are considered to be clinically significant by the investigator.

The height and weight of both parents, if available, should be obtained and entered into the EDC.

8.1.5.2. Medical and Treatment History

Relevant medical and treatment history for the past year will be collected at screening by the investigator or qualified designee. Details regarding the participant's history of AD, including date of diagnosis, relevant disease characteristics, and prior treatments for the previous year prior to enrollment, including systemic treatments, radiation, and surgical procedures, will be recorded. Acceptable documentation includes contemporaneous chart notes that record topical medication prescription and treatment outcome, or investigator documentation based on communication with the participant's treating physician. A medical history of other conditions related to AD will also be collected at this time.

In addition, information about previous AD treatment (within 12 months prior to screening) and their outcomes will be collected. For participants with safety issues (side effects) and/or insufficient therapeutic response, a collective term of inadequate response will be used.

Inadequate response is defined as inability of a given topical therapy to induce and maintain remission or to contain the disease severity at an acceptable level (comparable to IGA score of

0-2; none to mild eczema lesions) despite continuous treatment with a topical corticosteroid and a topical calcineurin inhibitor (if applicable) for at least 2 weeks or for the maximum duration recommended by the product prescribing information (whichever is shorter).

Participants with documented systemic treatment for AD can also be considered as inadequate responders to topical treatments.

Clinically relevant side effects/safety risks and/or skin tolerability issues are those that outweigh the potential treatment benefits and are the reason why a topical treatment cannot be initiated or continued.

8.2. Efficacy Assessments

8.2.1. Health Economics

Not applicable.

8.2.2. Body Surface Area

Total %BSA affected by AD will be estimated at each visit as outlined in the SoA (see Table 3 [VC period] and Table 4 [LTS period]). Body surface area assessment will be approximated to the nearest 0.1% using the handprint (Palmar) method as a guide. The approximate size of the participant's entire palmar surface (ie, the palm plus 5 digits, with fingers tucked together and thumb tucked to the side) should be considered as 1% BSA, and the approximate size of the participant's thumb should be considered as 0.1% BSA.

Alternatively, %BSA affected by AD may be measured using the calculation guidance of the diagrams, based on age group, in Appendix D. One of these 2 methods should be selected and consistently used throughout the study.

Participants must have BSA involvement (excluding scalp) of 3% to 20% at the screening and baseline visits for the VC period to enroll in the study; they may have 0% to 20% BSA involvement at Week 8 (baseline for the LTS period) to enter the LTS period.

During the LTS period, including Week 8 (baseline for the LTS period), %BSA will be evaluated by the investigator to determine whether the participant requires continuation of treatment or should (re)enter an observation/no treatment cycle.

8.2.3. Target Lesion Identification

A representative target lesion for participants who consent to photography will be identified during the screening visit, and the measurements of the same lesion will be confirmed/updated at the baseline visit (procedure is optional for nonphotography participants). The target lesion should be representative of the participant's overall disease and is to be treated with study cream. The target lesion should approximately measure at least 5 cm^2 in size and should not be on the hands, feet, or genitalia. A note should be made in the participant's source documents, and the photographs (at selected sites) can be marked with the location of the target lesion at each visit. The longest diameter and the span perpendicular to the longest diameter will be measured in centimeters.

8.2.4. Photography

At selected sites, participants will be asked but will not be required to consent to photography. For each visit with photography (baseline and Weeks 2, 4, and 8), a photograph of the target lesion (identified at the baseline visit, at least 5 cm^2 in size; see Section 8.2.3) will be taken via 2 views (close-up and regional body area) before any study procedure, even if the AD lesion has cleared or disappeared. A note should be made in the participant's source documents of the target lesion location, and the photographs can be marked with the location of the target lesion at each visit.

8.2.5. Investigator's Global Assessment

Investigator's Global Assessment is an overall eczema severity rating on a 0 to 4 scale that will be assessed during site visits as outlined in the SoA (see Table 3 [VC period] and Table 4 [LTS period]). The severity strata for the IGA are shown in Table 10.

Table 10: 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: FDA 2012.

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

Participants must have an IGA score of 2 or 3 at the screening and baseline visits for the VC period to enroll in the study; they may have an IGA score of 0 to 4 at Week 8 (baseline for the LTS period) to enter the LTS period.

During the LTS period, including Week 8 (baseline for the LTS period), IGA will be evaluated by the investigator to determine whether the participant requires continuation of treatment or should (re)enter an observation/no treatment cycle. If the IGA score is ≥ 1, the participant will start or continue active treatment with ruxolitinib cream (0.75% or 1.5%) BID. If the IGA score is 0 (clear), the participant will (re)enter an observation/no treatment cycle.

8.2.6. Eczema Area and Severity Index

Atopic dermatitis will be assessed as outlined in the SoA (see Table 3) using the EASI scoring system, which is a validated scoring system that grades the physical signs of AD to provide a measure of AD severity (ranging from 0 to 72). The EASI scoring system examines 4 regions of the body (head/neck, upper limbs, trunk, and lower limbs) and weights them. Each of the 4 body regions is assessed separately for erythema (E), induration/papulation/edema (I), excoriations (Ex), and lichenification (L) for an average degree of severity of each sign in each region. The

multiplier used in the scoring is based on age (< 8 years or ≥ 8 years). See Appendix E for the EASI calculation guides by age group.

The severity strata for the EASI are as follows: 0 = clear; 0.1 to 1.0 = almost clear; 1.1 to 7.0 = mild; 7.1 to 21.0 = moderate; 21.1 to 50.0 = severe; and 50.1 to 72.0 = very severe.

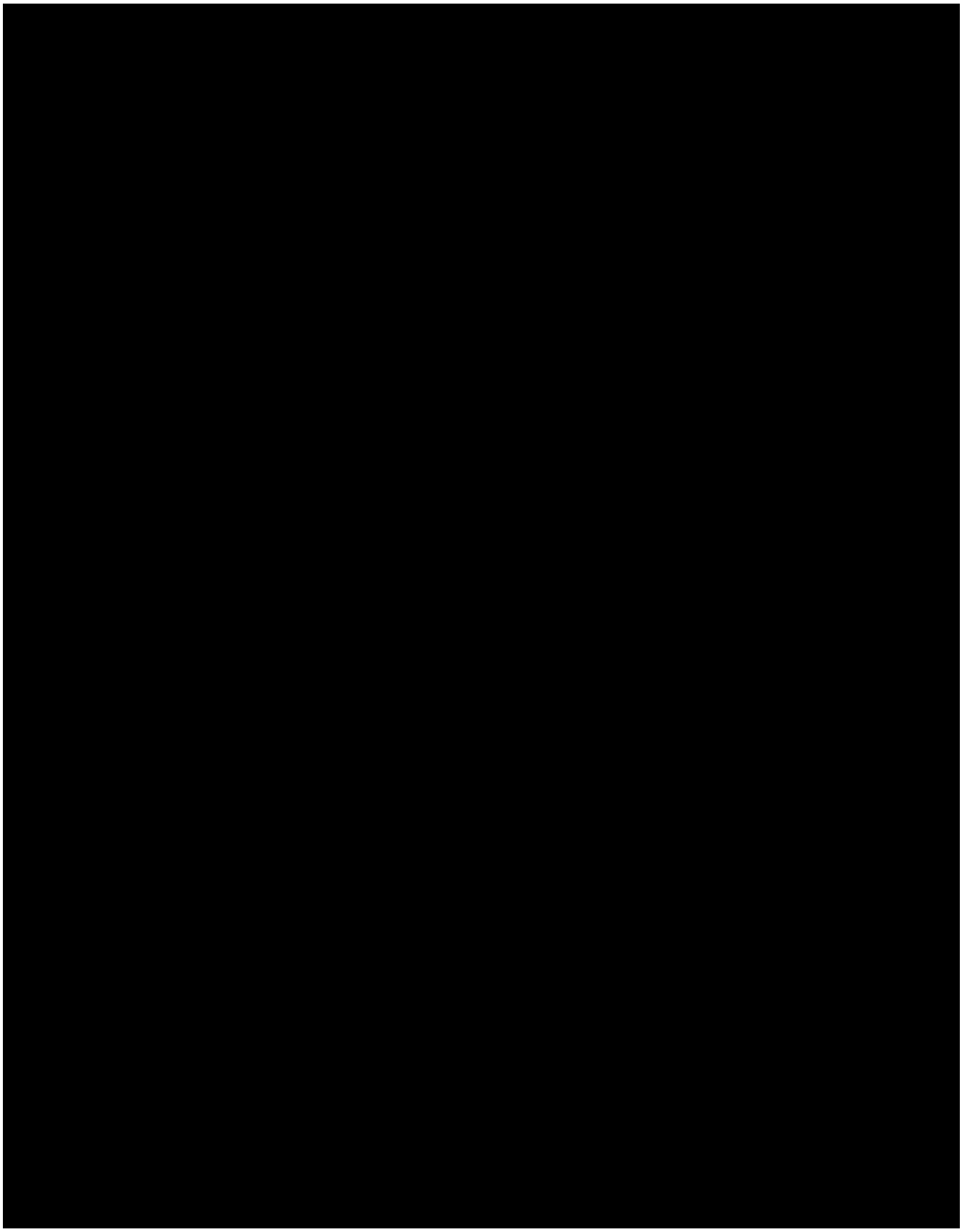
8.2.7. Itch Numerical Rating Scale

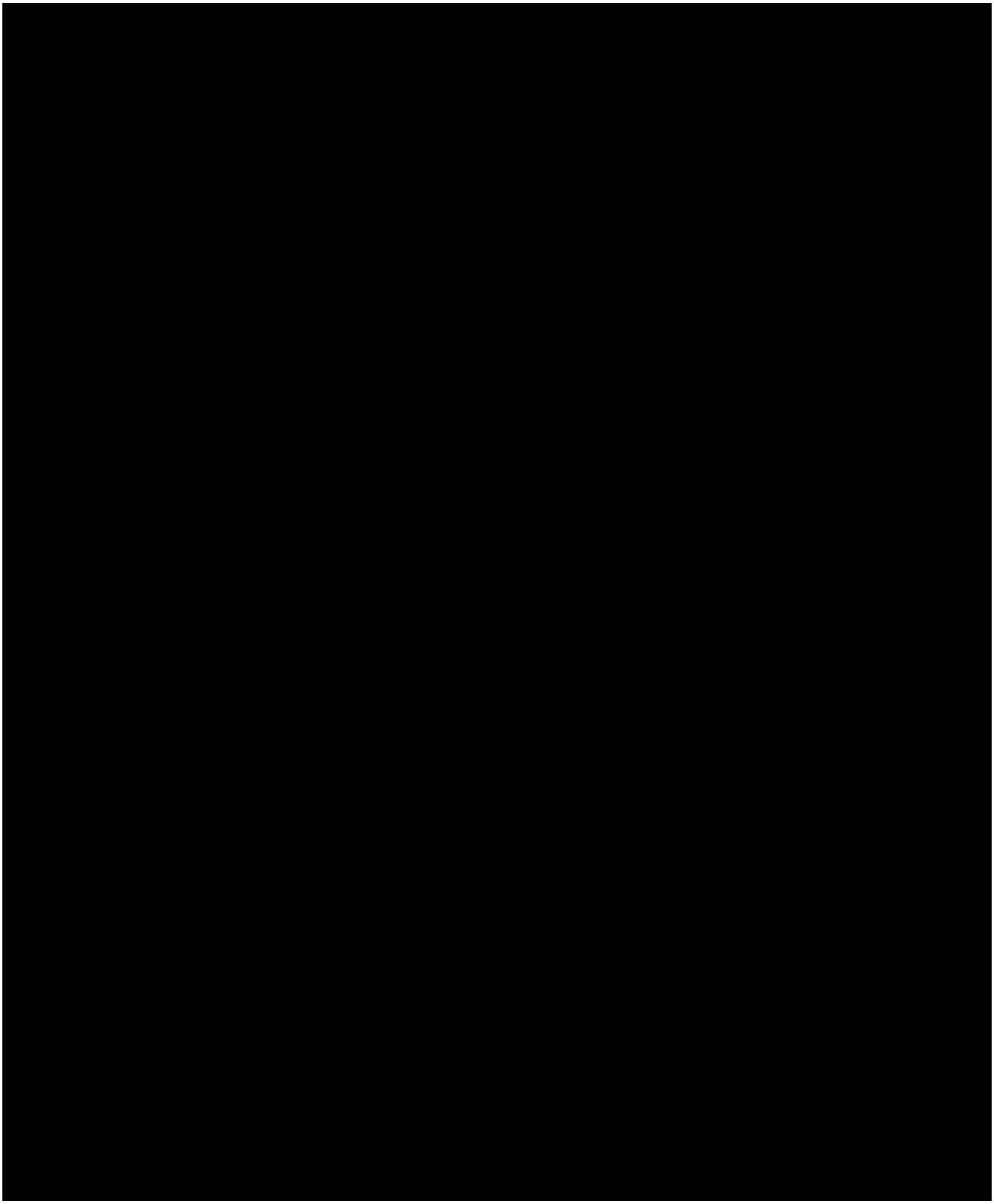
The Itch NRS will be administered based on the participant's age (at the time of consent), as follows:

- For participants ≥ 6 years of age, collect the Itch NRS. Baseline itch (defined as the average of the 7 days directly before Day 1, with Itch NRS values available for at least 4 of the 7 days) must be ≥ 4 on NRS.
- For participants < 6 years of age, do not collect the Itch NRS.

The Itch NRS is a daily participant-reported measure (24-hour recall) of the worst level of itch intensity (Pruritus Resources). Participants will be asked to rate the itch severity of their AD by selecting a number from 0 (no itch) to 10 (worst imaginable itch) that best describes their worst level of itching in the past 24 hours as outlined in the SoA (see Table 3). Participants will be issued a diary in which to record itch severity. The participants will be instructed to complete the diary each night beginning on the day of screening through the last application of study cream during the VC period. This is particularly important for the 7 days immediately prior to the Day 1/baseline, Week 2, Week 4, and Week 8 visits; therefore, Itch NRS scores are required for at least 4 of those 7 days during each of these 4 weeks to allow evaluation of participant eligibility and the Itch NRS endpoints. Detailed directions for the administration of a diary will be provided in the Study Reference Manual.

[redacted]





8.4. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (see Table 3 [VC period] and Table 4 [LTS period]).

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

8.4.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF (or assent) until at least 30 days after the last application of study cream. 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 cream. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

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

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

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

8.4.2. Physical Examinations

During the study, participants will be assessed by the investigator or medically qualified designee per institutional standard of care. Physical examinations will be conducted at the timepoints listed in Table 3 and Table 4.

8.4.2.1. Comprehensive Physical Examination

At the screening visit and Week 52/EOT or ET visit, a comprehensive physical examination should be conducted. The comprehensive physical examination will include assessment(s) of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes; as well as a brief neurological examination.

8.4.2.2. Targeted Physical Examination

At the visits indicated in the SoA (see Table 3 [VC period] and Table 4 [LTS period]), a targeted physical examination will be a symptom-directed evaluation (ie, conducted only if indicated by

symptoms, AEs, or other findings); clinically significant abnormalities (in the investigator's judgment) are to be reported as AEs and documented on the Adverse Events Form in the eCRF.

8.4.3. Vital Signs, Height, and Weight

Vital signs, height, and weight will be measured as outlined in the SoA (see Table 3 [VC period] and Table 4 [LTS period]).

Vital sign measurements (to be taken before blood collection for laboratory tests) include blood pressure, pulse, respiratory rate, and body temperature. Blood pressure and pulse will be taken with the participant in the sitting position after 5 minutes of rest. Abnormal vital sign results identified after the first application of study cream constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, or require concomitant therapy.

Height and weight will be assessed at the baseline, Week 8/ET, Week 24, and Week 52/EOT/ET visits. Individual growth measurements from the preceding year should be collected, if at all possible, from each participant's physician prior to the baseline visit. If these measurements cannot be obtained, the reason should be documented. Height will be measured using a stadiometer. The stadiometer should be calibrated, and a wall-mounted one is recommended. Participants should be measured without socks and 3 measurements taken to the nearest 0.1 cm. The average of the 3 height measurements of individual participants should be entered into the EDC. At the end of the study, these growth measurements will be compared against each participant's growth measurements from the previous year prior to entry into this trial.

8.4.4. Laboratory Assessments

See Table 11 for the list of clinical laboratory tests to be performed and the SoA (see Table 3 and Table 4) for the timing and frequency. Day 1 testing will be performed only if the interval between this visit and screening is > 2 weeks. A central laboratory will perform all clinical laboratory assessments for safety (blood chemistries and hematology assessments) [redacted] Additional testing may be required by the sponsor based on emerging safety data. All Protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual and the SoA (see Table 3 and Table 4). Information regarding collection, processing, and shipping of laboratory assessments is provided in the Laboratory Manual.

Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. All laboratory tests with values considered clinically significantly abnormal during participation in the study, or within 30 days after the last application of study cream, should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

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

Table 11: Required Laboratory Analytes

Serum Chemistries	Hematology	Serology
• Albumin • Alkaline phosphatase • ALT • AST • Bicarbonate • Blood urea nitrogen or urea • Calcium • Chloride • Creatinine • Glucose • Lactate dehydrogenase • Phosphorus • Potassium • Sodium • Total bilirubin • Direct bilirubin (if total bilirubin is elevated above ULN)	Complete blood count, including: • Hemoglobin • Hematocrit • Mean corpuscular volume • Platelet count • Mean platelet volume (MPV) • Red blood cell count • Reticulocyte count • White blood cell count Differential count, including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	• HIV antibody **Pregnancy Testing** Female participants who have reached menarche will have a urine test conducted at all required visits. A positive urine test must be confirmed by a serum test.

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.

[redacted]

8.4.4.2. Pregnancy Testing

A urine pregnancy test will be required for all female participants who have reached menarche. The urine pregnancy test will be performed locally as outlined in the SoA (see Table 3 and Table 4), and as medically indicated (eg, in case of loss of menstrual cycle, when pregnancy is suspected). If a urine pregnancy test is positive, the results must be confirmed with a serum pregnancy test. Day 1 testing will be performed only if the interval between this visit and screening is > 2 weeks.

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 treatment and continue participation in the study.

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

8.4.4.3. Serology

An HIV assessment will be performed at the screening visit to rule out HIV infection; required analytes are shown in Table 11. Serology and virology tests should be performed early in the

screening process due to the length of time needed to obtain the results. Additional tests may be performed if clinically indicated.

[redacted]

[redacted]

[redacted]

[redacted]

8.7. Unscheduled Visits

Unscheduled study visits may occur at any time medically warranted, including when participants develop new areas of AD. 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.

8.8. End of Treatment and/or Early Termination

The EOT coincides with the Week 52 visit. A participant that completes the Week 52/EOT visit will have reached the end of treatment with study cream.

If a decision is made that the participant will permanently discontinue study cream prior to the Week 52/EOT visit, then the ET visit should be conducted. If the ET visit coincides with a regular study visit, then the ET evaluations will supersede those of that scheduled visit, and the data should be entered in the ET page in the eCRF. If this decision does not coincide with a regular visit, reasonable efforts should be made to have the participant return to the site to have the ET procedures completed.

8.9. Follow-Up

8.9.1. Safety Follow-Up

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

- Follow-up visit should occur at the Week 52/EOT visit for participants who have been in an observation/no treatment cycle with an IGA score of 0 (clear) from Week 48 or earlier until Week 52
- Follow-up visit should occur 30 days after the last application of study cream if the Week 52/EOT or ET visit was not performed.

Adverse events and SAEs must be reported up until 30 days after the last application of study cream; ongoing AEs and SAEs must be followed up until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant return for the follow-up visit and report any AEs that may occur during this period.

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

9.1. Definition of Adverse Event

Adverse Event Definition
• An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug-related. • An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study cream.
Additional Guidance for Events Meeting the Adverse Event Definition
• Any safety assessments (eg, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease) are to be reported as an AE. • Abnormal laboratory test results are to be reported as an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study cream. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal laboratory test result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition/disease, including either an increase in the frequency and/or intensity of the condition, is to be reported as an AE. • New conditions detected or diagnosed after the start of study cream 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 cream (eg, overdose) or a concomitant medication are to be reported as an AE. • "Lack of efficacy" or "failure of expected pharmacological action" will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE. • A condition that leads to a medical or surgical procedure (eg, endoscopy, 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 that begins or worsens after informed consent is signed should be recorded on the Adverse Event Form in the eCRF. Adverse events/SAEs should be reported for enrolled participants, but only SAEs need to be reported for screen failure participants. Conditions that were present at the time informed consent/assent was given should be recorded on the Medical History Form in the eCRF.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and 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 as per SAE Completing Guidelines.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE/SAE.

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

- The severity grade (CTCAE v5.0 Grade 1 to 5). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study cream: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at the final safety follow-up visit.
- The action taken with regard to study cream as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the Adverse Event Form and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Non-Drug Therapy).

Assessment of Intensity

The severity of AEs will be assessed using CTCAE v5.0 Grades 1 through 5. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity.

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study cream and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are medical facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the possibility of a relationship.
- The investigator will also consult the Reference Safety Information in the IB for study cream 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 cream 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 or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study cream, the interventions required to treat the event, and the outcome.
- When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings, including histopathology.
- New or updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance (either via email/fax) until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
- Any updated SAE data (including SAEs being downgraded to nonserious) will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.

9.4. Reporting of Serious Adverse Events

All SAEs, regardless of suspected causality (eg, relationship to study cream or study procedure[s]), occurring after the participant has signed the ICF/assent through 30 days after the last application of study cream, must be reported to the sponsor (or designee) within 24 hours of learning of its occurrence, unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information after conclusion of study participation (ie, after the safety follow-up visit or 30 days after the last application of study cream). However, if the investigator learns of any SAE, including a death, at any time during this period, and after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study cream 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 of a SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study cream under clinical investigation are met.

If the SAE is not documented in the Reference Safety Information of the IB for the study cream (new occurrence) and is thought to be related to the study cream, the sponsor or its designee may urgently require further information from the investigator for 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 cream 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 a SAE or other specific safety information (eg summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure 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 via the EDC system (primary method) or by completing the Serious Adverse Event Report Form in English (only if the EDC system is not available). The contact information for Incyte Pharmacovigilance by email/fax is listed in the Study Reference Manual or as per the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.
- In circumstances where the EDC system is not accessible for reporting SAE information (initial and/or follow-up SAE information) to the sponsor within 24 hours, refer to the Incyte Reference Guide for Completing the Serious Adverse Report Form. Once the EDC system is functional, the SAE report should be retrospectively added to the EDC system and follow-up should be completed through the EDC. The original copy of the Serious Adverse Event Report Form and the email or facsimile confirmation sheet must be kept at the study site (refer to the Incyte Reference Guide for Completing the Serious Adverse Report Form or Study Reference Manual for details and for the email address or fax number).
- Follow-up information is also recorded in the eCRF and transmitted to Incyte Pharmacovigilance via the EDC system. The follow-up report should include information that was not provided previously, such as the outcome of the event, treatment provided, action taken with study cream because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.
- Contacts for SAE reporting can be found in the Study Reference Manual.

9.5. Emergency Unblinding of Treatment Assignment

In a medical emergency during the study, if the investigator deems it necessary to determine optimal medical management of the participant, emergency unblinding will be performed exclusively by the principal investigator and subinvestigator as described in the IRT Manual. The IRT system has an option to select for "Participant Unblinding" in the event that a participant's treatment needs to be unblinded in the case of a medical emergency. The

investigator/subinvestigator will proceed to either final confirmation or cancellation of the subjecting unblinding procedure. After providing a final confirmation to unblind the selected participant, the investigator/subinvestigator will proceed to enter their IRT password as a final security measure. Once a valid password has been entered for the user's account, IRT will display the participant's unblinded information to the user.

If a participant's treatment assignment is unblinded, the sponsor or its designee must be notified immediately by telephone followed-up with an email.

If an investigator, site personnel performing assessments, or participant is unblinded, the participant must be withdrawn from the study cream, unless there are ethical reasons to have the participant remain on the study cream. In these cases, the investigator must obtain specific approval from the sponsor's (or its designee's) medical monitor for the participant to continue in the study.

9.6. Pregnancy

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

- The study cream must be discontinued immediately (female participants only).
- 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 cream to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

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.

9.7. Warnings and Precautions

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

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

9.8. Treatment of Excessive Use

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

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.

10. STATISTICS

10.1. Sample Size Determination

Approximately 315 participants will be randomized 2:2:1 to ruxolitinib cream 1.5% BID, ruxolitinib cream 0.75% BID, or vehicle cream BID. The sample size calculation is based on the Fisher exact test for the primary efficacy endpoint. Based on the results from the 2 pivotal studies, INCB 18424-303 and INCB 18424-304, the response rate of IGA-TS at Week 8 is assumed to be 51% and 47% for the active arms (1.5% BID and 0.75% BID, respectively) versus 14% for placebo. Using a 2-sided alpha of 0.025, the sample size will have > 95% power to detect a difference between each of the 2 active treatment groups versus vehicle. In addition to providing adequate power for efficacy variables, the sample size is determined to provide a large database for safety evaluations.

10.2. Populations for Analysis

Table 12 presents the populations for analysis.

Table 12: Populations for Analysis

Population	Description
ITT	The ITT population includes all randomized participants. Treatment groups for this population will be defined according to the treatment assignment at randomization.
PP	The PP population includes randomized participants who are considered to be sufficiently compliant with the Protocol. In general, the following are important protocol deviations that may significantly affect the primary analysis: Missing data for the primary endpoint Overall application compliance less than 80% during the VC period Participants with one or more such deviations will be excluded from the PP population. In addition, important protocol deviations related to inclusion/exclusion criteria, discontinuation criteria, and use of prohibited concomitant medications will be reviewed. Decisions as to whether any of these deviations warrant exclusion from the PP population will be made prior to unblinding.
Safety	The safety evaluable population includes all participants who applied study cream at least once. Treatment groups for this population will be determined according to the actual treatment the participant received on Day 1.
LTS evaluable	All analyses for the LTS period will be conducted with the LTS evaluable population, which includes all participants who applied study cream at least once during the LTS period.
[redacted]	[redacted]

10.3. Level of Significance

A graphical procedure with gatekeeping testing strategy for the primary and key secondary analyses will be implemented. The underlying procedure is derived using the methodology developed by Bretz et al (2009). This method will guarantee a strong control of the family-wise error rate.

In Step 1, 2 families of 4 elementary hypotheses tests at Week 8 are grouped according to treatment comparison between each ruxolitinib cream group and the vehicle cream group, where

- Family 1 (1.5% BID vs vehicle):
  - H11: proportion of participants who achieve IGA-TS
  - H12: proportion of participants with a ≥ 4-grade improvement in Itch NRS score over baseline
- Family 2 (0.75% BID vs vehicle):
  - H21: proportion of participants who achieve IGA-TS
  - H22: proportion of participants with a ≥ 4-grade improvement in Itch NRS score over baseline

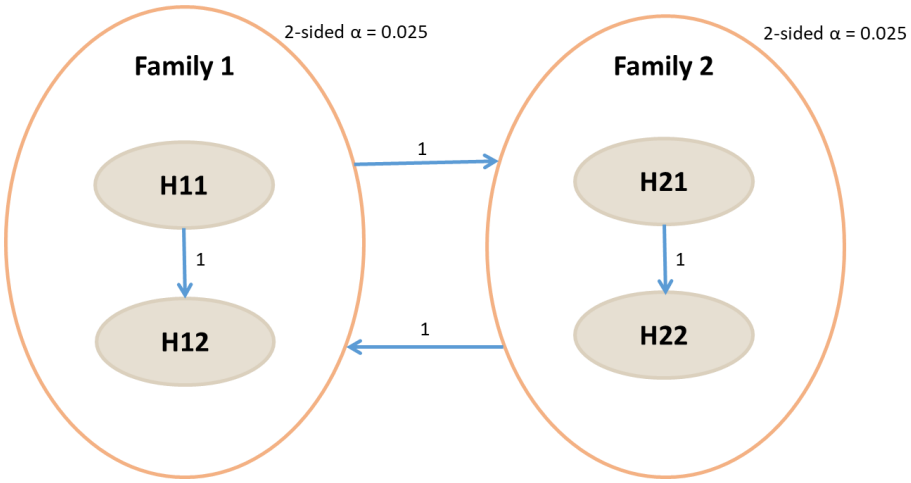
Step 2 has 2 families of 4 hypotheses tests:

- Family 3 (1.5% BID vs vehicle and 0.75% BID vs vehicle on Day 7 Itch NRS):
  - H13: proportion of participants with a ≥ 4-grade improvement in Itch NRS score over baseline to Day 7 (Week 1) between 1.5% BID and vehicle
  - H23: proportion of participants with a ≥ 4-grade improvement in Itch NRS score over baseline to Day 7 (Week 1) between 0.75% BID and vehicle
- Family 4 (1.5% BID vs vehicle and 0.75% BID vs vehicle on Day 3 Itch NRS):
  - H14: proportion of participants with a ≥ 4-grade improvement in Itch NRS score over baseline to Day 3 between 1.5% BID and vehicle
  - H24: proportion of participants with a ≥ 4-grade improvement in Itch NRS score over baseline to Day 3 between 0.75% BID and vehicle

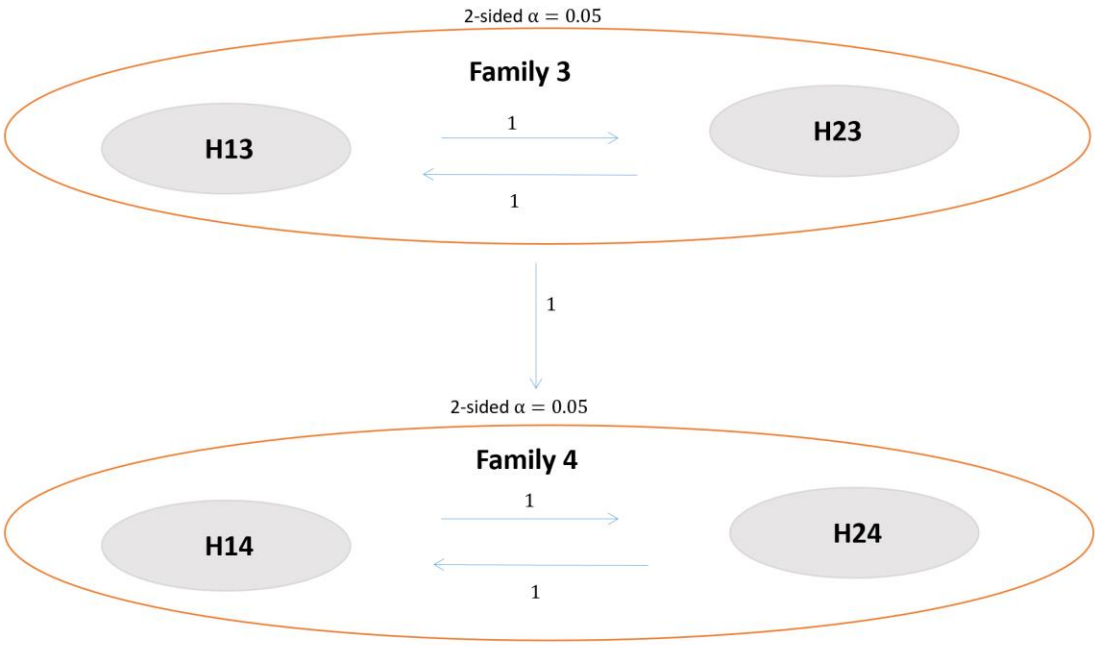
To control the overall Type I error rate, 2-sided $\alpha = 0.05$, the Bonferroni's method will be used. In Step 1, within Family 1 and 2, the endpoints are tested in a fixed sequence at Bonferronized 2-sided $\alpha = 0.025$ level. The key secondary endpoint will be tested only if the associated primary endpoint is rejected. For any treatment strength, if the 2 related null hypotheses can be rejected, then the fixed sequence for the other treatment strength can be conducted at the 2-sided $\alpha = 0.05$ level. If all null hypotheses in Family 1 and 2 are rejected, in Step 2, the endpoints in Family 3 (H13 and H23) will be tested using Bonferroni-Hochberg's procedure with overall 2-sided $\alpha = 0.05$ level. If both hypotheses in Family 3 are rejected, the endpoints in Family 4 (H14 and H24) will be tested similarly using Bonferroni-Hochberg's procedure with overall 2-sided $\alpha = 0.05$ level. The approach is visualized in Figure 9.

Figure 9: Control of the Overall Type I Error Rate

Step 1:



Step 2:



10.4. Statistical Analyses

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

10.4.1. Primary Analysis

The primary analysis will be based on the ITT population. The primary alternative hypothesis (superiority of each active ruxolitinib arm, 1.5% BID or 0.75% BID, compared with vehicle) will be tested at a 2-sided $\alpha = 0.025$ level using logistic regression. This model will include the treatment group (1.5% BID, 0.75% BID, and vehicle) and stratification factors (baseline IGA score and age). Exact logistic regression (Mehta and Patel 1995) will be used for all of the comparisons if any of the treatment strengths have an expected cell count < 5.

The difference in IGA-TS rates (ruxolitinib cream/vehicle) at Week 8 will be computed. The 95% confidence interval for the difference will be computed based on a large-sample normal approximation with continuity correction. All nonresponders during the VC period, as well as all participants who discontinue study treatment at any time before the timepoint of interest, or discontinue from the study for any reason, will be defined as nonresponders for the nonresponder imputation analysis. Subgroup analysis by baseline characteristic (eg, IGA score, country, and age) will be performed. Details will be provided in the SAP. The following approaches may be performed for sensitivity analyses:

- Longitudinal logistic regression with repeated measures:

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

  The primary endpoint binary response of each participant at Week 2, Week 4, and Week 8 will be included as the dependent variable. Treatment (1.5% BID, 0.75% BID, and vehicle BID), the randomization stratification factors (baseline IGA score and age), visit, and treatment by visit interaction will be included as fixed effects. Site level intercept and participant nested in site level intercept will be included as random effects. The within-participant and within-site errors will be modeled by an unstructured variance-covariance matrix. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom for this model.

- Multiple imputation:

  Multiple imputation with missing at random assumption will be used as an alternative method to handle missing data. A fully conditional specification method (van Buuren 2007) that assumes the existence of a joint distribution for all variables will be used to impute the IGA score. A regression model including treatment group, stratification factors (baseline IGA score and age), and baseline and scheduled postbaseline scores up to Week 8 will be specified for the fully conditional specification method. The imputation will be repeated a number of times to generate corresponding complete data sets, in order to reflect the uncertainty around the true values. The primary endpoint binary response will be derived for each of the imputed datasets, and the logistic regression described in Section 10.4.1 will be applied. The results will then be combined for the inference using Rubin's rule.

- Last observation carry forward:

  For the participants who are missing postbaseline assessments, the last observed nonmissing postbaseline values will be used to fill in missing values at Week 8. Then the proposed logistic regression described in Section 10.4.1 will be applied to the imputed dataset.

- Tipping point analysis:

  A tipping point sensitivity analysis will be conducted to examine the potential effects of missing data. The missing primary endpoint binary response at Week 8 in each treatment group will be replaced by a range of values to see how far they must be changed for the results of the study to tip from significant to not. Between-treatment comparisons will be performed using a chi-square test.

10.4.2. Secondary Analyses

Secondary efficacy analyses will be conducted on the ITT population. If the primary objective is achieved, the statistical comparisons for key secondary endpoints will be tested with the procedures specified in Figure 9.

The Itch NRS score for baseline will be determined by averaging the 7 daily NRS scores directly before Day 1 (Day –7 to Day –1). The by-visit Itch NRS score for postbaseline visits will be determined by averaging the 7 daily NRS scores directly before the visit day. If 4 or more daily scores are missing (out of the 7), the Itch NRS score at the visit will be set to missing. The same nonresponder imputation method as specified in the primary analysis will be used to handle missing Week 8 itch data, and the logistic regression described in Section 10.4.1 will be applied to compare each ruxolitinib cream group and the vehicle cream group for the key secondary endpoint of Itch NRS score responses at Week 8.

For the key secondary endpoints of Itch NRS score responses on Day 7 (Week 1) and Day 3, all participants who are missing Day 7 and/or Day 3 daily Itch NRS scores will be imputed using multiple imputation by fully conditional specification method. The variables to be included in the imputation regression model are treatment group, stratification factor, baseline itch score, and postbaseline daily itch score on Day 1 to Day 7. The details of the multiple imputation, including number of imputations and seed number, will be specified in the SAP. After the missing values have been imputed, the binary variable for the ≥ 4-point improvement in Itch NRS score on Day 7 and Day 3 will be derived. The logistic regression specified in Section 10.4.1 will be applied to each imputed dataset, and then the results will be combined for the inference.

All other secondary [redacted] efficacy variables will be summarized using descriptive statistics. For categorical measurements, summary statistics will include sample size, frequency, and percentages. Similar logistic regression models as specified in the primary and key secondary analysis will be used if applicable. For continuous measurements, summary statistics will include sample size, mean, median, standard deviation, standard error of the mean, minimum, and maximum. Continuous efficacy endpoints, including the actual measurement, change from baseline, and percentage change from baseline, may also be analyzed by the mixed-effect model with repeat measurement.

10.4.3. Safety Analyses

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after the first application of study cream. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study cream administration. AEs will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the National Cancer Institute CTCAE v5.0 using Grades 1 through 5.

The subset of AEs considered by the investigator to have a relationship to study cream will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study cream, then the AE will be considered treatment-related. The incidence of AEs and treatment-related AEs will be tabulated.

The clinical laboratory data will be analyzed using summary statistics; no formal treatment group comparisons are planned. Laboratory test values outside the normal range will be assessed for severity based on the normal ranges for the clinical reference laboratory. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated.

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature), height, and weight at each assessment time.

[redacted]

10.5. Interim Analysis

No formal interim analysis is planned for this study; however, the following analyses will be performed:

- The primary analysis will occur after the primary database lock, when all participants have completed the VC period. The sponsor will be unblinded after the primary database lock; however, investigators and participants will remain blinded to the individual study treatment assignment.
- The final analysis will occur when all participants have completed or withdrawn from the study.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

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

11.1.1. Identification of the Coordinating Principal Investigator

A coordinating principal investigator will be appointed by the sponsor before the end of the study. As part of their responsibilities, the coordinating principal investigator will review the final CSR. Agreement with the final CSR will be documented by the dated signature of the coordinating principal investigator.

11.2. Data Management

Data management will be performed in a validated EDC system. The investigator will be provided with access to an EDC system so that an eCRF can be completed for each participant.

The site will be provided with eCRF completion guidelines for instructions on data entry in the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements. Other data outside the EDC system required in the study conduct of the Protocol, such as documents or results transmitted to the sponsor via a central laboratory or specialized technical vendors and as designated by the sponsor, will have their own data flow management plans, study charters, [redacted], as applicable.

The sponsor (or designee) will be responsible for the following:

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

The investigator will be responsible for the following:

- Recording, or ensuring the recording of, all relevant data relating to the study in the eCRF.
- Delivering, or ensuring the delivery of, all other results, documents, data, know-how, or formulas relating to the study to the sponsor or designee electronically and/or centrally (eg, laboratory data, imaging data, [redacted] photographs, diary data) or as otherwise specified in the Protocol.

- Maintaining adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source data are, in general, all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
- Verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Maintaining accurate documentation (source data) that supports the information entered in the eCRF, sent to a central vendor designated by the sponsor, or as described in other study and data flow manuals.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed and available at the investigator's site. Examples of source documents are original documents, data, and records (eg, hospital records; electronic hospital records; clinical and office charts; laboratory notes; memoranda; participants' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives; microfilm or magnetic media; x-rays; participants' files; and e-records/records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

  Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current applicable medical records must be available.
- Sending participants' data, either as unique samples, copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
  - As required by privacy and data protection regulations and Incyte's privacy policies, if any photographs of participants are to be taken, the photographs must be limited to the area of the face or the body that is strictly necessary and the photographs should be masked (ie, identifying features such as eyes, mouth, scars, tattoos, or unique markings or features should be either obscured with a black bar or digitally pixelated so as to not permit the reidentification of the participants and preserve their confidentiality) by a specially designated photography vendor prior to sending the photographs to Incyte or any other third-party vendors for analysis or further processing.

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

11.3. Data Quality Assurance

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

Quality tolerance limits will be predefined in the Integrated Quality and Risk Management Plan to identify systematic issues that can impact participants' safety, efficacy results and analysis, and/or reliability of study results. These predefined parameters will be monitored during the study and can be adjusted during the study upon data review. Important deviations from the quality tolerance limits and remedial actions taken, including reporting to IRBs/IECs and health authorities if applicable, will be summarized in the CSR.

11.4. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable, and the sponsor operates comprehensive data privacy and data security programs that are applicable to this study. Appropriate notice, or notice and consent (as may be required by each applicable jurisdiction), for collection, use,

disclosure, and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws. Appropriate data protection terms that comply with applicable laws will be included in relevant study agreements.

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

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

11.5. Financial Disclosure

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

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

11.6. Publication Policy

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

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

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

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

11.7. Study and Site Closure

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

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

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

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

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For female participants in the study:

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

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

Acceptable birth control methods that result in a failure rate of more than 1% per year include the following[e]:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide[f]
- Cap, diaphragm, or sponge with spermicide[f]

For male participants in the study:

Male participants should use a condom during treatment through 90 days after the end of systemic exposure. If the male participant has a partner that is of childbearing potential, the partner should also use contraception through 90 days after the end of relevant systemic exposure. In addition, male participants must refrain from donating sperm during the study through 90 days after the end of relevant systemic exposure. Male participants who have had a vasectomy qualify as having met the requirement for a highly effective birth control method.

[a] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

[b] Contraception methods that in the context of this guidance are considered to have low user dependency.

[,c] Vasectomized partner is a highly effective method provided of avoiding pregnancy that partner is the sole sexual partner of the study participant and that the vasectomized partner has received medical assessment of the surgical success.

[d] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

[e] Choices are for US and Canada participants only and include above < 1% failure rate methods.

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

Source: Clinical Trials Facilitation and Coordination Group 2020.

[redacted]

APPENDIX C. COVID-19 PANDEMIC MITIGATION STRATEGIES AND INSTRUCTIONS

The COVID-19 global pandemic presents numerous challenges to the conduct of ongoing clinical trials. In line with the FDA and European Medicines Agency's Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic (2020), the following Protocol considerations are provided to ensure participant safety is maintained and adequate benefit/risk analyses are applied relative to the completion of study procedures and maintaining the investigational product supply chain.

Recognizing the flexibility required to manage the impact of the pandemic on this clinical trial, additional details will be added to respective study reference manuals and project plan documents and communicated to the investigative sites as needed. For any additional questions, please confer with the medical monitor.

Number of Study Participants

The evolving situation of the pandemic may result in a substantial number of participants dropping out of the study early, which could affect the data integrity of the trial. Because of this risk, the sponsor may decide to recruit additional participants in the study, beyond the expected number, to mitigate such risk.

Study Visits

There are a number of on-site visits that would be required to ensure study validity. If there are local travel restrictions or isolation requirements, or the investigator determines it to be unsafe for participants to attend the scheduled study visit, the site staff may conduct certain visits via telemedicine (phone or video calls) to minimize participant risk as follows:

- VC period
  - The following visits must be performed in person:
    - Screening
    - Day 1 (Baseline) – if baseline visit cannot be performed on-site within the screening period of 28 (+ 7) days, the participant will be considered to have failed screening. Participants who fail screening due to COVID-19 may be rescreened (see Section 5.4) at a later time, if feasible.
    - Week 8/ET (with a window of ± 7 days)
  - The following visits may be conducted via telemedicine, if necessary:
    - Week 2
    - Week 4
- LTS period
  - The following visits should be in person whenever possible:
    - Week 24 (± 7 days)
    - Week 52/EOT/ET (± 10 days)
  - Other visits during the LTS period may be conducted via telemedicine if necessary.

- Telemedicine visits
  - At a minimum, a review of AEs, concomitant medications, and study cream application compliance must be completed and recorded in the EDC.
  - No efficacy assessments can be performed even if the telemedicine visit is a video call or photography of the active lesion is provided. Note: The presence or absence of active AD lesions may be verified through a video call, if available.
  - Participants should continue to complete the daily Itch NRS, [redacted] in their diary if the visit affected is during the VC period. If the participant is in the LTS period of the study, the start and end dates of treatment cycles must be recorded.
  - All assessments not performed will be recorded in the EDC as protocol deviations and reason documented as COVID-19.

Investigational Medicinal Product Dispensing and Distribution

In order to ensure the continuity of providing participants with clinical supplies, should they not be able to attend an onsite study visit, within the constraints imposed by the pandemic, the site staff may decide to supply study treatment to participants as follows:

- Adequate supplies of study cream can be shipped to the participant by the study staff using a third-party service with approval from the participant. The third-party vendor will be agreed upon with the sponsor.
- The participant may request, with prior arrangement/agreement with the site, an authorized individual (a relative or delegate) to retrieve the study cream from the study site if the participant is unable to personally to do so.

Clinical Trial Monitoring

Study monitoring visits may be postponed; however, the site monitor will continue to employ off-site monitoring practices such as routine communication methods (eg, phone calls, emails, video visits) with the sites to get information on trial progress, participant status, and issue resolution as detailed in the Data Monitoring Guidelines, Remote source data verification.

If the study site monitor cannot be on-site to perform the final drug accountability for reconciliation purposes, and the operation cannot be postponed, it may be performed by a pharmacist from the hospital pharmacy or by the study coordinator/data manager with suitable training. The study cream can be returned to the sponsor by the hospital pharmacy directly or destroyed in accordance with local practices, if applicable, and with sponsor approval.

Direct Contracts With Third Parties/Specialized Service Companies

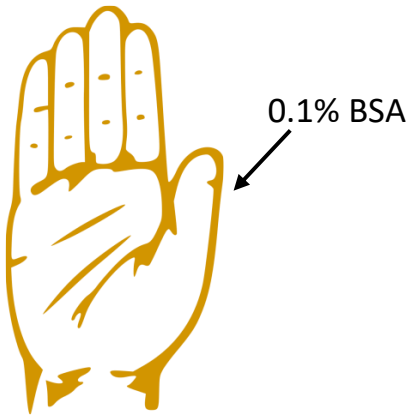
If necessary, direct contracts can be established with third-party local physicians to conduct activities related to the clinical management of participants for whom the investigator is responsible and maintains oversight. In such situations, the investigator is required to provide the local physician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

Reimbursement of Extraordinary Expenses

The sponsor will arrange to reimburse the participant (participant's parent[s]/legal guardian) for any extraordinary expenses for AEs that are related to study cream, keeping appropriate documentation as evidence (eg, travel expenses for the local laboratory visit[s], the costs of local [proximate] laboratory tests).

APPENDIX D. BODY SURFACE AREA CALCULATION GUIDES

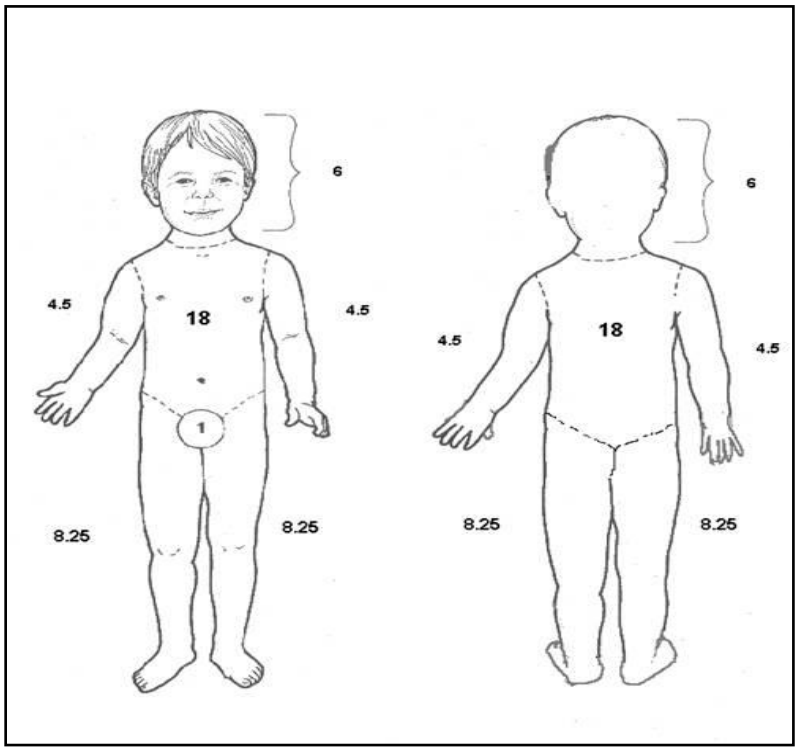
1. Handprint Method (use of participant's hand)



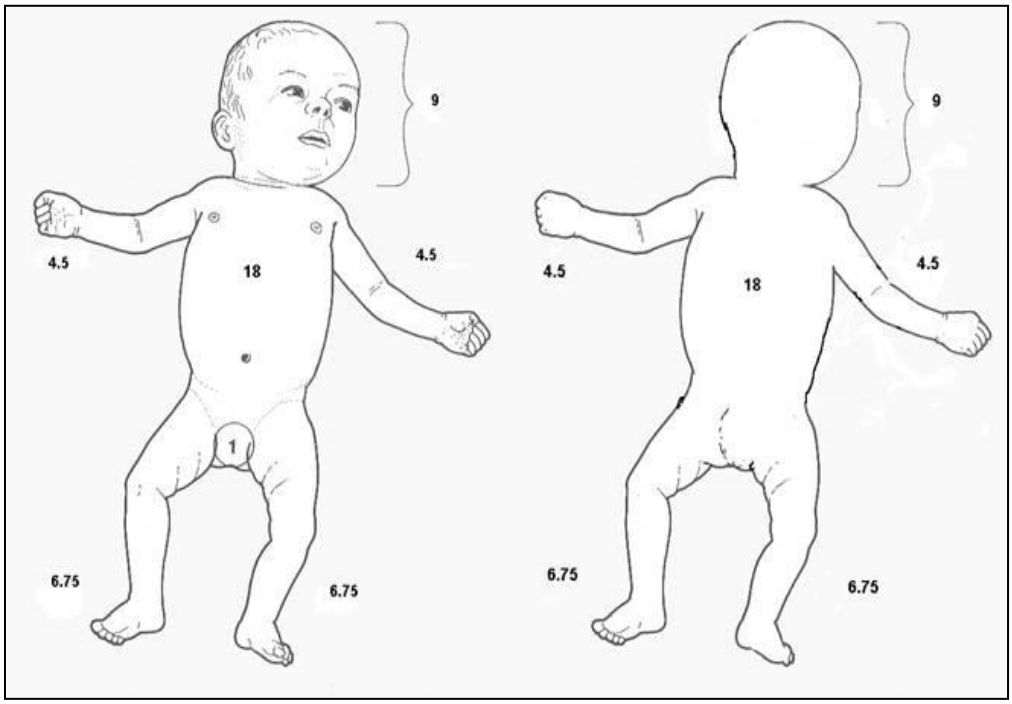
- 1% BSA = the palm plus 5 digits, with fingers tucked together and thumb tucked to the side (handprint)
- Thumb as 0.1% BSA.

2. BSA Calculation Guides

a) BSA for Children ≥ 3 and < 11 Years of Age



b) BSA for Infants ≥ 3 Months and < 3 Years of Age



APPENDIX E. ECZEMA AREA AND SEVERITY INDEX

The EASI score examines 4 areas of the body and weights them as follows:

- Subjects 8 years of age and older:
  - Head/Neck (H) = 0.1, Upper limbs (UL) = 0.2, Trunk (T) = 0.3, and Lower limbs (LL) = 0.4.
- Subjects 0 to 7 years of age:
  - Head/Neck (H) = 0.2, Upper limbs (UL) = 0.2, Trunk (T) = 0.3, and Lower limbs (LL) = 0.3.

The percentage of area involved for each of the 4 body regions is weighted as follows: 0 = no eruption, 1 = some to < 10%, 2 = 10% to 29%, 3 = 30% to 49%, 4 = 50% to 69%, 5 = 70% to 89%, and 6 = 90% to 100%.

Each of the 4 body regions is assessed separately for erythema (E), induration/papulation/edema (I), excoriations (Ex), and lichenification (L) for an average degree of severity of each sign in each region with: 0 = none, 1 = mild, 2 = moderate, and 3= severe, with half-step allowed.

EASI Score Calculation Tool for 8 Years of Age and Older

Body Region	Erythema (0-3)	Edema/ Papulation (0-3)	Excoriation (0-3)	Lichenification (0-3)	Region Score (0-6)	Multiplier	Score per Body Region
Head/neck	(+	+	+	)	**X**	**X 0.1**	
Trunk	(+	+	+	)	**X**	**X 0.3**	
Upper limbs	(+	+	+	)	**X**	**X 0.2**	
Lower limbs	(+	+	+	)	**X**	**X 0.4**	
						The final EASI score is the sum of the 4 region scores:	_____ **(0-72)**

EASI Score Calculation Tool for 0 to 7 Years of Age

Body Region	Erythema (0-3)	Edema/ Papulation (0-3)	Excoriation (0-3)	Lichenification (0-3)	Region Score (0-6)	Multiplier	Score per Body Region
Head/neck	(+	+	+	)	**X**	**X 0.2**	
Trunk	(+	+	+	)	**X**	**X 0.3**	
Upper limbs	(+	+	+	)	**X**	**X 0.2**	
Lower limbs	(+	+	+	)	**X**	**X 0.3**	
						The final EASI score is the sum of the 4 region scores:	_____ **(0-72)**

APPENDIX F. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1	06 MAY 2021
Amendment 2	02 AUG 2021
Amendment 3	19 AUG 2021
Amendment 4	06 APR 2022
Amendment 5	29 JUL 2022
Amendment 6	22 FEB 2023

Amendment 6 (22 FEB 2023)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to add 2 key secondary endpoints. Details of these and other minor changes are listed below.

1. **Section 1, Protocol Summary (Table 1: Primary and Key Secondary Objectives and Endpoints); Section 3, Objectives and Endpoints (Table 7: Objectives and Endpoints); Section 10.3, Level of Significance; Section 10.4.2, Secondary Analyses**

   Description of change: The proportion of participants with a ≥ 4-point improvement in Itch NRS score from baseline to Day 7 (Week 1) and from baseline to Day 3 were added as key secondary endpoints. Statistical details were also added for these 2 additional key secondary endpoints.

   Rationale for change: To include an alpha-controlled assessment of early itch reduction with ruxolitinib cream.

2. **Section 1, Protocol Summary (Table 2: Key Study Design Elements)**

   Description of change: [redacted], MD, was added as the coordinating principal investigator.

   Rationale for change: A coordinating principal investigator is required.

3. **Section 10.2, Populations for Analysis**

   Description of change: Overall application compliance, which is an example of important protocol deviations that may significantly affect the primary analysis as part of the definition of the PP population, was modified from less than 60% to less than 80%.

   Rationale for change: [redacted]

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

Amendment 5 (29 JUL 2022)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to increase the overall sample size. The changes have no safety implications for this population of participants. Details of these and other minor changes are listed below.

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

   Description of change: The sample size for this trial is being increased from 250 to 315 participants.

   Rationale for change: The evaluable population for the key secondary endpoint (proportion of participants with a ≥ 4-point improvement in Itch NRS score from baseline to Week 8) requires participants 6 years of age or older who have nonmissing baseline Itch NRS scores. It was discovered that this subgroup was under-enrolled at a time when the overall enrollment was close to final. Based on the enrollment status on 14 JUL 2022, among 255 participants screened, approximately 116 participants were qualified in that subgroup. To ensure enough power for this key secondary endpoint, at least 180 participants are required in this subgroup, and to achieve that the overall population will be increased from 250 to 315.

   The sample size calculation of 180 in this subgroup is based on the results from the 2 pivotal studies, INCB 18424-303 and INCB 18424-304, in which the response rate for the key secondary endpoint at Week 8 is assumed to be 52% and 42% for the active arms (ruxolitinib 1.5% cream BID and ruxolitinib 0.75% cream BID, respectively) versus 16% for vehicle cream BID. Using a 2-sided alpha of 0.025, the sample size will have > 90% power to detect a difference between ruxolitinib 1.5% cream BID versus vehicle cream BID and 70% power to detect a difference between ruxolitinib 0.75% cream BID versus vehicle cream. In addition to providing adequate power for all efficacy variables, the sample size increase is also providing a larger database for safety evaluation.

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities: Vehicle-Controlled Period); Section 5.1, Inclusion Criteria (Inclusion Criterion 8); Section 8.2.3, Target Lesion Identification; Section 8.2.4, Photography**

   Description of change: Instructions were added such that only participants who are participating in photography are required to identify and measure target lesions at the screening and baseline visits. For participants not participating in photography, the identification and measurement of target lesions are optional.

   Rationale for change: Clarification was added that only participants who are participating in photography are required to identify and measure target lesions.

3. **Section 5.1, Inclusion Criteria (Inclusion Criterion 6); Section 8.2.7, Itch Numerical Rating Scale**

   Description of change: Instructions were added such that participants who are aged 6 years to < 12 years must record Itch NRS scores for at least 4 of the 7 days immediately prior to the Day 1/baseline, Week 2, Week 4, and Week 8 visits.

   Rationale for change: Clarification added in order to adequately calculate average baseline and weekly Itch NRS scores.

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

   Description of change: Removed the last study visit as a possible last timepoint for reporting SAEs so that all SAEs are reported through 30 days after the last application of study cream.

   Rationale for change: Changed in order to align with other sections for AE/SAE reporting timelines.

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

Amendment 4 (06 APR 2022)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to [redacted]. These changes have no safety implications for this population of participants. Details of these and other minor changes are listed below.

1. **Section 1, Protocol Summary (Table 1: Primary and Key Secondary Objectives and Endpoint); Section 3, Objectives and Endpoints (Table 7: Objectives and Endpoints); Section 10.3, Level of Significance; Section 10.4, Primary Analysis**

   Description of change: The endpoint of the proportion of participants who achieve EASI75 at Week 8 has been moved from the key secondary endpoints to the other secondary endpoints. The gatekeeping testing strategy described in Section 10.3 and the primary analysis description in Section 10.4 have been modified accordingly. Further, the gatekeeping testing strategy has been modified so that the primary and key secondary endpoints are both tested for the 1.5% ruxolitinib cream strength before testing for the 0.75% strength.

   Rationale for change: [redacted].

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

   Description of change: Exceptions for dispensing and applying the study cream at site visits were updated to include Week 8 if the IGA score is 0.

   Rationale for change: Clarification that at the Week 8 visit, if the IGA score is 0, no study cream should be applied.

3. **Section 1, Protocol Summary (Table 3: Schedule of Activities: Vehicle-Controlled Period); Section 5.4, Screen Failures; Section 8.1.1, Informed Consent Process; Section 8.1.2, Screening Procedures**

   Description of change: Participants on prior medications requiring a 4-week washout period will have a 35-day screening window and must reconsent if rescreened ≥ 35 days after the initial screening.

   Rationale for change: To clarify that the 35-day screening window pertains to the 4-week washout period noted in Exclusion Criterion 5b.

4. **Section 1, Protocol Summary (Table 4: Schedule of Activities: Long-Term Safety Period)**

   Description of change: Added clarification that application of study cream at site visits only pertains to participants with active AD lesions at the time of visit.

   Rationale for change: Clarification to be consistent with Section 6.1.

5. **Section 1, Protocol Summary (Table 4: Schedule of Activities: Long-Term Safety Period); Section 8.9.1, Safety Follow-Up**

   Description of change: Clarified that participants who are in an observation/no treatment cycle from the Week 48 visit or earlier until the Week 52/EOT visit can complete the safety follow-up and Week 52/EOT visits at the same time.

   Rationale for change: For consistency with changes previously made to Section 4.1.

[redacted]

7. **Section 4.1, Overall Design**

   Description of change: Removed the option for the investigator (in consultation with the medical monitor) to determine if a participant experiencing a lack of efficacy after 8 weeks of continuous treatment in the LTS period should be discontinued, to match the language in Section 7.1.1.

   Rationale for change: [redacted].

8. **Section 5.2, Exclusion Criteria**

   Description of change: Exclusion Criterion 6c has been modified to clarify that COVID-19 vaccination is allowed before the baseline visit.

   Rationale for change: Clarification.

9. **Section 5.2, Exclusion Criteria**

   Description of change: Exclusion Criterion 6d has been modified to note that the frequency of "bleach" baths must remain the same throughout the study.

   Rationale for change: Consistency with Section 6.6.2.

10. **Section 5.2, Exclusion Criteria;** [redacted]

    Description of change: Exclusion Criterion 11, which excluded participants with inadequate venous access in nonlesional areas for laboratory blood draws, has been removed. [redacted]

    Rationale for change: [redacted]

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

    Description of change: Further instructions have been added regarding approval to treat additional areas of AD with study cream.

    Rationale for change: Providing additional guidance.

12. **Section 6.5, Dose Modifications**

    Description of change: Clarification has been provided to the dose-modification rules.

    Rationale for change: Providing additional guidance.

13. **Section 6.5.1, Criteria and Procedures for Application Interruptions and Adjustments of Study Cream**

    Description of change: Added caution that participants should be closely monitored for the development of signs and symptoms of infection and added instructions for study cream interruption in case of infection.

    Rationale for change: Added for consistency with current US labeling.

14. **Section 6.6.2, Restricted Medications and Procedures**

    Description of change: Clarification has been provided to indicate that the use of allergen immunotherapy is allowed if the participant is on a stable dose at baseline and continues at the same dose.

    Rationale for change: Previously, allergen immunotherapy was not recommended, but the sponsor felt that it should be allowed throughout the study if a stable dose.

15. **Section 6.6.2, Restricted Medications and Procedures; Section 6.6.3, Prohibited Medications and Procedures**

    Description of change: The use of systemic corticosteroids is no longer completely prohibited. Short-term use in response to an AE for participants in the LTS period is now allowed, and the decision to keep the participant in the study (or early termination) will be made in consultation with the medical monitor.

    Rationale for change: The sponsor believes that the short-term use of systemic corticosteroids will not impact assessment of the long-term safety of ruxolitinib cream

16. **Section 8.2.7, Itch Numerical Rating Scale**

    Description of change: The definition for baseline itch has been updated to state that the average must include Itch NRS values for at least 4 of the 7 days.

    Rationale for change: The sponsor believes that having Itch NRS values for at least 4 of the 7 days directly before baseline is an appropriate minimum for the calculation of the average baseline Itch NRS score for assessment of Inclusion Criterion 6.

17. **Section 8.4.3, Vital Signs, Height, and Weight**

    Description of change: It was clarified that at each visit in which the participant's height is measured, it is the average of 3 measurements that should be entered in the EDC rather than each of the 3 measurements.

    Rationale for change: Previously, it was implied that all 3 measurements at a given visit should be recorded, whereas only 1 value (the average) is required.

18. **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 3 (19 AUG 2021)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to [redacted] concerning Amendment 1. These changes have no safety implications for this population of participants. Details of these and other minor changes are listed below.

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

   Description of change: Added details of the countries where the study will be conducted as well as the number of sites.

   Rationale for change: [redacted].

2. **Section 4.1, Overall Design**

   Description of change: Clarified that participants who are in an observation/no treatment cycle from the Week 48 visit or earlier until the Week 52/EOT visit can complete the safety follow-up and Week 52/EOT visits at the same time.

   Rationale for change: The intent of the safety follow-up visit is to assess participants at least 30 days after the last application of study treatment; for participants who do not apply study treatment from the Week 48 visit onward due to having no active AD lesions, the Week 52/EOT visit would occur at approximately 30 days or more after the last application of study treatment. Hence, it is appropriate to combine the Week 52/EOT and safety follow-up visits for these participants.

3. **Section 5.2, Exclusion Criteria**

   Description of change: Exclusion Criterion 3 was changed in Amendment 2 to state that exclusionary laboratory test results had to be clinically significant. This is not the case, so "clinically significant laboratory results" has been replaced with "clinical laboratory test results," which was the language used in Amendment 1.

   Rationale for change: A change made in Amendment 2 was deemed inappropriate, and the text reverted to that used in Amendment 1.

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

   Description of change: For participants whose total areas of AD to be treated exceed 20% BSA in either the VC period or LTS period, the option to treat these additional areas has been removed, and instructions have been added that these participants should be discontinued from study treatment.

   Rationale for change: The intent was only to allow participants to treat areas of AD up to a maximum of 20% BSA in this study, so the 2 instances that suggested otherwise needed to be corrected.

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

   Description of change: Added a reason for discontinuation: if the extent of AD to be treated (ie. any body part excluding the scalp) exceeds 20% BSA during either the VC period or the LTS period.

   Rationale for change: Participants are only allowed to treat areas of AD up to a maximum of 20% BSA in this study, so it has been made clear that if the extent of AD exceeds 20% BSA, a participant must be discontinued from study treatment.

6. **Section 10.2, Populations for Analysis (Table 12: Populations for Analysis)**

   Description of change: Added examples of protocol deviations that would exclude participants from the PP population.

   Rationale for change: [redacted].

7. **Section 10.4.1, Primary Analysis**

   Description of change: Added full details of the planned sensitivity analyses for the handling of missing data and the tipping point analysis.

   Rationale for change: [redacted].

8. **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 (02 AUG 2021)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to revise Exclusion Criterion 3, which is overly restrictive, to create consistency across the AD program and for ease of recruitment, minimizing screen failures for nonsignificant clinical laboratory results. These changes have no safety implications for this population of participants. Additional changes are listed below.

1. **Protocol Summary (Table 3: Schedule of Activities: Vehicle-Controlled Period; Table 4: Schedule of Activities: Long-Term Safety Period)**

   Description of change: Added guidance to study drug application during site visits during the VC period; clarified BSA and IGA assessments and ranges at the Week 8 visit; deleted Day 1/baseline compliance check; [redacted]; added recommendation on use of a topical anesthetic prior to blood draw; and specified serologic testing for HIV at screening.

   Rationale for change: To provide additional guidance for clarity and correct an administrative error (Day 1/baseline compliance check).

2. **Protocol Summary (Table 3: Schedule of Activities: Vehicle-Controlled Period); Section 5.2, Exclusion Criteria (Exclusion Criterion 6); Section 6.1, Study Treatments Administered; Section 61.1, Study Treatment Application Guidance; Section 6.5, Dose Modifications; Section 6.5.1, Criteria and Procedures for Application Interruptions and Adjustments of Study Drug; [redacted]; Section 8.4.4.2, Pregnancy Testing**

   Description of change:

   - Protocol Summary and Section 8.4.4.2: Clarified that Day 1 pregnancy testing will be performed only if the interval between screening and Day 1 is > 2 weeks.
   - Section 5.2: Changed inactivated vaccines and live vaccines to live-attenuated vaccines and added topical antipruritics to the 1-week washout period before baseline.
   - Section 6.1: Added allowance for study drug applications to be approximately 8 hours apart.
   - Section 6.1.1: Updated application instructions to use a fingertip to apply study drug in small amounts.
   - Section 6.5 and Section 6.5.1: Added text that changes in frequency of application are not allowed and that treatment may be temporarily withheld at a lesional site but may be continued elsewhere and must be recorded as a dose interruption in the AE eCRF page.
   - [redacted]

   Rationale for change: To provide additional guidance for clarity.

3. **Section 5.2, Exclusion Criteria (Exclusion Criteria 2 and 3)**

   Description of change: Added "day" to 880 µg (880 µg/day) to Exclusion Criterion 2g; moved the criterion regarding medical history of hepatitis B virus or hepatitis C virus from Exclusion Criterion 4 to Exclusion Criterion 2i; revised Exclusion Criterion 3 to apply to clinically significant laboratory test results at screening; deleted Exclusion Criterion 3a (any value < 0.75 × LLN [other than bilirubin]); moved Exclusion Criterion 3b to Exclusion Criterion 3d and revised "any value > 2.5 × ULN" to "AST or ALT ≥ 2.5 × ULN"; added Exclusion Criterion 3d heading "liver function tests"; revised Exclusion Criterion 3e to change the estimated GFR from < 15 to < 30 mL/min/1.73 m^2; added Exclusion Criteria 3c and 3g regarding cytopenias at screening and any other clinically significant laboratory result that, in the opinion of the investigator, poses a significant risk to the participant, respectively; and moved Exclusion Criterion 9 regarding serologic testing for HIV to Exclusion Criterion 3f.

   Rationale for change: Exclusion Criteria 2 were revised for updates and clarification; Exclusion Criteria 3 were revised, added, or moved to be consistent with exclusion criteria from other AD protocols. In addition, original Exclusion Criteria 3a and 3b were overly restrictive; Exclusion Criterion 3d was revised to group the 2 liver function tests for clarity; and Exclusion Criterion 3e, per recommendation by Canada Health Authorities, was revised to provide a more conservative estimated GFR value.

4. **Section 6.5.1, Criteria and Procedures for Application Interruptions and Adjustments of Study Drug (Table 9: Guidelines for Interruption and Restarting of Treatment Applications if Adverse Event Is Deemed Related to the Study Drug)**

   Description of change: Deleted ALT and AST (> 3 × ULN), revised ANC to < 750/µL (without fever) and < 1000/µL (with fever), and updated AST or ALT (from > 5 to > 20 × ULN).

   Rationale for change: To provide a more succinct guideline because ALT and AST > 3 × ULN is covered by "any other Grade 3 or higher laboratory abnormality" assessment, to define ANC levels with fever or without fever, and to update AST or ALT to > 20 × ULN to be consistent with CTCAE v5.0 grading.

5. **Section 6.6.2, Restricted Medications and Procedures; Section 6.6.3, Prohibited Medications and Procedures**

   Description of change: Moved allergen immunotherapy and live-attenuated vaccinations from prohibited medications to restricted medications.

   Rationale for change: Allergen immunotherapy and immunizations with a live-attenuated vaccine are standard of care for this pediatric population and therefore may be allowed during the VC period should the investigator deem it necessary.

6. **Appendix C, COVID-19 Pandemic Mitigation Strategies and Instructions (Study Visits)**

   Description of change: [redacted]

   Rationale for change: Administrative error.

7. **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 (06 MAY 2021)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to incorporate revisions requested by the Canadian Health Authority and to address European regulatory requirements. Additional changes are summarized below.

1. **Protocol Summary (Table 3: Schedule of Activities: Vehicle-Controlled Period; Table 4: Schedule of Activities: Long-Term Safety Period); Section 8.1.5.1, Demographics and General Medical History; Section 8.4.3, Vital Signs, Height, and Weight**

   Description of change: Added guidance to capture height and weight of not only each participant, but also both parents of each participant (if available), and to record these data in the EDC.

   Rationale for change: To provide clarity that the growth measurements will be entered into the EDC and evaluated at the end of the study.

[redacted]

3. **Section 2, Introduction**

   Description of change: Revised the order of the sections for clarity and added text.

   - Moved Section 2.2, Study Rationale, to Section 2.3.
   - Moved Section 2.2.1, Scientific Rationale for Study Design, to Section 2.3.1.
   - Moved Section 2.2.2, Justification for the Selected Treatment Regimen, to Section 2.3.2.
   - Moved Section 2.2.2.2, INCB 18424-303 and INCB 18424-304, to Section 2.2.1 and changed the heading to INCB 18424-303 and INCB 18424-304: Phase 3 Adolescent/Adult Studies.
   - Moved Section 2.2.2.3, INCB 18424-102: Pharmacokinetic Pediatric Study, to Section 2.2.2.
   - Created Section 2.2, Pivotal Phase 3 Studies and Pilot Pediatric Study, for Section 2.2.1, INCB 18424-303 and INCB 18424-304: Phase 3 Adolescent/Adult Studies, and Section 2.2.2, INCB 18424-102: Pharmacokinetic Pediatric Study.

- Moved Section 2.2.2.1, INCB 18424-206, to part of Section 2.3.2, Justification for the Selected Treatment Regimen, and added text to provide further information for the justification of the selected treatment regimen.

Rationale for change: Administrative corrections.

4. **Section 5.2, Exclusion Criteria (Criteria 2h, 3b, and 3d)**

   Description of change:

   - Exclusion Criterion 2h: Added a criterion to exclude participants who are on maintenance dialysis.
   - Exclusion Criterion 3b: Added text to clarify that the laboratory test criterion for the ULN does not include for serum creatinine levels.
   - Exclusion Criterion 3d: Added a clinical laboratory test criterion for the lower limit of the estimated GFR.

   Rationale for change: To address Canadian Health Authority request.

5. **Section 5.2, Exclusion Criteria (Criteria 6c)**

   Description of change: Clarified the requirement for inactivated vaccines.

   Rationale for change: To simplify the immunization requirement.

6. **Section 6.1, Study Treatments Administered; Section 6.1.1, Study Treatment Application Guidance**

   Description of change: Deleted text regarding redispensing of study drug, replaced Figure 8 (Fingertip Unit of a Cream), and deleted the study drug application instructions.

   Rationale for change: To simplify the study drug dispensing process, to provide a better representation of the cream, and to avoid overlap of information that will be included in the Study Manual.

7. **Section 8.4.4.1, Blood Sample Collection**

   Description of change: Deleted capillary sampling.

   Rationale for change: To minimize laboratory sampling options.

8. **Section 8.1.5.2, Medical and Treatment History**

   Description of change: Added text for clarity on what would be defined as documentation needed for previous AD medication history. Defined the collective meaning of "inadequate response" for clarity of data collected.

   Rationale for change: To address European regulatory requirements (for the intended target population/indication).

9. **Appendices**

   Description of change: Revised the appendices as follows.

   [redacted]

   - Moved original Appendix B (COVID-19 Pandemic Mitigation Strategies and Instructions) to Appendix C.
   - Moved original Appendix C (Body Surface Area Calculation Guides) to Appendix D.
   - Deleted original Appendix D (Centers for Disease Control And Prevention Growth Charts [for the US Region]) and Appendix E [United Kingdom–World Health Organization Growth Charts [for the EU Region])
   - Changed original Appendix F (Eczema Area and Severity Index) to Appendix E.

   [redacted]

10. **Appendix C, COVID-19 Pandemic Mitigation Strategies and Instructions**

    Description of change: [redacted]

    Rationale for change: [redacted]

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.

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