

**Official Title: A Topical Ruxolitinib Evaluation in Atopic Dermatitis Study 2 (TRuE-AD2)  
A Phase 3, Double-Blind, Randomized, 8-Week, Vehicle-Controlled Efficacy and Safety Study  
of Ruxolitinib Cream Followed by a Long-Term Safety Extension Period in Adolescents and  
Adults With Atopic Dermatitis**

**NCT Number:** NCT03745651

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## Clinical Study Protocol



### INCB 18424-304

#### Topical Ruxolitinib Evaluation in Atopic Dermatitis Study 2 (TRuE-AD2)

A Phase 3, Double-Blind, Randomized, 8-Week, Vehicle-Controlled  
Efficacy and Safety Study of Ruxolitinib Cream Followed by a  
Long-Term Safety Extension Period in Adolescents and Adults With  
Atopic Dermatitis

<b>Product:</b>	<b>Ruxolitinib Cream</b>
<b>IND Number:</b>	██████
<b>EudraCT Number:</b>	<b>2018-003713-18</b>
<b>Phase of Study:</b>	<b>3</b>
<b>Sponsor:</b>	<b>Incyte Corporation 1801 Augustine Cut-Off Wilmington, DE 19803</b>
<b>Original Protocol (Version 0):</b>	<b>01 NOV 2018</b>
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<b>Amendment (Version) 2:</b>	<b>13 FEB 2019</b>

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study Protocol, applicable Good Clinical Practices, and applicable laws and country-specific regulations in which the study is being conducted.

The information in this document is confidential. No part of this information may be duplicated, referenced, or transmitted in any form or by any means (electronic, mechanical, photocopy, recording, or otherwise) without prior written consent.

## INVESTIGATOR'S AGREEMENT

I have read the INCB 18424-304 Protocol Amendment 2 (Version 2 dated 13 FEB 2019) 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.

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(Printed Name of Investigator)

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(Signature of Investigator)

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(Date)

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## LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AA	alopecia areata
AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BID	twice daily
BSA	body surface area
BSA assessment – Palmar method	1% BSA for each participant is approximately equal to the surface of their palm plus 5 digits; handprint may be used interchangeably
CFR	Code of Federal Regulations
C <sub>max</sub>	Maximal plasma concentration
CDLQI	Children Dermatology Life Quality Index
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EASI50	≥50% improvement in EASI score
EASI75	≥75% improvement in EASI score
EASI90	≥90% improvement in EASI score
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
EQ-5D-5L	EQ-5D is a validated, self-administered, generic, utility questionnaire wherein participants will rate their current health state based on the following criteria: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.
ET	early termination
FDA	Food and Drug Administration
flare	an episode of worsening of atopic dermatitis, such that it requires re-initiation or escalation of treatment (IGA of at least 2)
GCP	Good Clinical Practice
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HIPAA	Health Insurance Portability and Accountability Act of 1996

<b>Abbreviations and Special Terms</b>	<b>Definition</b>
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee
IGA	Investigator's Global Assessment
IGA-TS	Investigator's Global Assessment Treatment Success (IGA score of 0 or 1 with $\geq 2$ grade improvement from baseline)
IL	interleukin
IRB	institutional review board
IRT	interactive response technology
Itch NRS	Itch Numerical Rating Scale
ITT	intent-to-treat
JAK	Janus kinase
LDL	low-density lipoprotein
LL	lower limbs
LPLV	last participant last visit
LTS	long-term safety
MedDRA	Medical Dictionary for Regulatory Activities
ni.	non-inferiority
NOAEL	no-observed-adverse-effect level
PASI	Psoriasis Area Severity Index
PD	pharmacodynamic
PDE	phosphodiesterase
PGA	Physician's Global Assessment
PGIC	Patient Global Impression of Change
PK	pharmacokinetic
POEM	Patient-Oriented Eczema Measure
PP	per Protocol
PROMIS <sup>®</sup>	Patient-Reported Outcomes Measurement Information System
QD	once daily
RNA	ribonucleic acid
SAE	serious adverse event
SCORAD	SCORing Atopic Dermatitis – tool used to assess extent and severity (intensity) of eczema
Skin Pain NRS	Skin Pain Numerical Rating Scale

<b>Abbreviations and Special Terms</b>	<b>Definition</b>
SoA	schedule of activities
SPF	sun protection factor
██████	████████████████████
TARC	thymus and activation-regulated chemokine
TC	triamcinolone
TEAE	treatment-emergent adverse event, AEs reported for the first time or worsening of a pre-existing event after first dose of study treatment
██████	████████████████████
TSH	thyroid-stimulating hormone
TSLP	thymic stromal lymphopoietin
ULN	upper limit of normal
VC	vehicle-control
VHP	Voluntary Harmonisation Procedure
WPAI:SHP v2.0	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem Version 2.0

## 1. PROTOCOL SUMMARY

**Protocol Title:** Topical Ruxolitinib Evaluation in Atopic Dermatitis Study 2 (TRuE-AD2)

A Phase 3, Double-Blind, Randomized, 8-Week, Vehicle-Controlled Efficacy and Safety Study of Ruxolitinib Cream Followed by a Long-Term Safety Extension Period in Adolescents and Adults With Atopic Dermatitis

**Protocol Number:** INCB 18424-304

**Objectives and Endpoints:** Table 1 presents the primary and key secondary endpoints and objectives.

**Table 1: Primary and Key Secondary Objectives and Endpoints**

Objectives	Endpoints
<b>Primary</b>	
To establish the efficacy of ruxolitinib cream in participants with AD.	<ul style="list-style-type: none"><li>• Proportion of participants achieving IGA-TS at Week 8</li></ul>
<b>Key Secondary</b>	
To further assess efficacy of ruxolitinib cream.	<ul style="list-style-type: none"><li>• Proportion of participants who achieve EASI75 at Week 8.</li><li>• Proportion of participants with a <math>\geq 4</math>-point improvement in Itch NRS score from baseline to Week 8.</li><li>• Proportion of participants with a clinically meaningful improvement in the PROMIS Short Form – Sleep Disturbance (8b) 24-hour recall score at Week 8.</li></ul>

### Overall Design

Table 2 presents the key study design elements. Further study details are presented after the table. Table 3 provides the SoA for VC period, and Table 4 provides the SoA for the LTS period.

Adherence to the study design requirements, including those specified in the SoAs, is essential and required for study conduct.

**Table 2: Key Study Design Elements**

<b>Study Phase</b>	Phase 3
<b>Clinical Indication</b>	Atopic Dermatitis
<b>Population</b>	Adolescents aged $\geq 12$ to 17 years, inclusive, and men and women aged $\geq 18$ years who have been diagnosed with AD of at least 2 years duration, an IGA score of 2 to 3, and %BSA involvement (excluding scalp) of 3% to 20%.
<b>Number of Participants</b>	Approximately 600 participants
<b>Study Design</b>	Randomized (2:2:1), double-blind, 8-week VC period followed by a randomized, double-blind, 44-week LTS extension period. In the LTS period, participants initially randomized to vehicle will receive either ruxolitinib 0.75% or 1.5% cream.
<b>Estimated Duration of Study Participation</b>	Screening: up to 28 days Vehicle-controlled period: 8 weeks Double-blind, randomized LTS period: 44 weeks Follow-up: 30 (+ 7) days after last application of study drug or last visit Total: up to 60 weeks
<b>DSMB/DMC</b>	No

**Treatment Groups and Duration:**

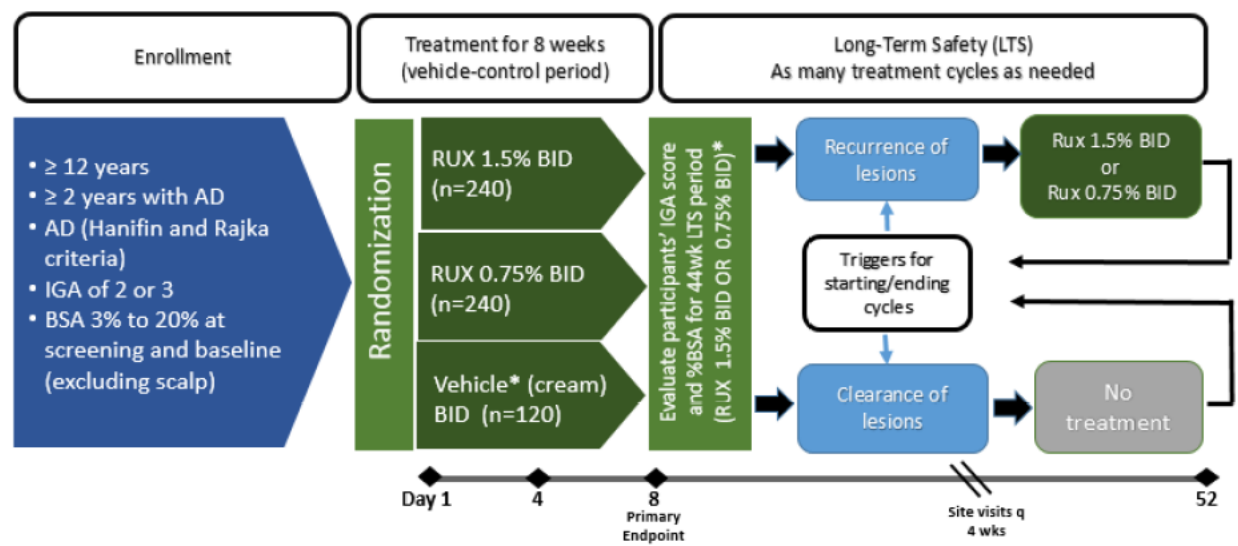
Adolescents aged  $\geq 12$  to 17 years, inclusive, and men and women aged  $\geq 18$  years who meet the inclusion criteria and have been diagnosed with AD of at least 2 years duration, an IGA score of 2 to 3, and %BSA involvement of 3% to 20% (excluding scalp) will be enrolled and receive treatment with ruxolitinib 0.75% cream BID, ruxolitinib 1.5% cream BID, or vehicle cream in a 2:2:1 randomization for a total duration of 8 weeks (with a screening period of approximately 28 days) during the VC period of the study. Adolescents will make up approximately 20% of the overall study population.

At Week 8, all participants who successfully complete the VC period of the study and all Week 8 assessments will be offered participation in the LTS treatment period with ruxolitinib 0.75% or 1.5% cream BID. The required %BSA range and IGA score entry into the LTS period is 0% to 20% and 0 to 4 grade, respectively. Participants who were initially treated with either ruxolitinib 0.75% or 1.5% cream will remain in their respective treatment regimen, while those participants who were initially treated with vehicle will be randomized to either ruxolitinib 0.75% or 1.5% cream BID. During this LTS period, participants will have study visits every 4 weeks until the end of the study (52 weeks total).

After the Week 8 visit, during the LTS period, participants will self-evaluate recurrence of AD and will treat those areas of the skin with active AD changes (not to exceed up to 20% BSA). If lesions clear between study visits, participants will stop treatment application 3 days after they have disappeared. In the event that the new lesions are significantly more extensive than from the previous visit, the participant should call the study site to discuss with the investigator whether additional evaluation at the clinic is required. The investigator, if needed, will have the option of having the participant return for an unscheduled visit.

The study schema is shown below in [Figure 1](#). All participants will have follow-up assessments 30 (+ 7) days after the last application of study drug.

**Figure 1: Study Design Schema**



\*At week 8 (LTS baseline), participants initially on vehicle will be randomized to either Rux 1.5% or 0.75% cream BID. Additionally, to qualify for the LTS period, the IGA score of 0 to 4 and %BSA of 0% to 20% will be required.

**Table 3: Schedule of Activities: Vehicle-Controlled Period**

Visit Day (Range)	Screening	Vehicle-Controlled Treatment				Notes
	Days -28 to -1	Day 1 (Baseline)	Week 2 (± 3 d)	Week 4 (± 3 d)	Week 8*/EOT (± 3 d)	*All assessments for the Week 8 visit must be performed before participants may enter the LTS period.
<b>Administrative procedures</b>						
Informed consent (including assent)	X					
Contact IRT	X	X	X	X	X	
Inclusion/exclusion criteria review	X	X				
Demography and general and disease medical history	X					
Prior/concomitant medications	X	X	X	X	X	
Apply study drug		X	X	X	X	1st AM application under site supervision.
Weigh/dispense or re-dispense study drug and distribute study drug diary and reminder card		X	X	X	X	Used tubes will be replenished, and unused tubes may be re-dispensed.
Collect/weigh study drug and collect/review study drug diary			X	X	X	
Assess compliance		X	X	X	X	
<b>Safety assessments</b>						
AE assessments and targeted physical examinations	X	X	X	X	X	Body systems with symptoms should be physically examined. Ad hoc photography of skin-related AEs should also occur as applicable.
Comprehensive physical examination	X				X	
Vital signs/body weight/height	X*	X	X	X	X*	*Height and weight at screening and Week 8.
12-lead ECG	X					12-lead ECG performed within 2 months before baseline is acceptable.

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

Visit Day (Range)	Screening	Vehicle-Controlled Treatment				Notes
	Days -28 to -1	Day 1 (Baseline)	Week 2 (± 3 d)	Week 4 (± 3 d)	Week 8*/EOT (± 3 d)	*All assessments for the Week 8 visit must be performed before participants may enter the LTS period.
Efficacy assessments						
Evaluate %BSA affected by active AD	X	X	X	X	X*	*At Week 8, to qualify for LTS period, the %BSA range is 0% to ≤ 20%.
Target lesion	X	X*	X	X	X	*A lesion of ≥ 10 cm <sup>2</sup> needs to be identified at baseline (excluding the hands, feet and genitalia)
Photography (target lesion close-up/ regional body area)		X	X	X	X	Ad hoc photography (at selected sites) of skin-related AEs is recommended.
EASI	X	X	X	X	X	
SCORAD		X	X	X	X	
IGA	X	X	X	X	X*	*At Week 8, to qualify for LTS period, the IGA range is 0 to 4.
Itch NRS	Diary is completed each evening from screening through the last application of study drug in the vehicle-controlled period.					
Skin Pain NRS						
Patient-reported outcome questionnaires – to be evaluated prior to any other study procedures/assessments; see Section 8.2.7						
DLQI/CDLQI		X	X	X	X	
PGIC			X	X	X	
POEM		X	X	X	X	
EQ-5D-5L questionnaire	X	X	X	X	X	
WPAI:SHP questionnaire	X	X	X	X	X	
PROMIS sleep questionnaires (24-hour recall)	Diary is completed daily from screening through the last application of study drug in the vehicle-controlled period.					PROMIS Short Form – Sleep-Related Impairment (8a) collected in the evening before sleeping.  PROMIS Short Form – Sleep Disturbance (8b) collected in the morning after the participant wakes up.
PROMIS sleep questionnaires (7-day recall)					X	PROMIS Short Form – Sleep-Related (8a) and Short Form – Sleep-Disturbance (8b) will be completed at Week 8 (this will be the baseline assessment for the 7-day recall questionnaires, collected during the Week 8 study visit).



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

Visit Day (Range)	Screening	Vehicle-Controlled Treatment				Notes
	Days -28 to -1	Day 1 (Baseline)	Week 2 (± 3 d)	Week 4 (± 3 d)	Week 8*/EOT (± 3 d)	*All assessments for the Week 8 visit must be performed before participants may enter the LTS period.
<b>Laboratory assessments</b>	<i>Blood draw for clinical laboratory tests must be performed before the in-clinic study drug application.</i>					
Serum chemistries	X	X	X	X	X	
Hematology	X	X	X	X	X	
Serology	X*					*HIV antibody.
Pregnancy testing	X*	X	X	X	X	*Female participants of childbearing potential will have a serum test at screening and follow-up and a urine test at all other visits. A positive urine test must be confirmed by a serum test.
FSH level	X					For confirmation of nonchildbearing status of women who are postmenopausal defined as amenorrhea at least 12 months before screening.
Urinalysis	X					
PK plasma sampling (trough)			X	X	X	Time of last study drug application to be written in eCRF. Blood samples must not be drawn from the area that has been treated with study drug.

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

Visit Day (Range)	LTS Extension Treatment						Follow-Up	Notes
	Week 12 (±7 d)	Weeks 16, 20, and 24 (±7 d)	Weeks 28, 32, and 36 (±7 d)	Weeks 40, 44, and 48 (±7 d)	Week 52 ET/EOT (±7 d)	Unscheduled Visits	30 (+7) days After Last Dose of Study Drug	
Administrative procedures								
Contact IRT	X	X	X	X	X	X	X	
Prior/concomitant medications	X	X	X	X	X	X	X	
Apply study drug	X	X	X	X	X			1st AM application under site supervision.
Weigh/dispense or re-dispense study drug and distribute study drug diary and reminder card	X	X	X	X		X		Used tubes will be replenished and unused tubes may be re-dispensed
Collect/weigh study drug and collect/review study drug diary	X	X	X	X	X	X		
Capture start and end date of a treatment cycle	X	X	X	X	X	X	X	The start/end-date will be captured by the participant. The end date of a treatment cycle will be +3 days after lesions clear. Refer to Study Manual.
Safety assessments								
AE assessments and targeted physical examinations	X	X	X	X	X	X	X	Body systems with symptoms should be physically examined. Ad hoc photography of skin-related AEs should also occur as applicable.
Comprehensive physical examination					X			
Vital signs/body weight/height	X	X*	X	X	X*	X	X	*Height and weight at Weeks 24 and 52/EOT.
Efficacy assessments								
Evaluate %BSA affected by active AD	X	X	X	X	X	X	X	Participants may only treat up to 20% BSA.
IGA	X	X	X	X	X	X	X	

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

Visit Day (Range)	LTS Extension Treatment						Follow-Up	Notes
	Week 12 (±7 d)	Weeks 16, 20, and 24 (±7 d)	Weeks 28, 32, and 36 (±7 d)	Weeks 40, 44, and 48 (±7 d)	Week 52 ET/EOT (±7 d)	Unscheduled Visits	30 (+7) days After Last Dose of Study Drug	
Patient-reported outcome questionnaires – to be evaluated prior to any other study procedures/assessments; see Section 8.2.7								
DLQI/CDLQI	X	X*			X	X	X	*At Week 24 only.
POEM	X	X*			X	X	X	*At Week 24 only.
EQ-5D-5L questionnaire	X	X*	X*		X		X	*At Weeks 24 and 36 only
WPAI:SHP questionnaire	X	X*	X*		X		X	*At Weeks 24 and 36 only.
PROMIS sleep questionnaires (7-day recall)	X	X*			X			*At Week 24 only. PROMIS Short Form – Sleep-Related Impairment (8a). PROMIS Short Form – Sleep Disturbance (8b). Note: Recall period changed from past 24 hours to past 7 days during LTS period.
Laboratory assessments	Blood draw for clinical laboratory tests must be performed before the in-clinic study drug application.							
Serum chemistries	X	X	X	X	X	X	X	
Hematology	X	X	X	X	X	X	X	
Pregnancy testing	X	X	X	X	X	X	X*	*Female participants of childbearing potential will have a serum test at screening and follow-up and a urine test at all other visits. A positive urine test must be confirmed by a serum test.
PK plasma sampling (trough)	X	X	X	X	X	X	X	Time of last study drug application to be written in eCRF.  Blood samples must not be drawn from the area that has been treated with study drug.

[REDACTED]

[REDACTED]

## **2. INTRODUCTION**

Ruxolitinib cream is a topical formulation of ruxolitinib phosphate under development for the treatment of participants with AD, AA, vitiligo, and plaque psoriasis. Ruxolitinib phosphate is an inhibitor of the JAK family of protein tyrosine kinases. Isogenic and inflammatory cytokines are strongly implicated in the pathogenesis of psoriasis, AA, and AD. Because JAKs serve to translate extracellular signals from a number of relevant cytokines and growth factors upregulated in inflammatory diseases such as psoriasis, AA, and AD, JAK inhibitors represent potential therapeutic agents for these disease states.

### **2.1. Background**

#### **2.1.1. Atopic Dermatitis**

Atopic dermatitis is a chronic, recurring, inflammatory, and itchy skin condition that affects worldwide up to 25% of children and up to 12% of adults ([Eichenfield et al 2014](#), [Hanifin et al 2007](#), [Harrop et al 2007](#), [Rönmark et al 2012](#), [Vinding et al 2014](#)). Its incidence in the industrialized countries appears to be increasing, and it is associated with substantial cost (\$3.8 billion per year in direct medical costs alone; [Ellis et al 2002](#)). Although AD is 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](#)). This disease evolution leading to the possible development of other atopic conditions, including food allergy, asthma, and allergic rhinitis, is often termed as "atopic march."

According to the recent Global Burden of Disease project, worldwide AD is one of the 50 most prevalent diseases, and it has the second highest disability ranking of all nonmalignant skin diseases ([Hay et al 2014](#)).

#### **2.1.2. Diagnosis of Atopic Dermatitis**

One of the earliest and most recognized sets of diagnostic criteria is the Hanifin and Rajka criteria, which requires that 3 of 4 criteria and 3 of 23 minor criteria be met ([Purvis 2014](#)).

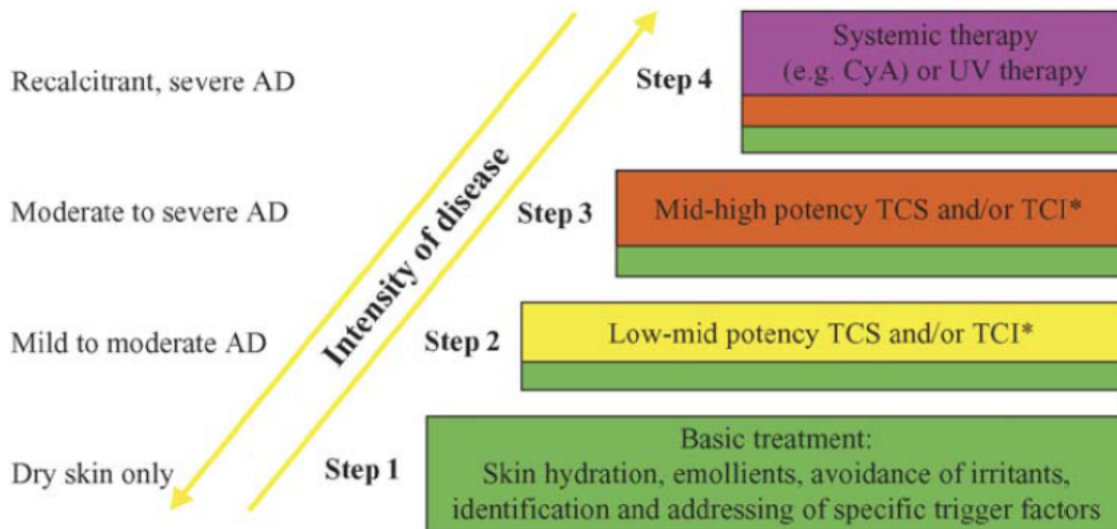
Essential features that are present in this disease are pruritus, eczema (acute, subacute, chronic), chronic or relapsing history, and typical morphology and age-specific patterns, including the following: 1) facial, neck, and extensor involvement in infants and children; 2) current or previous flexural lesions in any age group; 3) sparing of the groin and axillary regions.

The clinical pattern of AD varies with age. Infants usually show acute erythematous and often develop exudative papules on the face or scalp. The childhood (age 2 years to puberty) and adult phases 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) that 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.

### 2.1.3. Current Treatment and Unmet Needs for Atopic Dermatitis

The management of AD reflects this disease's multifactorial pathology and can be illustrated by the step-wise approach in Figure 2.

**Figure 2: Stepwise Approach to the Management of Atopic Dermatitis**



TCS = Topical corticosteroids, TCI = Topical calcineurin inhibitors, CyA = Cyclosporine A

\* Over the age of 2 years

Note: Systemic therapies also include new biologic agents (eg, Dupixent®).

Source: Akdis et al 2006.

There are limited options and a significant medical need for topical therapies for AD that are both effective and safe. Moderate to potent topical corticosteroids and calcineurin inhibitors have well-known safety restrictions limiting their use to 4 and 8 weeks, respectively. Crisaborole (Eucrisa® 2016) ointment, which was recently approved in the United States, has no such safety limitations but also has a relatively low efficacy. Janus kinases are intracellular signaling enzymes that act downstream of key proinflammatory cytokines known to promote AD pathogenesis.

Ruxolitinib is a potent, selective inhibitor of JAK1 and JAK2, and its topical formulation may offer a novel therapeutic approach in AD with dual anti-inflammatory and antipruritic properties.

Consequently, efforts have been made to find new treatment possibilities that would more appropriately address the medical needs of AD patients. Despite the advances in biologic treatments for psoriasis, only 1 targeted therapy exists for AD (Thaçi et al 2016). For patients with more severe AD, the most recent addition in the systemic drug armamentarium is dupilumab (Dupixent® 2017). 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 (Dupixent 2017) in both the United States and Europe.

There are also additional systemic drugs being developed for more severe AD, including biologic agents against IL-31 and IL-13. Recent studies with oral JAK inhibitors indicated that these drugs may be effective in the treatment of AD ([Levy et al 2015](#)) 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](#)).

#### **2.1.4. Role of Janus Kinases in Atopic Dermatitis**

Ruxolitinib is a small molecule inhibitor of the JAKs, which play an important role in signal transduction following cytokine and growth factor binding to their receptors. Excessive production of cytokines and growth factors has been associated with a number of chronic inflammatory conditions, including psoriasis, AA, AD, vitiligo, and other potential autoimmune diseases of the skin. [REDACTED]

Th2 cytokines (interleukins IL-4, IL-5, and IL-13) and epithelial cytokines TSLP play a central role in the pathogenesis of AD by activating inflammatory pathways in multiple cell types, impairing epidermal barrier structure and function, and inducing allergen sensitization ([Moreno et al 2016](#)).

A number of drugs currently being developed for AD are designed to block these cytokines and are highly promising new biologic agents; in addition to the recently approved dupilumab, lebrikizumab and tezepelumab are both being clinically tested ([Beck et al 2014](#)). However, these new drugs cannot be used topically and will likely be limited in use in patients with more severe AD. The type 2 cytokines IL-4 and IL-13 signal through JAK1. Taken together, simultaneous disruption of multiple type 2 inflammatory cytokine-associated pathways via JAK inhibition may serve as a novel therapeutic modality of a nonsteroidal, anti-inflammatory agent in AD.

[REDACTED] To date, a topical JAK inhibitor with sufficient skin penetration has not yet been approved in AD. [REDACTED]

## **2.2. Ruxolitinib**

### **2.2.1. Oral Ruxolitinib**

A Phase 1 study of oral ruxolitinib was conducted in 49 children with various malignancies (28 with solid tumors and 21 with hematological neoplasms; ADVL1011). Five dose levels were tested (15, 21, 29, 39, and 50 mg/m<sup>2</sup> per dose BID) in participants aged 2.4 to 21.4 years. All doses evaluated were tolerated. The safety profile in these pediatric participants was consistent with that seen in adults and did not disclose any abnormalities limited to these age groups only.

A thorough QT study was conducted in 50 healthy participants. There was no indication of a QT/QTc-prolonging effect of ruxolitinib in single doses up to a supratherapeutic dose of 200 mg, indicating that ruxolitinib has no effect on cardiac repolarization.



The AE profile of ruxolitinib was also assessed in 198 healthy participants, participants with various degrees of renal (n = 32) or hepatic (n = 24) impairment, and participants with rheumatoid arthritis (n = 59). Adverse events were, in general, mild and resolved without interventions.

Ruxolitinib is approved for the treatment of patients with intermediate- or high-risk myelofibrosis and for the treatment of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea.

In the randomized period of the 2 pivotal studies in myelofibrosis, COMFORT-I and COMFORT-II, discontinuation because of AEs regardless of causality was observed in 11.3% of participants. The most frequently reported adverse drug reactions were thrombocytopenia and anemia. Hematological adverse reactions (any CTCAE grade) included anemia (82.4%), thrombocytopenia (69.8%), and neutropenia (16.6%). Anemia, thrombocytopenia, and neutropenia are dose-related effects. The 3 most frequent nonhematological adverse reactions were bruising (21.6%), dizziness (15.3%), and headache (14.0%). The 3 most frequent nonhematological laboratory abnormalities were increased ALT (27.2%), increased AST (18.6%), and hypercholesterolemia (16.9%).

Long-term follow-up in participants with myelofibrosis has shown that, as expected, the numbers and proportions of AEs and SAEs has increased; however, no new safety signals have emerged (median duration of exposure for this population is 27.6 months, with 1345.78 patient-years of exposure).

In Study INCB 18424-258, in participants with myelofibrosis with a platelet count between 50 and  $100 \times 10^9/L$ , beginning treatment with 5 mg BID was well-tolerated, avoided levels of thrombocytopenia associated with a high risk of significant bleeding, and provided an opportunity to increase the dose of ruxolitinib in a safe manner.

Overall, the safety profile of ruxolitinib in the polycythemia vera population is generally consistent with that observed in the myelofibrosis population. Ruxolitinib was generally well-tolerated in participants with polycythemia vera, and only a small proportion of participants discontinued ruxolitinib because of AEs (3.6%). Most of the AEs were managed by dose modifications. Hematological toxicities were less frequent and less severe in participants with polycythemia vera as compared with those observed in participants with myelofibrosis. No new safety signals emerged from a study in pancreatic cancer in combination with capecitabine.

Please refer to the ruxolitinib cream [IB](#) for more details.

## **2.2.2. Ruxolitinib Cream**

### **2.2.2.1. Preclinical Drug Disposition Summary**

The relative bioavailability of topical ruxolitinib cream was markedly [REDACTED] lower than after oral administration. The primary clearance pathway is via metabolism CYP3A4 is the predominant CYP isozyme responsible for the metabolism of ruxolitinib. Several metabolites of ruxolitinib retain JAK-related pharmacological activity.

[REDACTED]



#### **2.2.2.2. Preclinical Safety**

In animal studies, ruxolitinib cream was not a contact sensitizer and did not produce significant dermal or ocular irritation, acute phototoxicity, or photoallergic potential. Ruxolitinib cream (up to 1.5%) applied BID for up to 9 months in the Gottingen minipig was not associated with any adverse effects. In a 2-year dermal carcinogenicity study in mice, ruxolitinib was not associated with any macroscopic, neoplastic, or nonneoplastic findings.

The toxicity of ruxolitinib has been evaluated following oral administration to mice, rats, and dogs. Findings in these studies were primarily those associated with the mechanism of action of ruxolitinib, including decreases in red blood cells, reticulocytes, eosinophils, and lymphocytes have been observed along with lymphoid depletion in bone marrow and lymphoid organs. Opportunistic infections considered secondary to immune suppression, were noted in dogs. Systemic exposures in these studies exceeded those anticipated with topical application. Ruxolitinib was not teratogenic when administered to pregnant rats or rabbits; there were no adverse developmental effects at doses below those associated with maternal toxicity. Ruxolitinib was not mutagenic in a bacterial mutagenicity assay (Ames test) or clastogenic in in vitro chromosomal aberration assay (cultured human peripheral blood lymphocytes) or in vivo in a rat bone marrow micronucleus assay.

In a toxicity study of orally administered ruxolitinib in juvenile rats beginning on Days 7, 14, or 21 postpartum, dose-related effects on body weight gain and decrements in various bone measures were observed in all cohorts. Hematology and other microscopic findings were similar to those previously observed in general toxicology studies. Other than the bone findings, there were no other novel toxicities in juvenile animals. In animals administered ruxolitinib beginning on Day 21 postpartum (considered approximately equivalent to a 2 year old human), bone findings occurred at exposures higher than those anticipated with topical application. The clinical relevance of this study in humans is not clear.

Please refer to the ruxolitinib cream [IB](#) for more details.

#### **2.2.2.3. Clinical Safety**

Ruxolitinib is a novel, potent, and selective inhibitor of the JAKs, specifically JAK1 and JAK2 with modest to marked selectivity against TYK2 and JAK3. Ruxolitinib potently ( $IC_{50} < 5$  nM) inhibits JAKs, yet it does not significantly inhibit ( $< 30\%$  inhibition) a broad panel of 26 kinases when tested at 200 nM (approximately 100 times the average  $IC_{50}$  value for JAK enzyme inhibition). Ruxolitinib also potently inhibited the phosphorylation of STAT proteins and the production of proinflammatory factors induced by cytokines such as IL-23 and interferon  $\gamma$ .

Topical application of ruxolitinib demonstrated excellent efficacy in an in vivo model of immune-based skin inflammation, the delayed-type hypersensitivity model in mice, including reduced ear swelling, reduced immune cell infiltrates, and normalization of tissue histology. Furthermore, ruxolitinib was also efficacious in the inflammatory phase of the dorsal delayed-type hypersensitivity model when applied in a clinically relevant cream formulation.

### 2.2.2.3.1. Systemic Bioavailability

The PK analysis was performed in 3 clinical studies in psoriasis: INCB 18424-201, -202, and -203. In summary, the PK of ruxolitinib following topical administration in participants with psoriasis was characterized by low systemic bioavailability in the range of [REDACTED] and consequently plasma concentrations that represent only a fraction of that observed following oral administration. Preliminary PK information from Part A of INCB 18424-204 in participants with AA reveals generally comparably low levels of systemic bioavailability when ruxolitinib cream is applied to the scalp.

Pediatric participants are currently being evaluated in a pilot 4-week safety and PK study (INCB 18424-102) and, to date, the efficacy, safety, and PK outcomes have been generally similar to those seen in adult participants (Study INCB 18424-206).

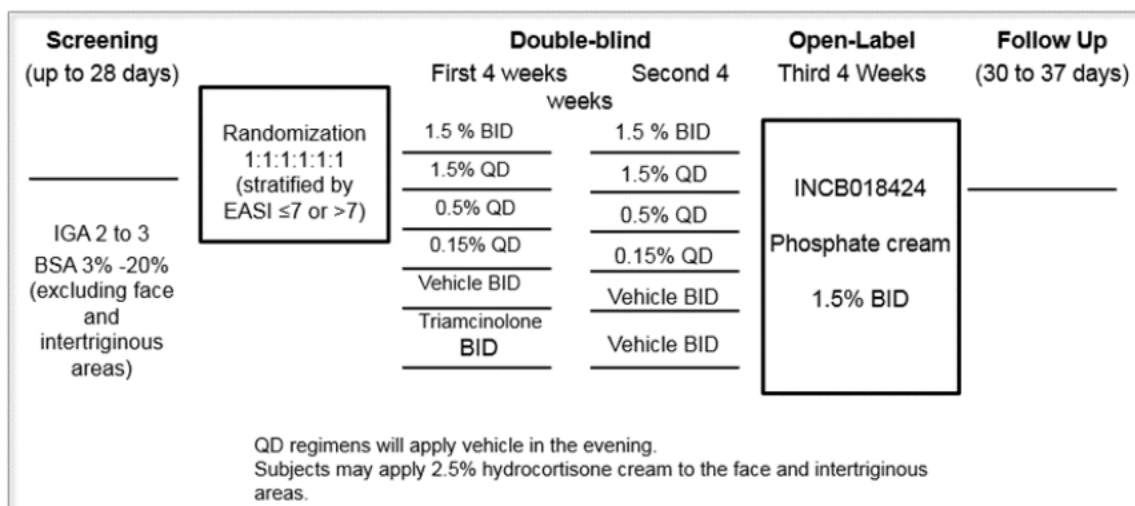
Such similarities, particularly for therapeutic responses, are in line with the anticipation based on the fact that the skin of children  $\geq 2$  years old is fully matured and functional and not materially different from that of adults ([Michel et al 1997](#)). In general, while the disease presentation may show some age-related differences in terms of distribution and chronicity of skin lesions, these tend to be minor in nature and do not warrant a different therapeutic approach, particularly for pediatric patients above 2 years of age ([Akdis et al 2006](#), [Eichenfield et al 2014](#)).

### 2.2.2.4. Efficacy of Ruxolitinib Cream

#### 2.2.2.4.1. Atopic Dermatitis

INCB 18424-206 (see [Figure 3](#)) was a Phase 2, randomized, vehicle- and active (TC 0.1% cream)-controlled dose-ranging study in participants with AD. The study was double-blinded for vehicle, ruxolitinib doses, and active control. A total of 307 participants were randomized equally to ruxolitinib 1.5% cream BID, 1.5% QD, 0.5% QD, and 0.15% QD; vehicle BID; and active control (TC 0.1% cream BID) and stratified by EASI score ( $\leq 7$  and  $> 7$ ). Participants received blinded study drug for 8 weeks, and those who were randomized to TC applied triamcinolone 0.1% cream BID for 4 weeks and vehicle cream for the following 4 weeks, so as to not exceed the allowable triamcinolone application duration. Participants then were permitted to enter an open-label extension and apply ruxolitinib 1.5% cream BID for an additional 4 weeks.

**Figure 3: INCB 18424-206 Study Schema**



In total, 307 participants were randomized to one of the 6 treatment groups in the double-blind period of the study. Of these, 260 participants completed the 8-week double-blind therapy and 46 discontinued for a variety of reasons, including adverse event (n = 3), lack of efficacy (n = 1), lost to follow-up (n = 13), noncompliance with study drug (n = 5), physician decision (n = 2), pregnancy (n = 1), protocol deviation (n = 1), and withdrawal by subject (n = 20).

The primary endpoint was mean percentage change from baseline in the EASI score at Week 4.

- Mean percentage change from baseline EASI score at dose 1.5% BID showed 71.6% improvement at Week 4 (primary endpoint), as compared with 15.5% vehicle ( $p < 0.0001$ ), and 78.5% improvement at Week 8, as compared with 26.9% vehicle ( $p < 0.0001$ ).

EASI50/75/90 and IGA response results showed all strengths to be efficacious and statistically superior to vehicle. In addition, efficacy was time- and regimen-related, with 1.5% QD and 1.5% BID numerically greater than the other treatment groups including TC.

All cream strengths continued to demonstrate improvement through Week 8 (*Note:* TC was only for 4 weeks).

- 1.5% ruxolitinib cream BID was shown to be noninferior to TC on mean EASI (Week 4).
- 1.5% ruxolitinib cream BID was more efficacious than TC by IGA response at Week 4: 38% versus 25.5% ( $p < 0.001$ ), respectively.
- 1.5% ruxolitinib cream BID was numerically better than TC on itch (worst level of itch recorded at all timepoints). A clinically meaningful and strength-related reduction in itch severity ( $\geq 2$  grade reduction) was observed within 2 days of treatment initiation with 1.5 % ruxolitinib cream BID and exceeded that of the active comparator (TC). Clinically meaningful improvements with 1.5% cream were observed within 24 hours and were more pronounced than with TC.

[REDACTED]

In summary, application of ruxolitinib cream 1.5% cream BID for 8 weeks significantly ( $p = 0.0095$ ) reduced TARC levels in circulation as compared with vehicle-treated participants. The former was the only treatment group demonstrating a statistically significant difference.

[REDACTED]

Additional details regarding this study can be found in the ruxolitinib cream [IB](#).

#### **2.2.2.4.2. Psoriasis**

The 3 clinical studies in participants with plaque psoriasis, ruxolitinib cream (0.5%, 1.0%, or 1.5%) was evaluated in over 200 participants with application of 4 to 12 weeks duration. Observed AEs were mild to moderate in intensity and most judged unrelated to study medication, with no associated SAEs or withdrawals. Overall, ruxolitinib cream was demonstrated to be safe and well-tolerated when applied QD or BID for 28 days to plaque psoriasis affecting 2% to 20% of the BSA.

Additional details regarding this study can be found in the ruxolitinib cream [IB](#).

#### **2.2.2.4.3. Alopecia Areata and Vitiligo**

Study INCB 18424-204 is a study in AA where ruxolitinib 1.5% cream BID was also well-tolerated, with the majority of participants treated for 48 weeks. The study was conducted in 2015 through 2017 but terminated early in OCT 2017 owing to lack of efficacy in the primary Week 24 analysis after all participants completed the Week 48 visit or discontinued.

Study INCB 18424-211 is an ongoing, 3-part, randomized, double-blind and vehicle-controlled study in vitiligo. Enrollment into the study was completed by 21 MAR 2018 with 157 participants randomized to treatment groups. As of 15 JUN 2018, few and only minor application site reactions have been observed across treatment groups (study data is blinded). Moreover, most of them related to all treated body locations of vitiligo and did not indicate that the tolerability of the study drug was any different on the face versus on other body areas.

Additional details may be found in the ruxolitinib cream [IB](#).



## 2.3. Study Rationale

Atopic dermatitis is a chronic, relapsing, inflammatory, and itchy skin condition that affect up to 15% to 20% of children and 5% to 10% of adults. The clinical pattern of AD varies with age. Infants usually show acute erythematous and often develop exudative papules on the face or scalp. The childhood (2 years of age to puberty) and adult phases 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) that 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.

Since the early 2000s, only 2 new classes of nonsteroidal topical therapies, topical calcineurin inhibitors (with a boxed warning for serious infections and potential for skin carcinogenicity) and PDE4 inhibitors, have been introduced and provide a safe treatment alternative ([Papier and Strowd 2018](#)). In addition to these 2 therapies, a PDE4 inhibitor ointment was approved at the end of 2016 in the United States for patients with AD 2 years and older (crisaborole ointment; Eucrisa). While not associated with any notable safety concerns when used on larger %BSA, it showed relatively limited efficacy over its vehicle (approximately 10%; [Eucrisa 2016](#)).

These therapies are limited options; therefore, there is still a significant medical need for topical treatments for AD that are both effective and safe, particularly in children. Janus kinases are intracellular signaling enzymes that act downstream of key proinflammatory cytokines known to promote AD pathogenesis. Recent studies suggest that JAK inhibition may have antipruritic effects by acting directly on sensory nerve fibers ([Oetjen et al 2017](#)). Ruxolitinib cream is a potent, selective inhibitor of JAK1 and JAK2 and may offer a novel therapeutic approach with dual anti-inflammatory and antipruritic properties. Ruxolitinib cream is being developed for topical application for AD, a route of administration that should achieve high local concentrations of ruxolitinib in the skin while limiting systemic exposure.

### 2.3.1. Scientific Rationale for Study Design

This is a confirmatory study in a larger participant population with AD with the objective to further evaluate and confirm the prior findings with regard to the efficacy and safety of the proposed treatment regimens. The population to be studied comprises participants amenable to topical therapy of their AD,  $\geq 12$  years of age with AD lesions covering between 3% to 20% of the total BSA, and IGA of 2 to 3.

Ruxolitinib 1.5% cream BID up to 20% BSA has been well-tolerated in participants with psoriasis, AA, AD and vitiligo clinical studies with few AEs reported and no evidence of systemic effects.

In the dose-range finding study in AD, 1.5% ruxolitinib cream BID for 8 weeks was found to be the most efficacious among investigated study arms with acceptable safety and tolerability profile (see Section 2.2.2.4.1 for more details). The maximum clinical effect with this treatment regimen was achieved by Week 8 and did not change significantly thereafter.

[REDACTED]

The randomized LTS period of the study will provide additional safety information when drug is used intermittently for a longer period (up to 44 weeks in total). It will also provide data about the duration of treatment effect after stopping therapy and the nature and number of disease exacerbation (flare) episodes.

### **2.3.2. Justification for Selected Treatment Regimen**

The dose-range finding study, INCB 18424-206, investigated 6 treatment groups (ruxolitinib 0.15% cream QD, 0.5% QD, 1.5% QD, and 1.5% BID; TC 0.1% BID for 4 weeks then vehicle BID for 4 weeks; and vehicle BID) over 8 weeks in a double-blind fashion followed by an open-label treatment with ruxolitinib 1.5% cream BID for another 4 weeks. All ruxolitinib cream treatment groups were found to be effective and statistically superior against the vehicle with a robust dose response (in mean EASI change and IGA response over baseline). By Week 8, 1.5% BID showed the highest and clearly demarcated efficacy versus other strengths with levelling of response thereafter and a prompt and most pronounced decrease on itch versus other ruxolitinib cream treatment groups. Moreover, it demonstrated non-inferiority and numerically better efficacy compared with a topical mid-potent corticosteroid (TC 0.1% cream) at Week 4.

Application of ruxolitinib 0.15% cream QD, 0.5% QD, 1.5% QD, and 1.5% BID resulted in mean total trough plasma concentrations of [REDACTED] respectively, after 4 weeks of treatment. These mean values are at least [REDACTED] the approximate IC<sub>50</sub> for JAK1/2 inhibition in whole blood assays of [REDACTED] with about 6% of participants receiving 1.5% QD or BID exceeding [REDACTED] (half the approximate IC<sub>50</sub>). Trough plasma concentrations increased as dose strength and frequency of dosing were increased.

All ruxolitinib cream treatment arms were well-tolerated on application sites and were found to have no notable AEs, and vital signs or physical examinations were unremarkable throughout the study. In the laboratory assessments, no changes in chemistry or leukocytes, neutrophils or lymphocytes were observed. Minor changes in hemoglobin [REDACTED] and platelets [REDACTED] were observed primarily in the ruxolitinib 1.5% cream BID regimen during the double-blind period, which continued in the open-label extension. These changes were mostly within the limits of normal, transient (platelets), and asymptomatic and were not clinically meaningful.

The proposed treatment regimens of ruxolitinib cream for this study are 0.75% BID and 1.5% BID. All study active treatments demonstrated clear and well-demarcated dose responses. Although ruxolitinib 0.75% cream BID was not tested, the distinctive dose responses seen allowed the projection of its efficacy level to be between 1.5% BID and 0.5% QD. [REDACTED]

[REDACTED]

## 2.4. Benefit/Risk Assessment

Ruxolitinib presents a low risk of cutaneous toxicity both in animals and clinical studies. Ruxolitinib cream tested positive in a photoclastogenicity assay; hence, there may be a risk of skin reaction to the combined exposure of ruxolitinib and sunlight. Ruxolitinib cream did not act as a contact sensitizer nor did it produce significant dermal irritation or demonstrate phototoxicity or photoallergenic potential. This lack of adverse cutaneous effects has been supported by clinical studies to date, where cutaneous AEs have been infrequent and of similar frequency and severity as with vehicle control treatment. Participants should be cautioned to avoid excessive exposure to either natural or artificial sunlight (including tanning booths, sun lamps, etc).

The primary clinical risks noted with orally administered ruxolitinib treatment for polycythemia vera or myelofibrosis are the potential sequelae of decreased hematopoietic proliferation secondary to the inhibition of growth factor pathways by JAK2 antagonism. Dose-dependent, reversible thrombocytopenia has been observed in participants with myelofibrosis, as well as anemia and less frequently neutropenia. An increased rate of infection is an additional potential risk of immunomodulation. In healthy participants and rheumatoid arthritis participants with greater bone marrow reserve, the effects on hematopoietic proliferation appear to be less pronounced. Ruxolitinib cream has 3% to 5% of the relative systemic availability of oral treatment, which was studied in participants with psoriasis. Owing to its low systemic bioavailability, ruxolitinib cream is not expected to bring about clinically significant changes in hematology laboratory investigations.

The results of the INCB 18424-206 dose range-finding study in adults with AD are provided and discussed in more detail in Section 2.2.2.4.1. The efficacy outcomes for all treatment groups can be summarized as follows:

- IGA response and EASI50/75/90 response rates showed all ruxolitinib cream treatment regimens to be efficacious and statistically superior to its vehicle.
- Efficacy was time- and regimen-related, with 1.5% cream QD and 1.5% cream BID numerically greater than the other treatment groups, including the active control (TC 0.1% cream BID).
- All ruxolitinib cream strengths continued to demonstrate improvement through Week 8.
- Prompt effect on itch was observed with all active treatment groups within 24 hours after study baseline.
- The therapeutic response to 1.5% ruxolitinib cream BID plateaued after Week 8 (in IGA response and mean EASI change; note: this was the only treatment applied continuously for 12 weeks).

All active treatment groups were found to have no notable AEs and were well-tolerated on application sites. They were also unremarkable for laboratory values, vital signs, or physical examinations.

While minor changes in select hematology parameters (red blood cells and platelet counts) were noted in the laboratory assessments (primarily on 1.5% cream BID regimen), they were mostly within the limits of normal range of values, transient (platelets), asymptomatic, and clinically insignificant and did not necessitate any remedial action.

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

More detailed information can be found in the ruxolitinib cream [IB](#).



### 3. OBJECTIVES AND ENDPOINTS

Table 5 presents the objectives and endpoints.

**Table 5: Objectives and Endpoints**

Objectives	Endpoints
<b>Primary</b>	
To establish the efficacy of ruxolitinib cream in participants with AD.	<ul style="list-style-type: none"> <li>Proportion of participants achieving IGA-TS at Week 8.</li> </ul>
<b>Key Secondary</b>	
To further assess the treatment effects of ruxolitinib cream.	<ul style="list-style-type: none"> <li>Proportion of participants who achieve EASI75 at Week 8.</li> <li>Proportion of participants with a <math>\geq 4</math>-point improvement in Itch NRS score from baseline to Week 8.</li> <li>Proportion of participants with a clinically meaningful improvement in the PROMIS Short Form – Sleep Disturbance (8b – 24-hour recall) score at Week 8.</li> </ul>
<b>Secondary</b>	
To evaluate the safety and tolerability of ruxolitinib cream.	The frequency, duration, and severity of AEs; performing physical examinations; collecting vital signs; and collecting laboratory data for hematology, serum chemistry, and urinalysis.
To further evaluate efficacy of ruxolitinib cream.	<ul style="list-style-type: none"> <li>Proportion of participants achieving an IGA-TS at Weeks 2 and 4.</li> <li>Proportion of participants achieving an IGA of 0 or 1 at each visit.</li> <li>Proportion of participants with a <math>\geq 4</math>-point improvement in Itch NRS score from baseline to Weeks 2 and 4.</li> <li>Proportion of participants who achieve EASI50 at each visit during the VC period.</li> <li>Proportion of participants who achieve EASI75 at Weeks 2 and 4.</li> <li>Proportion of participants who achieve EASI90 at each visit during the VC period.</li> <li>Mean percentage change from baseline in EASI score at each visit during the VC period.</li> <li>Mean percentage change from baseline in SCORAD score at each visit during the VC period.</li> <li>Change from baseline in Itch NRS score at each visit during the VC period.</li> <li>Time to achieve Itch NRS score improvement of at least 2, 3, or 4 points.</li> <li>Change from baseline in Skin Pain NRS score at each visit during the VC period.</li> <li>Proportion of participants with a clinically meaningful improvement in the PROMIS Short Form – Sleep-Related Impairment (8a) 24-hour recall score at Weeks 2, 4, and 8.</li> <li>Change from baseline in PROMIS Short Form – Sleep-Related Impairment (8a) 24-hour recall and Short Form – Sleep Disturbance (8b) 24-hour recall score at Weeks 2, 4, and 8.</li> <li>PROMIS Short Form – Sleep-Related Impairment (8a) 7-day recall and Short Form – Sleep Disturbance (8b) 7-day recall score at Weeks 8, 12, 24, and 52.</li> <li>Change from baseline in AD afflicted %BSA at every visit.</li> </ul>

**Table 5: Objectives and Endpoints (Continued)**

Objectives	Endpoints
To evaluate the participants' Quality of Life and other patient-reported outcomes.	<ul style="list-style-type: none"> <li>• Change from baseline in POEM score at each visit.</li> <li>• Change from baseline in DLQI score at Weeks 2, 4, 8, 12, 24, and 52 and at unscheduled visits.</li> <li>• Mean PGIC score at Weeks 2, 4, and 8.</li> <li>• Proportion of participants with each score on the PGIC at Weeks 2, 4, and 8.</li> <li>• Proportion of participants with a score of either 1 or 2 on the PGIC at Weeks 2, 4, and 8.</li> <li>• Change from baseline in EQ-5D-5L score during the VC period.</li> <li>• Change from baseline in WPAI-SHP v2.0 at Weeks 2, 4, 8, 12, 24, 36, and 52.</li> </ul>
To evaluate the pharmacokinetics of ruxolitinib cream in plasma.	Trough plasma concentrations of ruxolitinib at all study visits.

## **4. STUDY DESIGN**

### **4.1. Overall Design**

This is a randomized, VC study in adolescent and adult ( $\geq 12$  years old) participants with AD eligible for topical therapy. Approximately 600 participants will be randomized 2:2:1 to ruxolitinib 0.75% cream BID, ruxolitinib 1.5% cream BID, or vehicle cream. In addition, approximately 20% of the overall study population will consist of adolescents. Participants with baseline IGA score of 2 will constitute up to approximately 25% of the overall study population. Participants with AD involvement of 3% to 20% BSA and IGA score of 2 to 3 will receive blinded study treatment for 8 weeks.

For participants who have met all study inclusion criteria and none of the exclusion criteria, study drug assignment will be obtained. Key entry criteria for participants to be eligible for the 8-week VC treatment period is a diagnosis of AD (as defined by the Hanifin and Rajka criteria) with a duration of disease for at least 2 years, IGA score of 2 to 3, and a %BSA involvement of 3% to 20% (excluding scalp) at screening and baseline.

Participants who develop additional 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 drug. Approval to treat additional areas may occur via telephone during the VC period, although the investigator, at his/her discretion, may ask the participant to return for an unscheduled visit. Through Week 8, participants should continue to treat areas identified for treatment at baseline even if the areas begin to improve.

At Week 8, the study's primary endpoint, participants will be assessed for efficacy with a percentage of participants achieving a treatment response in IGA score. Participants will also be assessed for safety and tolerability by monitoring the frequency, duration, and severity of AEs; performing physical examinations; and collecting vital signs and clinical/laboratory assessments at various timepoints during the study.

Participants who complete Week 8 assessments with no additional safety concerns will be offered to continue into the LTS period with the same treatment regimen, except for those initially on vehicle, who will be equally assigned at Week 8 to 1 of the 2 active treatment groups. At that time, the IGA score required for the participants to enter the LTS period is 0 to 4. With regard to %BSA, there is no required lower limit; participants may have BSA in the range of 0% to 20%.

In the LTS period, participants will have study visits every 4 weeks until the end of the study (52 weeks total). At those visits, AD lesions will be evaluated by the investigator to confirm if the participant still requires continuation of therapy ( $IGA \geq 1$ ) or can otherwise (re)enter the observation/no treatment cycle ( $IGA = 0$ ).

During the LTS period (ie, after the Week 8 visit), participants will self-evaluate recurrence of AD and will treat areas of the skin with active AD changes (not to exceed 20% BSA). If lesions clear between study visits, participants will stop treatment applications 3 days after they have disappeared. Participants will restart treatment of their AD at the first sign of recurrence. In the event that new lesions are outside of the usual location and/or are more wide spread than at baseline, the participant is required to contact the site for approval. Approval to treat additional areas may occur via telephone during the LTS period, 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.

## **4.2. Overall Study Duration**

Participants will be on study for a duration of up to 60 weeks (28 days screening, 8 weeks of treatment in the VC period, 44 weeks of treatment in the LTS period, and a 30 (+ 7)-day safety follow-up; 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 discontinued study drug and have completed applicable follow-up assessments.

A participant is considered to have completed the study if he/she has completed all study visits, including the 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 in writing of the study's completion or early termination, 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. Adolescents aged  $\geq 12$  to 17 years, inclusive, and men and women aged  $\geq 18$  years.
2. Participants diagnosed with AD as defined by the Hanifin and Rajka (1980) criteria.
3. AD duration of at least 2 years.
4. Participants with an IGA score:
  - a. VC period: 2 to 3 at screening and baseline
  - b. LTS period: 0 to 4 at Week 8
5. Participants with %BSA (excluding scalp) of AD involvement:
  - a. VC period: 3% to 20% at screening and baseline
  - b. LTS period: 0% to 20% at Week 8
6. Participants who agree to discontinue all agents used to treat AD from screening through the final follow-up visit.
7. Participants who have at least 1 "target lesion" that measures approximately 10 cm<sup>2</sup> or more at screening and baseline. Lesion must be representative of the participant's disease state and not be located on the hands, feet, or genitalia.
8. Willingness to avoid pregnancy or fathering of children based on the criteria below:
  - a. Woman of nonchildbearing potential (surgically sterile with a hysterectomy and/or bilateral oophorectomy OR postmenopausal, defined by last menstrual period  $\geq 12$  months of amenorrhea before screening confirmed by FSH levels at screening) and at least 50 years of age) are exempt from pregnancy testing.
  - b. Woman of childbearing potential who has a negative serum pregnancy test at screening and a negative urine pregnancy test before the first dose on Day 1 and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up (30 [+ 7] days after EOT) (see [Appendix A](#)). Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the participant and their understanding confirmed.
  - c. Adolescents who are prepubescent.

- d. Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) or from sperm donation from screening through 90 days after treatment with ruxolitinib cream. Permitted methods that are at least 99% effective in preventing pregnancy (see [Appendix A](#)) should be communicated to the participant and their understanding confirmed.
9. Ability to comprehend and willingness to sign an ICF or written informed consent of the parent(s) or legal guardian and written assent from the participant when possible.

*Note: Adolescent participants who become legal adults during the study will be asked for their signed consent to continue the study, and in the event of lack thereof, will be discontinued from further participation.*

## 5.2. Exclusion Criteria

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

1. Participants who have an unstable course of AD (spontaneously improving or rapidly deteriorating) as determined by the investigator in the 4 weeks prior to baseline.
2. Participants with concurrent conditions and history of other diseases:
  - a. Immunocompromised (eg, lymphoma, acquired immunodeficiency syndrome, Wiskott-Aldrich syndrome).
  - b. Chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before baseline.
  - c. Active acute bacterial, fungal, or viral skin infection (eg, herpes simplex, herpes zoster, chicken pox) within 1 week before baseline.
  - 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 classical areas of involvement such as the face or the folds.
  - f. Other types of eczema.
3. Any serious illness or medical, physical, or psychiatric condition(s) that, in the investigator's opinion, would interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data. For example:
  - a. Clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study drug administration, New York Heart Association Class III or IV congestive heart failure, and arrhythmia requiring therapy or uncontrolled hypertension (blood pressure > 150/90 mmHg) unless approved by medical monitor/sponsor.
  - b. Participants with a history of malignancy in the 5 years preceding enrollment into this study, except for adequately treated, nonmetastatic malignancies.
  - c. Low hemoglobin (< 10 g/dL).

- d. Severe renal disease on dialysis (serum creatinine > 2 mg/dL).
  - e. Current and/or liver disease history, including known hepatitis B or C, with hepatic or biliary abnormalities.
4. Participants using any of the following treatments within the indicated washout period before baseline:
- a. 5 half-lives or 12 weeks, whichever is longer – biologic agents (eg, dupilumab).
  - b. 4 weeks – systemic corticosteroids or adrenocorticotrophic hormone analogs, cyclosporin, methotrexate, azathioprine, or other systemic immunosuppressive or immunomodulating agents (eg, mycophenolate or tacrolimus).
  - c. 2 weeks – immunizations and sedating antihistamines, unless on long-term stable regimen (nonsedating antihistamines are permitted).
  - d. 1 week – use of other topical treatments for AD (other than bland emollients), such as corticosteroids, calcineurin inhibitors, coal tar (shampoo), antibiotics, antibacterial cleansing body wash/soap. 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.
5. Participants who have previously received JAK inhibitors, systemic or topical.
6. Ultraviolet light therapy or prolonged exposure to natural or artificial sources of UV radiation (eg, sunlight or tanning booth) within 2 weeks prior to baseline and/or intention to have such exposure during the study, which is thought by the investigator to potentially impact the participant's AD.
7. Positive serology test results at screening for HIV antibody.
8. Liver function tests: AST or ALT  $\geq 2 \times$  ULN; alkaline phosphatase and/or bilirubin  $> 1.5 \times$  ULN (isolated bilirubin  $> 1.5 \times$  ULN is acceptable if bilirubin is fractionated and direct bilirubin  $< 35\%$ ).
9. Pregnant or lactating participants, or those considering pregnancy.
10. History of alcoholism or drug addiction within 1 year before screening or current alcohol or drug use that, in the opinion of the investigator, will interfere with the participant's ability to comply with the administration schedule and study assessments.
11. Current treatment or treatment within 30 days or 5 half-lives (whichever is longer) before baseline with another investigational medication or current enrollment in another investigational drug protocol.
12. Participants who, in the opinion of the investigator, are unable or unlikely to comply with the administration schedule and study evaluations.
13. Participants who are committed to a mental health institution by virtue of an order issued either by the judicial or the administrative authorities.
14. Employees of the sponsor or investigator or are otherwise dependents of them.

### **5.3. Lifestyle Considerations**

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

If sunscreen, makeup, or other cosmetics has been applied to the areas to be treated, participants should wash the treatment areas with mild soap and water and pat dry before application of study drug.

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 the planned study drug application.

### **5.4. Screen Failures**

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the 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 be assigned a new screening number.

### **5.5. Replacement of Participants**

Participants will not be replaced during the study.



## **6. STUDY TREATMENT**

### **6.1. Study Treatment Administered**

In this study, ruxolitinib cream or matching vehicle will be applied as a thin film BID, with applications at least 8 hours apart in the morning and in the evening at least 1 hour before bedtime. The strengths for ruxolitinib cream are 0.75% and 1.5% in a cream formulation and the matching vehicle cream formulation that does not contain active drug.

On the first clinic visit day and subsequent study visits, the participant or guardian applies a thin film of study drug by applying small amounts of study drug until all the affected areas to be treated are covered. The amount of study drug used per application will be determined by weighing a tube before and after the participant or guardian applies study drug to the affected areas.

On subsequent study visit days, participants should not apply the study drug at home (morning application). The first application of the day will be done at the clinic.

In general, the amount of study drug used per day (BID application) should not exceed one-fourth (1/4) of the 60 g tube per day. One 60 g tube should be sufficient for approximately 4 days of applications for those participants who have approximately 20% BSA of lesions on their body.

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 drug to be dispensed. All areas identified at baseline should continue to be treated through the end of the VC period (Week 8) unless the participant meets criteria for stopping study drug. If there are new areas to be treated, including expansion of existing areas or development of new areas, after consultation with the investigator, study drug should be applied to these areas in addition to the areas treated at baseline (up to 20% BSA), and the percentage of BSA to be treated will be recalculated and increased. This new estimate will be entered into the IRT system to calculate the number of tubes of study drug to be dispensed.

During the LTS period starting at the Week 8 visit, participants will have study visits every 4 weeks until the end of the study (52 weeks total). At those visits, AD lesions will be evaluated by the investigator to confirm whether the participant still requires continuation of therapy ( $IGA \geq 1$ ) or can otherwise (re)enter the observation/no treatment cycle ( $IGA = 0$ ). At Week 8, a participant will receive a prespecified number of tubes with study medication 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 drug to be dispensed.

In-between study visits, the participant will self-evaluate recurrence of AD and will treat all areas identified with active AD changes (not to exceed 20% BSA). If lesions clear between study visits, participants will stop treatment applications 3 days after they have disappeared. Participants will restart treatment of their AD at the first sign of recurrence. In the event that new lesions are outside of the usual location and/or are more widespread than at baseline, the participant is required to contact the site for approval. Approval to treat additional areas may

occur via telephone during the LTS period, although the investigator, at his/her discretion, may ask the participant to return for an unscheduled visit.

Application instructions will be provided by the site study staff, and the participant will record their daily applications via a diary card given to the participants during each study visit. Refer to the Study Pharmacy Manual for participant instructions for handling study of drug. [Table 6](#) presents the study treatment information.

**Table 6: Study Treatment Information**

	<b>Study Treatment 1</b>	<b>Study Treatment 2</b>	<b>Study Treatment 3</b>
<b>Study treatment name:</b>	Ruxolitinib	Ruxolitinib	Vehicle
<b>Dosage formulation:</b>	Cream	Cream	Cream
<b>Unit dose strength(s)/dosage level(s):</b>	0.75%	1.5%	Not applicable
<b>Administration instructions:</b>	Topical: BID (morning and evening applications). A thin film is applied to the affected areas in the morning and in the evening at least 1 hour before bedtime.	Topical: BID (morning and evening applications). A thin film is applied to the affected areas in the morning and in the evening at least 1 hour before bedtime.	Topical: VC period: BID (morning and evening application). A thin film is applied to the affected areas in the morning and in the evening at least 1 hour before bedtime. LTS period: Not applicable
<b>Packaging and labeling:</b>	Study treatment 1 will be provided in 60 g tube. Each tube will be labeled as required per country requirement.	Study treatment 2 will be provided in 60 g tube. Each tube will be labeled as required per country requirement.	Vehicle will be provided in 60 g tube. Each tube will be labeled as required per country requirement.
<b>Storage:</b>	15°C-30°C (59°F-86°F)	15°C-30°C (59°F-86°F)	15°C-30°C (59°F-86°F)
<b>Status of treatment in participating countries:</b>	Investigational	Investigational	Not applicable

## 6.2. Preparation, Handling, and Accountability

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

Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply study treatment. Immediately after application of ruxolitinib cream, participants are to wash hands thoroughly with soap and warm water. Refer to the Study Pharmacy Manual for participant instructions for handling of study drug.

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

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

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

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

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional standard operating procedures. If local procedures mandate on-site destruction of investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

Further guidance and information for the final disposition of unused study treatments are provided in the 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 (2, 3) and region (North America or other), the participant study number, track participant visits, randomize according to the defined parameters, maintain the blinding, and manage study drug inventory. Full details will be provided in the IRT Manual. Study treatment will be dispensed at the study visits summarized in the SoAs (see [Table 3](#) and [Table 4](#)).

### **6.4. Study Treatment Compliance**

Compliance with all study-related treatments must be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with ruxolitinib cream will be evaluated by participants' adherence to the application regimen and drug accountability documented by the site staff and monitored by the sponsor/designee (tube counts).

In general, the application compliance will be determined by the number of actual versus anticipated number of applications, which should be within 80% to 120% of the prescribed number of applications during the VC period, unless otherwise discussed/approved by the sponsor. Participants will be instructed to bring all study drugs with them to the study visits in order for site personnel to conduct tube counts to assess study drug accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

## **6.5. Modifications to Treatment Regimen**

Through Week 8, participants should continue to treat areas identified for treatment at baseline even if the area begins to improve. Participants who develop new AD lesions during the course of the study 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. Approval to treat additional areas may occur via telephone during the VC period, although the investigator may request to have the participant come in to have an unscheduled visit, if needed.

After Week 8, for participants enrolled in the LTS period, only areas with active disease should be treated. Once the lesions are cleared, participants should continue to apply study drug for an additional 3 days on the areas of the body where lesions were last present before discontinuing the treatment. In the event that the new lesions are significantly more extensive than from the previous visit, the participant should call the study site to discuss with the investigator whether additional evaluation at the clinic is required.

### **6.5.1. Criteria and Procedures for Application Interruptions of Study Drug**

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

In some circumstances, it may be necessary to temporarily interrupt treatment with ruxolitinib cream. 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 drug. Additionally, the investigator must obtain approval from the sponsor before restarting study drug. Participants who experience a recurrence of the initial AEs upon restarting the study drug may need the study drug to be permanently discontinued.

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

**Table 7: Guidelines for Interruption and Restarting of Study Drug**

ADVERSE EVENT <sup>a</sup>	ACTION TAKEN
<b>Chemistry</b>	
ALT ( $> 3 \times \text{ULN}$ ) or AST ( $> 3 \times \text{ULN}$ )	<ul style="list-style-type: none"> <li>Laboratory abnormalities should be confirmed with repeat testing within 48 hours whenever possible and immediate delivery of the laboratory results requested.</li> <li>Study drug applications must be interrupted.</li> <li>At the discretion of the investigator, after consultation with the sponsor, study drug application may be restored once these have resolved.</li> </ul>
<b>Hematology</b>	
Grade 2 decrease in ANC ( $< 1.5 \times 10^9/\text{L}$ )	<ul style="list-style-type: none"> <li>Laboratory abnormalities should be confirmed with repeat testing within 48 hours whenever possible and immediate delivery of the laboratory results requested.</li> <li>Study drug applications must be interrupted. At the discretion of the investigator, after consultation with the sponsor, study drug application may be restored once these have resolved.</li> </ul>
Any other Grade 3 or higher laboratory abnormality (eg, hemoglobin with the exception of asymptomatic elevations in triglyceride, cholesterol, or amylase)	<ul style="list-style-type: none"> <li>Laboratory abnormalities should be confirmed with repeat testing within 48 hours whenever possible and immediate delivery of the laboratory results requested.</li> <li>Study drug applications must be interrupted. At the discretion of the investigator, after consultation with the sponsor, study drug application may be restored once these have resolved.</li> </ul>
Any Grade 4 laboratory abnormality or AST or ALT ( $> 5 \times \text{ULN}$ )	<ul style="list-style-type: none"> <li>Laboratory abnormalities should be confirmed with repeat testing within 48 hours whenever possible and immediate delivery of the laboratory results requested.</li> <li>Discontinue study drug if lab abnormalities are confirmed.</li> </ul>

<sup>a</sup> In the opinion of the investigator related to study drug.

### 6.5.2. Criteria for Permanent Discontinuation of Study Drug 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 drug treatment and will require that the study drug be permanently discontinued. Unacceptable severity is defined as follows:

- Occurrence of an AE that is related to treatment with the study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromised the participant's ability to continue study-specific procedures, or is considered to not be in the participant's best interest.
- Participant presents with a worsening of 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.

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 dose of study treatment and within 30 days after the last dose 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 dose 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 such as Eucerin<sup>®</sup> cream.  
*Note:* Emollients should not be used within the following periods from the application of study drug: 4 hours before and 2 hours after application.
- Bathing during the study should be limited to once daily for no longer than 15 minutes. During baths, tepid (not hot) water and mild cleansing agents (eg, Basis<sup>®</sup> bar or Dove<sup>®</sup>) 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 drug 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:

- Use of any over-the-counter, nonprescription preparations (including vitamins, minerals, and phytotherapeutic, herbal, or plant derived preparations) within 7 days before the baseline visit through the follow-up visit, unless deemed acceptable by the investigator.
- Use of any prescription medication (including immunizations, phytotherapeutic, herbal, or plant-derived preparations) within 7 days before the baseline visit through the follow-up visit, unless deemed acceptable by the investigator.
- 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 drug 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 drug.

### **6.6.3. Prohibited Medications and Procedures**

The following are not permitted during the study:

- Any investigational medication other than the study drug.
- Topical corticosteroids, tacrolimus, pimecrolimus, and PDE4-inhibitors (Eucrisa<sup>®</sup>).
- 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, methotrexate, cyclosporine A, azathioprine and biological therapies, or other immunosuppressant agents.
- Allergen immunotherapy
- Phototherapy or tanning beds.
- Live or live-attenuated vaccination.

### **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 DISCONTINUATION/WITHDRAWAL**

### **7.1. Discontinuation of Study Treatment**

#### **7.1.1. Reasons for Discontinuation**

Participants **must** be discontinued from study treatment for the following reasons:

- Due to lack of efficacy response during the LTS (defined as no change/improvement in either %BSA or IGA when treated continuously for 8 weeks).
- The participant becomes pregnant.
- Consent is withdrawn.  
*Note:* Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case no further data, except data in 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 progression and survival.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Any adverse event 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, at 2 consecutive study visits, a participant's drug usage exceeds one 60 g tube per 4 days. 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 drug/treatment 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, the EOT visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit. The last date of the last dose of study drug(s)/treatment and the reason for discontinuation of study treatment 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 EOT visit should be performed.
- The date of the EOT visit should be recorded in the eCRF.
- Participants must be followed for safety until the time of the follow-up visit or until study drug/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 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**

### **8.1. Administrative and General Procedures**

#### **8.1.1. Informed Consent Form 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 from the participant and/or parent or guardian before any study-related procedures are conducted, unless otherwise specified by the Protocol.
- Note: Adolescent participants who become legal adults during the study will be asked for their signed consent to continue the study, and in the event of lack thereof, will be discontinued from further participation.*
- 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/assent must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF/assent 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 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 may not exceed 28 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

Procedures conducted as part of the participant's routine clinical management by their healthcare provider (eg, blood count) and obtained before signing of informed consent/assent may be used for screening or baseline purposes provided the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study (ie, within 28 days of Day 1). For participants who are enrolled in the study, information associated with eligibility requirements must be entered into the appropriate eCRF pages.

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

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 to update the study drug supply. Additional details are provided in the IRT Manual.

#### **8.1.4. Distribution of Study Reminder Cards and Diaries**

Starting at the Day 1 visit and each visit thereafter, a study drug-specific diary will be given to each participant in order to record use of the study drug. The completed diary will be collected during each of the participant's visits.

Qualified clinical site staff will review the participants' entries for compliance. Participants who are noncompliant with their study drug 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 treatment period of the study.

Participants will be provided with a reminder card starting on Day 1 and at all VC visits. The reminder card will indicate the date/time of the next visit and will also remind the participant that they should have their 1st morning application at the clinic under site supervision after their blood draws for PK and 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 last 2 years that are considered to be clinically significant by the investigator.

##### **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, including systemic treatments, radiation, and surgical procedures, will be recorded. A medical history of other conditions related to AD will also be collected at this time.

## 8.2. Efficacy Assessments

### 8.2.1. Investigator's Global Assessment

The IGA is an overall eczema severity rating on a 0 to 4 scale that will be assessed during site visits. The grades for the IGA are shown in [Table 8](#).

**Table 8: Investigator's Global Assessment**

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

Source: [www.homeforeczema.org](http://www.homeforeczema.org).

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

### 8.2.2. Eczema Area and Severity Index Score

Atopic dermatitis will be assessed as outlined in the SoA (see [Table 3](#)) using EASI scoring system (refer to Study Manual), which is a validated disease measurement for clinical studies ([Hanifin et al 2001](#)) that examines 4 areas of the body and weights them for participants of at least 8 years of age. 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 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; 50.1 to 72.0 = very severe ([Leshem et al 2015](#)).

### 8.2.3. SCORing Atopic Dermatitis

SCORAD is a tool to assess the extent and severity (ie, intensity) of eczema and will be completed before, during, and after treatment has begun to determine whether the treatment has been effective ([Oakley 2009](#)). This will be performed during all VC study visits (see [Table 3](#)), starting at baseline.

- To determine extent, the rule of 9 or handprint method is used to calculate the eczema affected area (A) as a percentage of the whole body. Scores are added up to give a possible maximum of 100%.
- To determine intensity, a representative area of eczema is selected (see below for target lesion). The intensity of each of the following signs of redness, swelling, oozing/crusting, scratch marks, skin thickening (lichenification), dryness (this is assessed in an area where there is no inflammation) is assessed as follows:
  - None (0)
  - Mild (1)
  - Moderate (2)
  - Severe (3)

Intensity scores are added together to give “B” (maximum score of 18).

- Subjective symptoms, that is, itch and sleeplessness, are scored by the participant using a visual analogue scale where “0” is no itch (or no sleeplessness) and “10” is the worst imaginable itch (or sleeplessness).

These scores are added to give “C” (maximum score of 20).

Total score gives approximate weights of 60% to intensity and 20% each to extent and subjective signs (ie, insomnia, etc) for the participant and will be calculated as follows:  $A/5 + 7B/2 + C$ .

### 8.2.4. Target Lesion Assessment

At baseline, a lesion that is representative of the participant's overall disease and is to be treated with study drug will be selected as the target lesion. This lesion will be identified, measured, and documented in the participant's medical record at each subsequent visit during the VC period (see [Table 3](#)). A note should be made in their medical record, and baseline photographs can be marked with the location of the target lesion. The target lesion should not be on the hands, feet, or genitalia. The target lesion should have an area of approximately 10 cm<sup>2</sup> or more in size. The longest diameter and the measurement perpendicular to the longest diameter will be measured in millimeters.



### 8.2.5. Body Surface Area

Total %BSA afflicted by AD will be estimated at each visit in the VC period as outlined in the SoAs (see [Table 3](#) and [Table 4](#)). Body surface area assessment will be approximated to the nearest 0.1% using the Palmar Method as guides, the palm plus 5 digits, with fingers tucked together and thumb tucked to the side (handprint), as 1% BSA and the thumb as 0.1% BSA.

### 8.2.6. Photography

At selected sites, for each visit with photography (baseline and Weeks 2, 4, and 8), photography of the target lesion will be conducted via 2 views (close-up and regional body area). Ad hoc photography of skin-related AEs is recommended at selected sites to provide additional photographic documentation.

### 8.2.7. Patient-Reported Outcomes

Quality of life (QoL) will be assessed (see SoAs [Table 3](#) and [Table 4](#)) using the following tools: DQLI, PGIC, POEM, EQ-5D-5L, WPAI:SHP, Itch NRS, Skin Pain NRS, PROMIS Short Form – Sleep-Related Impairment (8a), and PROMIS Short Form – Sleep Disturbance (8b).

In order to avoid bias in the participants' responses to the questionnaires, all these assessments should be completed before any other evaluations or study procedures on the day of the study visit and prior to discussions with the investigator or study site staff.

At the baseline visit, all patient-reported outcomes must be completed before the participant's first study drug application.

Participants will be issued a paper questionnaire or hand-held device (eDiary) for daily assessments. The participant will be instructed to complete the diary during specific timepoints needed for each assessment beginning on the day of screening through Week 8 or treatment discontinuation. Detailed directions for the administration of an eDiary will be provided in the Study Manual.

Daily assessments will be performed by participants via a diary starting at the screening visit and all visits during the VC period:

- The participant will rate (during the past 24 hours) the following:
  - Itch NRS – the worst level of itch will be recorded in the evening.
  - Skin Pain NRS – the worst level of pain will be recorded in the evening.
  - PROMIS questionnaires:
    - Short Form – Sleep-Related Impairment (8a) will be completed in the evening.
    - Short Form – Sleep-Disturbance (8b) will be assessed in the morning.

*Note:* At Week 8 only (LTS baseline) for both PROMIS Short Form – Sleep-Related Impairment (8a) and Short Form – Sleep-Disturbance (8b), the “past 7-day recall” assessment will also be completed using the tablet during the site visit.

- Assessments to be completed during all VC site visits include the following:
  - EQ-5D-5L – starts at screening
  - WPAI:SHP – starts at screening
  - DLQI/CDLQI – starts at Day 1
  - POEM – starts at Day 1
  - PGIC – starts at Week 2

Assessments to be completed at the site during the LTS period (see SoA [Table 4](#) for timepoints):

- EQ-5D-5L
- WPAI:SHP
- DLQI/CDLQI
- POEM
- PROMIS Short Form – Sleep-Related Impairment (8a) and Short Form – Sleep-Disturbance (8b):
  - As stated above, this assessment will be completed during the LTS site visits (except for unscheduled visits) starting at Week 8.

*Note:* The recall period for Weeks 8, 12, 24, and 52 during the LTS period changes to the “past 7 days” from “the previous 24 hours” in the VC period.

Refer to the Study Manual for detailed instructions.

#### **8.2.7.1. Dermatology Life Quality Index**

The DLQI is a simple, 10-question validated questionnaire to measure how much the skin problem has affected the participant over the previous 7 days as outlined in the SoAs (see [Table 3](#) and [Table 4](#); [Finlay and Khan 1994](#)). The participant, aged  $\geq 16$  years and over, will answer the questionnaire with either (1) very much, (2) a lot, (3) a little, or (4) not at all.

The questionnaire is analyzed under 6 headings as follows:

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



CDLQI is the youth/children's version of the DLQI and will be completed by adolescents aged  $\geq 12$  years to  $< 16$  years. It is self-explanatory and can be simply given to the participant who is asked to fill it in and who may ask the help of the parent or guardian. The questionnaire is analyzed under 6 headings as follows:

- Symptoms and feelings (Questions 1 and 2)
- Leisure (Questions 4, 5, and 6)
- School or holidays (Question 7)
- Personal relationships (Questions 3 and 8)
- Sleep (Question 9)
- Treatment (Question 10)

#### **8.2.7.2. Patient Global Impression of Change**

The PGIC is a participants' self-reporting measure that reflects their belief about the efficacy of treatment. The PGIC is a 7-point scale depicting a participant's rating of overall improvement and will be captured during site visits during the VC period ([Hurst and Bolton 2004](#)).

The participant will answer the following:

"Since the start of the treatment you've received in this study, your atopic dermatitis in areas treated with the study drug is: (1) very much improved, (2) much improved, (3) minimally improved, (4) no change, (5) minimally worse, (6) much worse, and (7) very much worse."

#### **8.2.7.3. Patient-Oriented Eczema Measure**

The POEM is a 7-question quality-of-life assessment that asks how many days the participant has been bothered by various aspects of their skin condition during the past 7 days obtained as outlined in the SoAs (see [Table 3](#) and [Table 4](#); [Charman et al 2004](#)).

#### **8.2.7.4. EQ-5D-5L**

The EQ-5D is a validated, self-administered, generic utility questionnaire wherein participants (adolescents and adults) rate their current health state based on the following criteria (dimensions): mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

The 5L indicates that for each dimension, there are 5 levels, which are as follows: no problems, slight problems, moderate problems, severe problems, and extreme problems.

During all VC period study visits (starting at screening) and at specific LTS visits (Weeks 12, 24, 36, 52, and follow-up visit), the participant will be asked to indicate his/her health state over the past 7 days, by ticking the box next to the most appropriate statement in each of the 5 dimensions. The digits for the 5 dimensions can be combined into a 5-digit number that describes the participant's health state ([EuroQol Research Foundation 2017](#)).

#### **8.2.7.5. Work Productivity and Activity Impairment Questionnaire: Specific Health Problem Version 2.0**

The WPAI:SHP v2.0 questionnaire is a validated 6-item instrument, completed during all site visits starting at screening, during the VC period, and at specific LTS visits (Weeks 12, 24, 36, 52 and follow-up visit) that measures the effect of overall health and specific symptoms on productivity at work and regular activities outside of it during the past 7 days (Reilly et al 1993).

#### **8.2.7.6. Itch Numerical Rating Scale**

The Itch NRS is a daily patient-reported measure (24-hour recall) of the worst level of itch intensity. Participants will be asked to rate the itching severity because 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 drug in the VC period. Detailed directions for the administration of an eDiary will be provided in the Study Manual.

#### **8.2.7.7. Skin Pain Numerical Rating Scale**

The Skin Pain NRS is a daily patient-reported measure (24-hour recall) of the worst level of pain intensity from 0 (no pain) to 10 (worst imaginable pain). Participants will be asked, “Rate the pain severity from your atopic dermatitis skin changes by selecting a number that best describes your worst level of pain in the past 24 hours,” as outlined in the SoA (see Table 3).

Participants will be issued a diary in which to record skin pain severity each evening, rating the worst pain in the past 24-hours. The participants will be instructed to complete the diary each night beginning on the day of screening through the last application of study drug in the VC period. Detailed directions for the administration of an eDiary will be provided in the Study Manual.

#### **8.2.7.8. PROMIS Sleep Questionnaires: Short Form – Sleep-Related Impairment (8a) and Short Form – Sleep Disturbance (8b)**

PROMIS® (Patient-Reported Outcomes Measurement Information System) is a set of widely used and accepted patient-reported outcome measurements that have been developed with strong clinical outcome assessment development methods and are psychometrically supported.

*Note:* The selected PROMIS Short Form – Sleep-Related Impairment (8a) and Short Form – Sleep-Disturbance (8b) questionnaires have been modified to be completed with a diary on a daily basis with a 24-hour recall: Short Form – Sleep-Related Impairment (8a) is collected in the evening, and Short Form – Sleep-Disturbance (8b) is collected in the morning during the VC period.

Starting at Week 8 and during the LTS period, these will be done with a 7-day recall period and be completed at the site during study visits. For timing, see SoAs Table 3 and Table 4.

These measures will be collected from both adolescents and adults via a diary during the VC period and on a tablet at the site during scheduled LTS period study visits. Refer to the Study Manual for detailed instructions.

#### **8.2.7.8.1. PROMIS Short Form – Sleep-Related Impairment (8a)**

The PROMIS Short Form – Sleep-Related Impairment (8a) questionnaire, is to be completed in the evening during the VC period. This assessment focuses on self-reported perceptions of alertness, sleepiness, and tiredness during usual waking hours and the perceived functional impairments during wakefulness associated with sleep problems or impaired alertness ([Buysse et al 2010](#)).

The questionnaire has 8 simple questions with a 5-point scale with a range in score from 8 to 40, with higher scores indicating greater severity of sleep-related impairment. Each item asks the participant to rate the severity of the participant's sleep impairment. The recall period will be the past 24 hours for the VC period and the past 7 days for the LTS period.

#### **8.2.7.8.2. PROMIS Short Form – Sleep Disturbance (8b)**

The PROMIS Short Form – Sleep Disturbance (8b) questionnaire is to be completed in the morning during the VC period. This assessment is self-reported perceptions of sleep quality, sleep depth, and restoration associated with sleep. Sleep disturbance does not focus on symptoms of specific sleep disorders and does not provide subjective estimates of sleep quantities (eg, total amount of sleep, time to fall asleep, amount of wakefulness during sleep; [Buysse et al 2010](#)). The sleep disturbance short form is generic rather than disease-specific.

The questionnaire is also 5-point scale with a range in score from 8 to 40, with higher scores indicating greater severity of sleep disturbance. Each item asks the participant to rate the severity of the participant's sleep disturbance. The recall period will be the past 24 hours for the VC period and the past 7 days for the LTS period.

#### **8.2.8. Health Economics**

Health economic data will be assessed through the WPAI and EQ-5D-5L Questionnaires (see Section [8.2.7.4](#) and [8.2.7.5](#)).

### **8.3. Safety Assessments**

Planned timepoints for all safety assessments are provided in the SoAs in [Table 3](#) and [Table 4](#).

See Section [6.5](#) for guidelines regarding the management of relevant laboratory or other safety assessment abnormalities.

### **8.3.1. Adverse Events**

Adverse events will be monitored from the time the participant signs the ICF/assent until at least 30 (+ 7) days after the last dose of study drug. Adverse events that begin or worsen after informed consent/assent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study drug. Conditions that were already present at the time of informed consent/assent 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 treatment/procedures, or that caused the participant to discontinue the study drug. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant, such as "How are you feeling?" is the preferred method to inquire about AE occurrences. Adverse events may also be detected when they are volunteered by the participant during the screening process or between visits, or through physical examinations, laboratory tests, or other assessments. The definition, reporting, and recording requirements for AEs are described in Section 9.

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

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

### **8.3.2. Physical Examinations**

At the screening visit and at Weeks 8 and 52/EOT, 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.

During the study, participants will be assessed by the investigator or medically qualified designee per institutional standard of care. These assessments should be an evaluation as indicated by participant symptoms, AEs, or other findings and documented on the AE eCRF.

Physical examinations will be conducted at the timepoints listed in Table 3 and Table 4.

### **8.3.3. Vital Signs**

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. Height and weight will also be assessed at screening, Weeks 8, 24 and 52/EOT. Abnormal vital sign results identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, or require concomitant therapy.

### **8.3.4. Electrocardiograms**

A single 12-lead ECG will be obtained at screening (12-lead ECG performed within 2 months before baseline is acceptable) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after 5 minutes of rest.

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


### **8.3.5. Laboratory Assessments**

See [Table 9](#) for the list of clinical laboratory tests to be performed and to the SoAs (see [Table 3](#) and [Table 4](#)) for the timing and frequency. A central laboratory will perform all clinical laboratory assessments for safety (ie, blood chemistries, hematology assessments, coagulation tests, endocrine function, and urinalysis), and will store the samples for PK and PD. 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 SoAs (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 dose of study treatment, 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 9: Required Laboratory Analytes**

Serum Chemistries	Hematology	Urinalysis With Microscopic Examination	Serology	Pregnancy Testing
Albumin Alkaline phosphatase ALT AST Blood urea nitrogen or urea Creatinine Glucose 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 (WBC) count  Differential count, including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein	HIV antibody	Female participants of childbearing potential have a serum test at screening and a urine test at all other visits. A positive urine test will be confirmed by a serum test.
		<b>Lipid Panel</b>	<b>Other</b>	
		Total cholesterol Triglycerides High-density lipoprotein Low-density lipoprotein Very-low density lipoprotein	FSH 	

*Note:* Additional tests may be required, as agreed upon by the investigator and sponsor, based on emerging safety data.

### 8.3.5.1. Pregnancy Testing

A serum pregnancy test will be required for all female participants of childbearing potential during screening and at the safety follow-up visit (30 [+ 7] days after EOT). Urine pregnancy tests will be performed locally, as outlined in the SoAs (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.

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

If a pregnancy is confirmed by a serum pregnancy test, see [Section 9.6](#) for reporting requirements.

### 8.3.5.2. Serology

HIV assessments will be performed at the screening visit to rule out HIV infection; required analytes are shown in [Table 9](#). 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.





[illegible]



## 8.8. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 (+ 7) days after the EOT visit (or after the last dose of study drug/treatment if the EOT visit was not performed).

Adverse events and SAEs must be reported up until at least 30 days after the last dose of study drug/treatment, the date of the follow-up visit, or 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
<ul style="list-style-type: none"><li>• An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.</li><li>• An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.</li></ul>
Events <u>Meeting</u> the Adverse Event Definition
<ul style="list-style-type: none"><li>• Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).</li><li>• Abnormal laboratory test results constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal lab result (eg, low hemoglobin, platelet count decreased).</li><li>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.</li><li>• New conditions detected or diagnosed after study treatment administration even though they may have been present before the start of the study.</li><li>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.</li><li>• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.</li><li>• "Lack of efficacy" or "failure of expected pharmacological action" per se 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.</li></ul>

### Events **NOT** Meeting the Adverse Event Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition or considered to be treatment-related by the investigator.
- Efficacy endpoints as outlined in Section 2 will not be reported as AE/SAEs, specifically, any event that is related to disease progression. Unblinded aggregated efficacy endpoint events and safety data will be monitored to ensure the safety of the participants in the study. Any suspected endpoint that upon review is not progression of the disease under study will be forwarded to Incyte Pharmacovigilance as a SAE within 24 hours of determination that the event is not progression of the disease under study.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE if it occurred after signing informed consent/assent. If present before entering the study, the condition should be captured as medical history.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

## 9.2. Definition of Serious Adverse Event

If an event is not an AE per 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 occurred. 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 (usually 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 of a pre-existing condition that did not worsen from baseline is not considered an AE.

**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. Other situations (Important Medical Event)**

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 invasive or malignant cancers (excluding the disease[s] under study in oncology protocols), 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/assent is signed should be recorded on the Adverse Event Form in the eCRF. 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 diagnostics 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 AE eCRF page.
- There may be 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 on the copies of the medical records before submission.
- 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 severity grade (CTCAE v4.03 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 treatment: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).

- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. *Note:* If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on 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 v4.03 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 medical 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 treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are 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 relationship.
- The investigator will also consult the RSI in the IB and/or Product Information, for marketed products, in his/her assessment.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment 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 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 send a follow-up SAE report with 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.
- 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 information will be recorded in the originally completed eCRF.
- Any updated SAE data will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.
- Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome.
- When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves.

#### **9.4. Reporting of Serious Adverse Events**

All SAEs, regardless of suspected causality (eg, relationship to study drug or study procedure[s]), occurring after the participant has signed the ICF/assent through the last study visit or 30 (+ 7) days after the last dose of study drug, whichever occurs later, 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 the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment 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 towards the safety of participants and the safety of a study treatment under clinical investigation are met.

If the SAE is not documented in the ruxolitinib cream IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, 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 treatment 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 also complete the Incyte Serious Adverse Event Report Form, in English. Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.
- Facsimile or email transmission of the Serious Adverse Event Report Form is the preferred method to transmit this information to the PhV/designee (eg, C3i/Telerox). The contact information of the sponsor's study-specific representatives is listed in the investigator manual provided to each site. The original copy of the Serious Adverse Event Report Form and the confirmation sheet must be kept at the study site.
- Follow-up information is recorded on an amended or new Serious Adverse Event Report Form, with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous Serious Adverse Event Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.
- In rare circumstances and in the absence of facsimile or computer equipment, notification by telephone is acceptable with a copy of the Incyte Serious Adverse Event Report Form sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Study 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 Study Manual. The IRT system has an option to select for "Emergency Code Break" action for a given participant. After entering the 6-digit study drug tube number and verification of the unmasking information, the investigator/subinvestigator will proceed to either final confirmation or cancellation of the code break procedure.

If a participant's treatment assignment is unblinded, the sponsor or its designee 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 treatment, unless there are ethical reasons to have the participant remain on the study treatment. In these cases, the investigator must obtain specific approval from the sponsor's (or its designee's) medical monitor for the participant to continue in the study.

## 9.6. Pregnancy

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

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

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

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

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

## **9.8. 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 600 participants will be randomized 2:2:1 to ruxolitinib 0.75% BID, 1.5% BID, or vehicle and stratified by baseline IGA (2, 3) and region (North America or other). The sample size calculation is based on the Fisher exact test for the statistical comparison on the primary efficacy endpoint. The Fisher exact test is used to provide a conservative evaluation of statistical power, and it is accurate when there is a small expected number of responders in the vehicle group. Based on the results from a Phase 2, randomized, dose-ranging study (INCB 18424-206), the IGA-TS at Week 8 is assumed to be 45% and 30% for active arms (1.5% BID and 0.75% BID, respectively) versus 10% 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 provide adequate power for efficacy variables, the sample size is determined to provide an adequate database for safety evaluation.

### **10.2. Populations for Analysis**

Table 10 presents the populations for analysis.



**Table 10: Populations for Analysis**

Population	Description
ITT	The ITT population includes all randomized participants. Treatment groups for this population will be defined according to the treatment assignment at randomization.
PP	The PP population includes randomized participants who are considered to be sufficiently compliant with the Protocol.
Safety	The safety population includes all participants who applied at least 1 dose of study drug. Treatment groups for this population will be determined according to the actual treatment the participant received on Day 1.
LTS evaluable	The LTS evaluable population includes all participants who applied at least 1 dose of ruxolitinib 0.75% or 1.5 % cream during the LTS period. All analyses for the LTS period will be conducted with the LTS evaluable population.
PK/ pharmacodynamic evaluable	The PK/pharmacodynamic evaluable population includes participants who applied at least 1 dose of ruxolitinib cream and provided at least 1 postdose blood sample for PK. The study pharmacokineticist will review data listings of participant administration and sample records to identify participants to be excluded from the analysis.

### 10.3. Type I Error Control

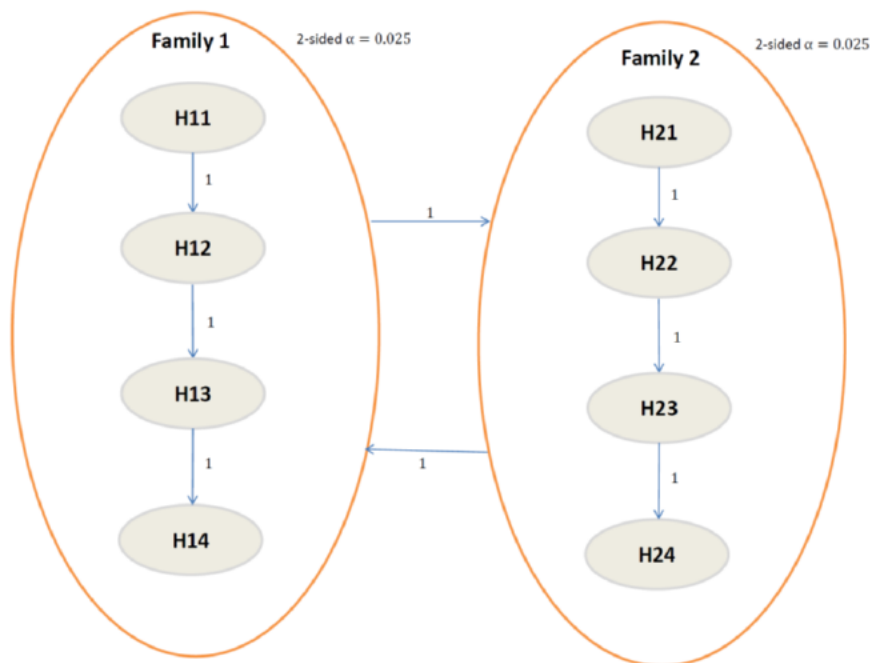
A graphical procedure with gatekeeping testing strategy for the primary and key secondary analyses will be implemented. The underlying procedure is derived using the methodology developed in Bretz et al (2009). This method will guarantee a strong control of the family-wise error rate.

Two families of 8 elementary hypotheses tests are grouped according to treatment comparison between each active dose group to vehicle, where

- Family 1 (1.5% BID vs vehicle):
  - H11: proportion of participants who achieve IGA-TS;
  - H12: proportion of participants who achieve EASI-75;
  - H13: proportion of participants with a  $\geq 4$ -grade improvement in Itch NRS over baseline;
  - H14: proportion of participants with a clinically meaningful improvement in the PROMIS Sleep Disturbance score.
- Family 2 (0.75% BID vs vehicle):
  - H21: proportion of participants who achieve IGA-TS;
  - H22: proportion of participants who achieve EASI-75;
  - H23: proportion of participants with a  $\geq 4$ -grade improvement in Itch NRS over baseline;
  - H24: proportion of participants with a clinically meaningful improvement in the PROMIS Sleep Disturbance score.

To control the overall Type I error rate, 2-sided  $\alpha = 0.05$ , the Bonferroni's method will be used. Within each family, the endpoints are tested in a fixed sequence at Bonferroniized 2-sided  $\alpha = 0.025$  level. The endpoint will be tested only if the associated primary (and secondary in previous steps) are rejected. For any dose level, if the 4 related null hypotheses can be rejected, then the fixed sequence for the other dose level can be conducted at 2-sided  $\alpha = 0.05$  level. The approach can be visualized in [Figure 4](#).

**Figure 4: Control of the Overall Type I Error Rate**



## 10.4. Statistical Analyses

The Statistical Analysis Plan 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 intent-to-treat population. The primary alternative hypothesis (superiority of ruxolitinib 1.5% BID or 0.75% BID compared with vehicle) will be tested using logistic regression. This model will include the treatment group (1.5% BID, 0.75% BID, and vehicle) and stratification factors (baseline IGA and region). The unadjusted p-values between each treatment group versus vehicle will be calculated based on Wald test, which will be compared with 0.025 using the Bonferroni procedure. Exact logistic regression ([Mehta and Patel 1995](#)) will be used for all of the comparisons if any of the dose levels have an expected cell count less than 5.

The difference in IGA-TS rates (ruxolitinib cream vs vehicle) at Week 8 will also be computed. The 95% confidence interval for the difference will be computed based on a large-sample normal approximation with continuity correction. All nonresponders in the VC treatment 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. Sensitivity analyses, including longitudinal logistic regression with repeated measurements and multiple imputation, may be performed. In addition, a tipping point analysis will be conducted to examine the potential effects of missing data. Subgroup analysis by baseline characteristic (eg, IGA, region, and age) will be performed. Details will be provided in the Statistical Analysis Plan.

#### **10.4.2. Secondary Analysis**

Secondary efficacy analyses will be conducted in 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 4](#). The endpoints will be analyzed using the similar method as specified in the primary analysis.

All other secondary and exploratory efficacy variables will be summarized using descriptive statistics. For categorical measurements, summary statistics will include sample size, frequency, and percentages. Similar 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 first dose of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study drug administration. Adverse events will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the National Cancer Institute CTCAE v4.03 using Grades 1 through 5.

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

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

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

[REDACTED]

### **10.5. Interim Analysis**

An interim analysis will not be performed for this 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 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 IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB/IEC requirements, institutional requirements, and applicable laws and country-specific regulations.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling participants who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws, but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.

- All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

## **11.2. Data Management**

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

The site will be provided 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.

The sponsor (or designee) will be responsible for:

- The data management of this study including quality checking of the data.
- 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.

The investigator will be responsible for:

- Ensuring participant data relating to the study is recorded in the eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, diary data) or as otherwise specified in the Protocol. The investigator is responsible for 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.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
  - Data reported on the CRF or 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. Also, current medical records must be available.

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

### **11.3. Data Privacy and Confidentiality of Study Records**

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

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

Records and documents, including signed ICFs/assents, pertaining to the conduct of this study must be retained by the investigator for 30 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

#### **11.4. Financial Disclosure**

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

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

#### **11.5. Publication Policy**

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

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

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

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



## **11.6. Study and Site Closure**

The sponsor 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 male participants in the study:

Male participants should use a condom from screening through 90 days after the end of systemic exposure. If the male participant has a partner that is of child-bearing 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 from screening through 90 days after the end of relevant systemic exposure. Males who have had a vasectomy qualify as having met the requirement for a highly effective birth control method.

### For female participants in the study:

Precautions to avoid pregnancy should be followed until the end of safety follow-up period (30 [+7] days after EOT).

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

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

<sup>a</sup> Contraception methods that in the context of this guidance are considered to have low user dependency.

<sup>b</sup> Vasectomized partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success.

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

Source: [Clinical Trial Facilitation Group 2014](#).

## APPENDIX B. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
<a href="#">Amendment (Version) 1:</a>	22 JAN 2019
<a href="#">Amendment (Version) 2:</a>	13 FEB 2019

### Amendment 2 (13 FEB 2019)

#### Overall Rational for the Amendment:

The primary purpose of this amendment is to incorporate revisions requested by the second review of the Voluntary Harmonisation Procedure (VHP).

1. **Section 1, Protocol Summary (Table 4, Schedule of Activities: Long-Term Safety Extension Period); Section 8.3.3, Vital Signs**

**Description of change:** Updated to indicate that height and weight are assessed at screening and Weeks 8, 24, and 52/EOT.

**Rationale for change:** To address VHP request.

2. **Section 5.1, Inclusion Criteria**

**Description of change:** Fixed a number formatting error for inclusion criterion 7.

**Rationale for change:** To correct.

3. **Section 6.1, Study Treatment Administered**

**Description of change:** Added text to clarify treatment application process for the participant.

**Rationale for change:** To clarify.

4. **Section 6.6.3, Prohibited Medications and Procedures**

**Description of change:** Deleted text to clarify that allergen immunotherapies are prohibited throughout the study.

**Rationale for change:** To address VHP request.

5. **Section 9.5, Emergency Unblinding of Treatment Assignment**

**Description of change:** Revised to be clear that emergency unblinding is permitted at any stage of the entire study and not only during the VC period.

**Rationale for change:** To address VHP request.

6. **Section 8.3.4, Electrocardiograms**

**Description of change:** Deleted text to clarify the electrocardiogram process.

**Rationale for change:** To clarify.

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 (22 JAN 2019)**

### **Overall Rational for the Amendment:**

The primary purpose of this amendment is to incorporate revisions requested by the Voluntary Harmonisation Procedure (VHP).

1. **Section 1, Protocol Summary (Tables 3 and 4, Schedule of Activities); Section 8.3.3, Vital Signs;** [REDACTED]

**Description of change:** Updated to indicate that height and weight are assessed as part of vital sign assessments and performed only at screening, Weeks 8 and 52, and EOT. In addition, clarified that [REDACTED] will be performed after a photograph of the target lesion is taken.

**Rationale for change:** Administrative corrections.

2. **Section 2.2.2.4.1, Atopic Dermatitis; Section 4.3, Study Termination**

**Description of change:** The reasons for discontinuation of 46 of 260 participants in the double-blind period of study INCB 18424-206 were listed. Text added to note that the current study will be terminated if there are any significant safety findings during the course of the study.

**Rationale for change:** To address VHP request.

3. **Section 4.1, Overall Design**

**Description of change:** Added text noting ratio of participants with an IGA score of 2 will constitute up to approximately 25% of the overall study population.

**Rationale for change:** Detail regarding the proportion of patients with IGA score of 2 versus 3 was added to ensure the population enrolled in the study reflects the intended treatment population (and specifically patients with a higher medical need).

4. **Section 5.1, Inclusion Criteria (Criterion 8b); Section 8.3.5.1, Pregnancy Testing; Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

**Description of change:** Updated to indicate that the safety follow-up visit is 30 (+7) days after EOT. Precautions to avoid pregnancy should be followed until this visit, and a pregnancy test will be performed at this visit.

**Rationale for change:** To address VHP request. In addition, to provide clear guidance that pregnancy testing will be done through the duration of the study up to the end of safety follow-up period (30 [+ 7] days after EOT).

5. **Section 5.1, Inclusion Criteria (Criterion 9); Section 8.1.1, Informed Consent Form Process**

**Description of change:** Text added to note that adolescent participants who become of legal age during the study will be discontinued from the study unless they sign a new ICF to continue the study.

**Rationale for change:** To address VHP request.



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

**Description of change:** Text added to limit the history of malignancy to within the past 5 years.

**Rationale for change:** To address VHP request and to provide additional detail regarding what was intended by history of malignancy.

**7. Section 5.2, Exclusion Criteria (Criteria 13 and 14)**

**Description of change:** Addition of criteria to exclude participants who have been committed to a mental institution due to an order from judicial or administrative authorities. In addition, participants should be excluded if they are employees or dependents of the sponsor or investigator.

**Rational for change:** To address VHP request.

**8. Section 6.6.3, Prohibited Medications and Procedures**

**Description of change:** Text added to clarify that allergen immunotherapies are prohibited unless the participant is on a stable and established regimen.

**Rationale for change:** Additional clarification for the use allergen immunotherapies.

**9. Section 9.5, Emergency Unblinding of Treatment Assignment**

**Description of change:** Text revised to indicate that an emergency unblinding procedure is possible during the entire clinical study and that the sponsor must be notified by telephone with a follow-up email.

**Rationale for change:** To address VHP request.

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

**Description of change:** Updated to include additional information about the Fisher exact test and a Phase 2 study reference for the IGA-TS values at Week 8.

**Rationale for change:** To address VHP request.

**11. Section 10.4.1, Primary Analysis**

**Description of change:** Text added to clarify the analysis to be performed.

**Rationale for change:** To address VHP request.

**12. Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

**Description of change:** Removed the footnote regarding hormonal contraception and the section containing acceptable birth control with failure rate of more than 1% per year.

**Rationale for change:** To address VHP request.

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

## Signature Manifest

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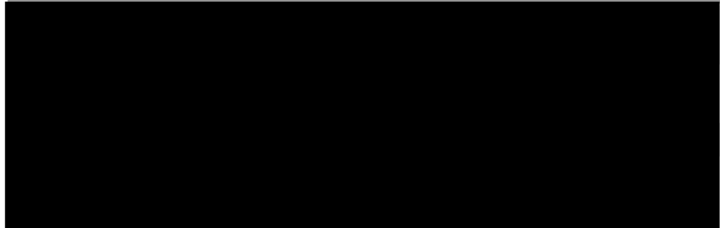
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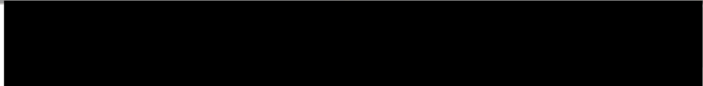
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#### Approval and Release

Name/Signature	Title	Date	Meaning/Reason
		13 Feb 2019, 04:03:06 PM	Approved
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